EFFICACY OF SWITCHING TO ARIPIPRAZOLE AND ZIPRASIDONE ON CLINICAL AND METABOLIC PROFILE AMONG SCHIZOPHRENIC PATIENTS WITH METABOLIC SYNDROME

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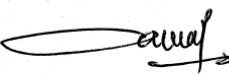Name of Degree: Doctor of Philosophy

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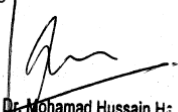Field of Study: Psychiatric Epidemiology

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Abstract

Introduction: Schizophrenia is a devastating mental illness that impairs mental and social functioning and often leads to the development of co-morbid diseases. They are at greater risk for metabolic dysfunctions than other individuals due to a number of reasons, including inactive lifestyle, poor dietary choices, and side effects of antipsychotic medications. Atypical antipsychotics were reported to be associated with increased risk of hyperglycaemia and hyperlipidemia, and subsequently increase the risk of metabolic syndrome. However, ziprasidone and aripiprazole have a favourable metabolic profile.

Objectives: i) To determine the prevalence of metabolic syndrome and its components among schizophrenia patients. ii) To determine the improvement and reversibility of metabolic syndrome, its components and lipid profiles after switching to aripiprazole or ziprasidone. iii) To determine the safety and efficacy of aripiprazole and ziprasidone in the treatment of schizophrenia patients with metabolic syndrome.

Methodology:Screening -The study was conducted at four mental institutions and four general hospitals. Study population were schizophrenia patients aged between 18 and 65 years old, who met the DSM-IV TR criteria for schizophrenia. Patients should receive antipsychotic treatment for at least 1 year and were not on mood stabilizer. Metabolic syndrome was defined by using the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria-modified for Asian waist circumference.

Randomized double-blind controlled trial was conducted for 6-month after screening.The dose of aripiprazole and ziprasidone, can be either increased or reduced based on clinical assessment. The total daily dosage of ziprasidone ranges from 80mg - 160mg.The total daily dosage of aripiprazole ranges from 10mg - 30 mg. The outcome measures included body mass index (BMI), waist circumference, blood

pressure(BP), fasting blood sugar (FBS) and lipid profile, adverse effects monitoring and clinical rating scale such as Positive and Negative Symptoms Scale (PANSS), Clinical Global Impression Scale (CGI), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathasia Scale (BAS) and Simpson Angus Scale (SAS).Intention-to-treat analysis and mixed-effects model with repeated measures (MMRM) for statistical analysis were done.

Results: A total of 527 patients were screened but only 270 schizophrenia patients fulfil all inclusion and did not have any exclusion criteria. The prevalence of metabolic syndrome was 46.7%. There was improvement in the prevalence of all metabolic syndrome component from baseline to 6-month after switching to aripiprazole or ziprasidone; waist circumference (aripiprazole 84.4% vs. 44.4%, ziprasizone 87.1% vs. 35.3%), HDL cholesterol (aripiprazole 54.4% vs. 33.3%, ziprasizone 52.9% vs. 23.5%), triglycerides (aripiprazole 50.0% vs. 21.1%, ziprasizone 37.6% vs. 12.9%), BP (aripiprazole 41.1% vs. 25.6%, ziprasizone 32.9% vs. 20.0%), FBS (aripiprazole 42.2% vs. 20.0%, ziprasizone 25.9% vs. 8.2%, $p < 0.05$). Switching to either aripiprazole or ziprasidone cause statistically significant reduction in prevalence of metabolic syndrome after 6 month of treatment (aripiprazole 58.9% vs. 30.0%, ziprasizone 51.8% vs. 15.3%, $p < 0.05$). There was statistically significant improvement in PANSS, CGI, BARS and SAS after switching to aripiprazole or ziprasidone.

Conclusion: The prevalence of metabolic syndrome in schizophrenia patients receiving antipsychotic in Malaysia was very high. Switching to aripiprazole or ziprazidone was effective in reversing the metabolic syndrome and its components among schizophrenia patients who had metabolic syndrome.

Abstrak

Pendahuluan: Skizophrenia adalah penyakit mental yang boleh menyebabkan kesengsaraan, melemahkan fungsi sosial dan mental, dan kerap menjurus kepada pencetusan penyakit-penyakit lain. Pengidapnya mempunyai risiko yang lebih tinggi untuk metabolik tidak berfungsi berbanding dengan orang ramai disebabkan beberapa faktor termasuk kehidupan yang tidak aktif, pemilihan pemakanan yang salah dan kesan sampingan ubat-ubatan antipsikotik. Antipsikotik atipikal telah dilaporkan mempunyai kaitan dengan pertambahan risiko hiperglisemia, hiperlipidemia dan seterusnya meningkatkan risiko sindrom metabolik. Walaubagaimanapun, ziprasidone dan aripiprazole mempunyai profil metabolik yang lebih selamat.

Objektif: i) Untuk mengetahui prevalen sindrom metabolik dan komponennya di kalangan pesakit skizophrenia. ii) Untuk mengetahui tahap pembaikan dan kebolehan untuk pulih dari sindrom metabolik dan komponennya serta profil lemak setelah ditukarkan ke ubat aripiprazole atau ziprasidone. iii) Untuk mengetahui keselamatan dan keberkesanan aripiprazole dan ziprasidone di dalam rawatan pesakit skizophrenia yang menghadapi masalah sindrom metabolik.

Kaedah: Kajian ini telah diadakan di empat institusi mental dan empat hospital umum kerajaan. Populasi kajian ini terdiri daripada pesakit skizophrenia yang berumur di antara 18 ke 65 tahun dan mereka memenuhi kriteria DSM-IV TR untuk skizophrenia. Pesakit mestilah menerima rawatan antipsikotik sekurang-kurangnya selama setahun dan tidak boleh mengambil ubat penstabil emosi. Sindrom metabolik telah didefinasikan mengunakan kriteria Program Kebangsaan Pendidikan Kolesterol Panel Rawatan Dewasa III (NCEP ATP III) diubahsuai mengikut ukuran pinggang orang Asia. Kajian rawak dwi rabun telah dijalankan selama 6 bulan selepas saringan. Dos ubat ziprasidone adalah di antara julat 80mg-160mg. Jumlah dos harian untuk aripiprazole adalah di dalam julat 10mg-30mg. Penanda aras kajian termasuk Index

Jisim Badan (BMI), ukuran lilit pinggang,tekanan darah, paras gula dan lemak ketika berpuasa, pengawasan kesan sampingan ubat, Skala Simptom Positif dan Negatif (PANSS), Skala Impresi Global Klinikal (CGI), Skala Pergerakan Luar Kawal Tidak Normal (AIMS), Skala Akathasia Barnes (BAS) dan Skala Simpson Angus (SAS). Analisa tindakan untuk saringan dan model kesan bercampur dengan pengukuran berulang (MMRM) telah digunakan di dalam analisa statistik.

Keputusan: Sejumlah 527 pesakit telah disaring tetapi hanya 270 pesakit skizophrenia memenuhi semua kriteria kemasukan dan tidak mempunyai kriteria pengasingan. Prevalen sindrom metabolik adalah sebanyak 46.7%. Terdapat penambahbaikan di dalam semua prevalen komponen sindrom metabolik dari permulaan sehingga 6 bulan selepas pertukaran rawatan kepada aripiprazole atau ziprasidone; ukuran lilit pinggang (aripiprazole 84.4% vs. 44.4%, ziprasizone 87.1% vs. 35.3%), HDL kolesterol (aripiprazole 54.4% vs. 33.3%, ziprasizone 52.9% vs. 23.5%), triglycerides (aripiprazole 50.0% vs. 21.1%, ziprasizone 37.6% vs. 12.9%), tekanan darah (aripiprazole 41.1% vs. 25.6%, ziprasizone 32.9% vs. 20.0%) , paras gula berpuasa (aripiprazole 42.2% vs. 20.0%, ziprasizone 25.9% vs. 8.2%, p<0.05). Penukaran kepada aripiprazole atau ziprasidione menyebabkan pengurangan prevalan sindrom metabolik selepas rawatan selama 6 bulan (aripiprazole 58.9% vs. 30.0%, ziprasizone 51.8% vs. 15.3%, p<0.05). Terdapat perbezaan dari segi statistik untuk PANSS, CGI, BARS dan SAS selepas penukaran kepada aripiprazole atau ziprasidione.

Kesimpulan: Prevalan sindrom metabolik di kalangan pesakit skizophrenia yang mengambil ubat antipsikotik di Malaysia adalah sangat tinggi. Penukaran ubat kepada aripiprazole atau ziprasidone adalah berkesan untuk memulihkan sindrom metabolik di kalangan pesakit skizophrenia yang mengalami masalah tersebut.

Acknowledgements

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List of Abbreviations

ADA-APA-AACE	American Diabetes Association, the American Psychiatric Association and the American Association of Clinical Endocrinologists
AIMS	Abnormal Involuntary Movement Scale
AUC	Area Under the Curve
BARS	Barnes Akathasia Scale
BMI	Body Mass Index
BP	Blood Pressure
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CBT	Cognitive behaviour therapy
CGI-S	Clinical Global Impression Scale - Severity of Illness
CHD	Coronary Heart Disease (CHD)
CLAMORS	Cardiovascular, Lipid and Metabolic Outcomes Research in Schizophrenia Study
CRP	C-reactive protein
CV	Cadiovascular
CVD	Cardiovascular Disease
CYP	Cytochrome P450
DALY	Disability-Adjusted Life Year
DSM IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision
EC	Ethics Committee
EGIR	European Group for the Study of Insulin Resistance

EE	Expressed Emotion
EPS	Extrapyramidal Side Effects
FBS	Fasting Blood Sugar
FDA	Food and Drug Administration
GEE	Generalized Estimating Equation
HDL-C	High-density lipoprotein Cholesterol
ICD 9	International Classification of Diseases 9
ICD 10	International Classification of Diseases 10
IDF	International Diabetes Federation
IPT	Integrated psychological therapy
LOCF	Last Observation Carried Forward
M.I.N.I.	Mini International Neuropsychiatric Interview
MMRM	Mixed-effects model repeated-measures
NHLBI	National Heart, Lung and Blood Institute
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NHANES III	Third National Health and Nutrition Examination Survey
PAI-1	Plasminogen Activator Inhibitor 1
PANSS	Positive and Negative Syndrome Scale
PI	Principle investigator
PROCAM	Prospective Cardiovascular Munster
SAE	Serious Adverse Event
SAS	Simpson Angus Scale
SE	Standard Error
sLDL	Small, dense low-density lipoprotein
SPSS	Statistical Package for Social Sciences

T2D	Type 2 Diabetes
UMMC	University Malaya Medical Centre
US	United States
WHO	World Health Organization

Chapter ONE: Introduction

Schizophrenia is a severe and persistent disabling brain disorders characterized by a disintegration of the process of thinking, of contact with reality and of emotional responsiveness. The breakdown in these processes manifests as symptoms of hallucinations, delusions, disorganized communication, poor planning, reduced motivation and blunted effect. All of these have a profound impact on social or occupational function of the afflicted individual (Awad et al.,1997a; Awad et al.,1997b).

1.1   History of Schizophrenia

Symptoms resembling schizophrenia had been described in as early as 2000 BC by ancient Egyptians. However only in 1887 when Emil Kraepelin (1856-1926) classified it as a discrete mental disorder with the term 'dementia praecox' for individuals who present with symptoms associated with schizophrenia by today's definition (Kraepelin,1907).

The psychiatrist Kurt Schneider (1887-1967) then listed the forms of psychotic symptoms that he thought distinguished schizophrenia from other psychotic symptoms. These were called first-rank symptoms or Schneider's first-rank symptoms (Schneider,1959). While these symptoms have contributed to the current diagnostic criteria, their reliability has been questioned (Bertelsen,2002). The first-rank symptoms include:

- Delusions of being controlled by an external force
- The belief that thoughts are being inserted into or withdrawn from one's conscious mind
- The belief that one's thoughts are being broadcast to other people

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- Hearing hallucinatory voices that comment on one's thoughts or actions or that have a conversation with other hallucinated voices.

In 1911, Eugen Bleuler proposed the term 'schizophrenia' (translated from Greek as 'splitting of the mind') to describe the separation of function between personality, thinking, memory and perception as seen in this mental disease. Blueler was also the first to describe the symptoms as 'positive' and 'negative' (Bleuler,1984).

Schizophrenia is not synonymous with dissociative identity disorder (or known as 'split personality'). It is a common misunderstanding partly due to the meaning of the term used ('splitting of the mind'). Although some people diagnosed with schizophrenia may hear voices and may experience the voices as distinct personalities, schizophrenia does not involve a person changing among distinct multiple personalities.

There were at least 15 different diagnostic systems for schizophrenia identified in the literature over the last 3 decades (Berner et al.,1983). While the operational approach in psychiatry has been considered by many as a progress in the right direction, it was also being increasingly criticized for a number of negative pragmatic consequences (Andreasen,1998; Maj,1998; Tucker,1998; Parnas and Zahayi,2002). The obvious unpredictability of the contemporary diagnosis poses a serious problem for etiological research especially genetic linkage research and early intervention studies (Jansson et al.,2002).

The issues of validity and reliability of psychiatric diagnosis are frequently conflated in the literature. For instance, in a study that made comparisons of International Classification of Diseases 9 (ICD-9) and International Classification of Diseases 10 (ICD-10) in first-admitted patients, it was found that only formal thought disorder and family history might be considered as 'concurrent/construct validity' indicators, (i.e. as

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extra-clinical measures) (Kendler,1990). On both indices, some investigators suggested that the ICD-10 appears to be less valid than the ICD-9 (Parnas and Bovet,1991; Kendler,1990). Clearly, continuing debate and research on the boundaries of schizophrenia was warranted to assess the validity of current diagnostic systems.

1.2 Epidemiology of Schizophrenia

The worldwide prevalence of schizophrenia is estimated to be around 1%, as reported in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV) (1994), though the rate may vary across the world, within countries, and among local neighbourhoods (Jablensky et al.,1992; Kirkbride et al.,2006; Kirkbride et al.,2007).

The onset of schizophrenia symptoms usually occurs in young adulthood (Castle et al.,1991). Diagnosis was largely based on the patient's self-reported experience and observed behaviour. Currently scientist still exploring the laboratory test for schizophrenia (Schwarz et al.,2010).

While it was a widely held view that schizophrenia was much more common in men (McGrath et al.,2004; Isohanni et al.,2006), a systematic review by Saha et al (2005) found that schizophrenia was just as common in women.

In Saha's review, a total of 1,721 prevalence estimates from 188 studies were identified. These estimates were drawn from 46 countries, including Argentina, Australia, Botswana, Canada, China, Croatia, the European countries, India, Indonesia, Iran, Israel, Japan, New Zealand, Papua New Guinea, Russia, Sri Lanka, Taiwan, United Kingdom, United States, Uzbekistan, Yugoslavia and others. The identified studies were divided into core studies (n=132), migrant studies (n=15) and studies based on other special groups (n=41). Based on combined prevalence estimates, the review found no significant differences in schizophrenia incidence between males and

females. In addition, there was also no substantial difference between urban, rural and mixed sites, although developing countries tended to have lower prevalence rates.

While 15 migrant studies were identified from eight countries (i.e. Australia, Germany, India, Israel, Taiwan, the Netherlands, United Kingdom and United States), only 5 studies were suitable to be included for analysis. Based on the limited data, the prevalence of schizophrenia in migrants was noted to be higher compared to the native population.

The special group studies came from 14 countries: Australia, Canada, Denmark, Finland, Germany, India, Israel, Japan, Romania, Spain, Sweden, Taiwan, United Kingdom and United States. Due to the marked heterogeneity of the data from the special group studies, it was not possible to perform a combined analysis. However, it was noted that prevalence estimates were very high in the homeless populations. On the other hand, religious groups (e.g. Amish) tended to have lower prevalence estimates.

1.3 Causes and Pathophysiology

The exact causes of schizophrenia are not known, but are believed to be a combination of biological, psychological and social factors (Nasrallah et al.,2011). Biological factors include genetically inherited brain abnormality (Shepherd et al.,2012) with or without obstetric complications (Brown and Derkits,2010), which can lead to subtle alterations in the brain that make a person susceptible to developing schizophrenia. Other factors, such as early environmental and psychosocial stressors (e.g. family stress or social stress during childhood or young adulthood) serve as precipitating or exacerbating factors (Day et al.,1987).

1.4 The Disease Burden of Schizophrenia

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Schizophrenia is known to be a major cause of disability. In a study of 17 health conditions in 14 countries, active psychosis was ranked the third-most-disabling condition, right after quadriplegia and dementia, and before paraplegia and blindness (Ustun et al.,1999). In addition to the direct burden, the patients are confronted with prejudice and discrimination. The stigma attached to schizophrenia creates a vicious cycle of discrimination leading to social isolation, unemployment, drug abuse, long-lasting institutionalisation or even homelessness (Rossler et al.,2005). All of these further decrease the chances for recovery and reintegration into normal life.

Schizophrenia is indeed the most burdensome and costly illness worldwide. The life expectancy is reduced by approximately 10 years, mostly as a consequence of suicide (Caldwell and Gottesman,1990; Erlangsen et al.,2012). According to the Global Burden of Disease Study, schizophrenia causes a high degree of disability, which accounts for 1.1% of the total disability-adjusted life years (DALYs) (Murray and Lopez,1996; Murray and Lopez,1997), which was a metric to quantify the overall disease burden. One DALY can be considered as 1 lost year of "healthy" life.

In the World Health Report, schizophrenia was listed as the 8th leading cause of DALYs worldwide in the age group of 15-44 years. While there are direct costs of providing care for individuals with schizophrenia, the indirect costs encompasses loss of productivity through impairments, disability and premature death, as well as some legal problems including violence (WHO,2001).

In addition to direct burden, there is considerable burden on the caregivers of schizophrenia patients. The caregivers are usually family members. The burden on families ranges from emotional reactions to the illness, the stress coping with disturbed behaviour, the disruption of household routine, the stigma they are confronted with, the restriction of social activities and economic difficulties. In a study that assessed a

cohort of caregivers of schizophrenia patients using the Involvement Evaluation Questionnaire (European version), it was found that 51% of caregivers experienced significant emotional distress. Higher patient's psychopathology, higher numbers of patient-rated needs, patients' lower global functioning and patients' poorer quality of life were found to be related to the severity of family burden (Parabiaghi et al.,2007).

1.5 Signs and symptoms

The symptoms of schizophrenia usually follow a waxing and waning course. However, the patient's pattern of symptoms might change over years (Nasrallah et al.,2011). Patients with schizophrenia manifest a variety of symptoms, which can fall into three broad categories (Peralta and Cuesta,2001; Oyebode,2002).

1.5.1 Positive symptoms

Positive symptoms of schizophrenia are easily noticeable behaviours not seen in healthy people. They include hallucinations, delusions, disorganized behaviour and disorganized speech.

1.5.2 Negative symptoms

The term 'negative symptoms' refers to the loss or absence of normal emotional and behavioural traits or abilities, such as flat or blunted effect and emotion, poverty of speech, anhedonia and lack of motivation. These symptoms are not obvious, therefore are harder to recognize as part of the disorder.

Despite the appearance of blunted affect, recent studies indicate that there is often a normal or even heightened level of emotionality in schizophrenia, especially in response to stressful or negative events (Cohen and Docherty,2004).

1.5.3 Cognitive symptoms

Cognitive symptoms or cognitive deficit are problems with attention (e.g. inability to sustain attention) (Kurtz,2005), certain types of memory (e.g. the ability to keep recently learned information and use it right away), and executive functioning (e.g. the ability to absorb and interpret information and make decision based on that information) (Bentall et al.,2007). These symptoms are subtle and are often detected only when neuropsychological tests are performed. Cognitive impairments often interfere with the patient's ability to lead a normal life and earn a living. This can cause great emotional distress.

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1.6 Diagnostic Criteria and Classification

The diagnosis of schizophrenia is largely based on self-reported experiences, as well as abnormalities in behaviour reported by family members, friends or co-workers, followed by secondary signs observed by a psychiatrist, social worker, clinical psychologist or other clinician in a clinical assessment.

There is a list of criteria that must be met for someone to be diagnosed with this mental illness. The current most widely used criteria for diagnosing schizophrenia are from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) (2000), and the World Health Organization's International Statistical Classification of Diseases, Tenth Revision (ICD-10) (WHO,1994a) .

While ICD-10 criteria are commonly used in Europe, DSM-IV-TR criteria are used in the USA and the rest of the world, and are more popular in research studies.

1.6.1 DSM-IV-TR Criteria

Based on DSM IV-TR criteria, a person must display certain characteristics or symptoms to be diagnosed with schizophrenia.

Characteristic symptoms

Presenting two or more of the following, each for a significant portion of time during a one-month period (or less, if successfully treated):

- Delusions

- Hallucinations

- Disorganized speech (e.g. frequent incoherence, speaking in abstracts)

- Severely disorganized behaviour (e.g. dressing inappropriately, crying frequently) or catatonic behaviour

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- Negative symptoms, such as affective flattening (lack in emotional response), alogia (lack in speech), or avolition (lack in motivation)

However, if delusions are bizarre or hallucinations involve commentary voices, only one of the above symptoms is required for diagnosis.

Duration

Individual must shows continuous signs of the disturbance for at least 6 months. This 6-month period must include at least 1 month of active-phase symptoms (or less, if successfully treated).

Social/occupational dysfunction

One or more major areas of functioning, such as work, interpersonal relations or self-care, are markedly below the level achieved prior to the onset for a significant portion of the time since the onset.

Note that schizophrenia cannot be diagnosed if symptoms of mood disorder or pervasive developmental disorder are present, or if symptoms are the direct result of a substance (e.g. abuse of a drug/medication) or a general medical condition.

Based on the predominance of certain symptoms and absence of others, the DSM-IV-TR distinguishes five clinical subtypes of schizophrenia:

- Paranoid type

Delusions and hallucinations are present but thought disorder, disorganized behaviour, and affective flattening are absent (DSM code 295.3, corresponding to ICD code F20.0).

- Disorganized type

Thought disorder and flat affect are present together in this subtype of schizophrenia (DSM code 295.1, corresponding to ICD code F20.1), also known as 'hebephrenic schizophrenia' in the ICD-10 criteria.

- Catatonic type

Prominent psychomotor disturbances are apparent. Symptoms can include catatonic stupor and waxy flexibility (DSM code 295.2, corresponding to ICD code F20.2).

- Undifferentiated type

Psychotic symptoms are present, but do not meet the criteria for paranoid, disorganized or catatonic types (DSM code 295.9, corresponding to ICD code F20.3).

- Residual type

Positive symptoms are present at a low intensity only (DSM code 295.6, corresponding to ICD code F20.5).

1.6.2 ICD-10 Criteria

ICD-10 classification and diagnosis of schizophrenia differs only slightly from the DSM IV-TR classification. The ICD-10 distinguishes nine symptomatic categories to diagnose schizophrenia:

(a)　　Thought insertion or withdrawal.

(b)　　Delusions of control, influence or passivity.

(c)　　Hallucinatory voices.

(d)　　Persistent delusions that is culturally inappropriate or completely impossible.

(e)　　Persistent hallucinations in any modality, accompanied by fleeting or delusions without clear affective content.

(f)　　Breaks in train of thought, incoherence or irrelevant speech, neologisms.

(g)　　Catatonic behaviour.

(h)　　Negative symptoms.

(i)　　Significant and consistent change in personal behaviour (such as idleness, self-absorbed attitude).

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The normal requirement for a diagnosis of schizophrenia is that a minimum of one very clear symptom (and usually two or more if less clear-cut) belonging to any one of the groups listed as (a) to (d) above, or symptoms from at least two of the groups referred to as (e) to (h), should have been clearly present for most of the time during a period of 1 month or more.

Based on the predominance of certain symptoms and absence of others, the ICD-10 also distinguishes schizophrenia into different subtypes. Apart from the five subtypes recognized in DSM-IV-TR, the ICD-10 recognizes a further two subtypes:

- Post-schizophrenic depression

This refers to a depressive episode arising in the aftermath of a schizophrenic illness, where some low-level schizophrenic symptoms may still be present (ICD code F20.4).

- Simple schizophrenia

Insidious but progressive development of prominent negative symptoms with no history of psychotic episodes is observed in this subtype (ICD code F20.6).

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1.7 Complications and Impact of Schizophrenia

Schizophrenia is associated with several complications that significantly affect the health and life of patients, as well as their family, friends and caregivers. This mental illness causes suffering to patients as a result of symptoms, lower quality of life, lost independence, poorer social integration, co-existing medical morbidity, and increased mortality (Becker et al.,2002). Schizophrenia also puts a considerable burden on the society, and leads to reduced economic productivity.

1.7.1 Outcome after First Episode

(a) Recovery

Follow up studies have shown a substantial number of schizophrenia patients achieving full recovery (i.e. sustained improvement in both symptoms and social/vocational functioning) when examined decades after an index admission (Harrison et al.,2001; Torgalsboen,2012).

In a study by Robinson et al (2004), for instance, data from a prospective study that followed up patients for a period of up to 9 years from their first episode of schizophrenia or schizoaffective disorder was examined. Their analysis suggested that patients with first-episode schizophrenia or schizoaffective disorder can recover. Although some patients with first-episode schizophrenia can achieve sustained symptomatic and functional recovery, the overall rate of recovery during the early years of the illness was low - only 13.7% of subjects met full recovery criteria for 2 years or longer. Almost half of the subjects achieved symptom remission though, and about a quarter had adequate social functioning for 2 years or more.

They also reported that better cognitive better cognitive functioning at stabilization was more likely to lead to full recovery, both adequate social or vocational functioning

and symptom remission. More cerebral asymmetry was also associated with full recovery and, adequate social and vocational functioning.

(b) Quality of Life

In a study that involved 50 first episode schizophrenic patients, who were mostly neuroleptic-naïve at study intake, found that negative symptom severity was positively and significantly correlated with later occupational impairment, financial dependence on others, impaired relationships with friends, impaired ability to enjoy recreational activities, and global assessment of functioning, i.e. negative symptoms moderately predicted poorer quality of life early in the course of schizophrenia (Ho et al.,1998).

Knowing that negative symptoms were a portent or poor quality of life may influence the clinician to go for atypical neuroleptic treatment (Singam et al.,2011; Buchanan et al.,2012) and stress the need for more intensive psychosocial interventions for patients with prominent initial negative symptoms (McGlashan et al.,1990).

Severe negative symptoms at the time of hospitalization might be a portent of poor outcome. In general, the psychotic and the disorganized symptom dimensions did not appear to predict subsequent quality of life (Schennach et al.,2011) .

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(c) Relapse

There was a high rate of relapse within 5 years of recovery from a first episode of schizophrenia and schizoaffective disorder. This risk was diminished by maintenance antipsychotic drug treatment as reported by Robinson et al(1999). Results showed that 5 years after initial recovery, the cumulative first relapse rate was 81.9%, and the second relapse rate was 78.0%. By 4 years after recovery from a second relapse, the cumulative third relapse rate was 86.2%.

Discontinuing antipsychotic drug therapy increased the risk of relapse by almost 5 times. Subsequent analyses controlling for antipsychotic drug use showed that patients with poor pre-morbid adaptation to school and pre-morbid social withdrawal relapsed earlier. Other factors, such as baseline symptoms, neuroendocrine measures, time to response of the initial episode, adverse effects during treatment, and presence of residual symptoms after the initial episode were not significantly related to time to relapse (Robinson et al.,1999).

(d) Treatment Response

In general, first-episode patients appeared to be more sensitive to the pharmacologic effects of antipsychotic drugs than older chronic patients in that they exhibited higher rates of recovery, more frequent extrapyramidal side effects, and required lower drug doses (Remington et al.,1998; Petersen et al.,2008). However, following their recovery first-episode patients experienced a high rate of psychotic relapse particularly if they discontinued antipsychotic medication (Gitlin et al.,2001; Ucok et al.,2006).

1.7.2 Social Burden

Impaired information processing was probably the most harmful symptom of schizophrenia, as it significantly affects patients' social functioning, leading to lower rates of employment, marriage and independent living compared to other healthy individuals (Shrivastava et al.,2011).

Schizophrenia might also cause patients to abuse substance. Alcohol and drug abuse were common in schizophrenia patients, particularly in younger men (Weiser et al.,2003; van Nimwegen et al.,2005; Jones et al.,2011). Substance abuse was associated with increased hostility and violence, and problems such as non-compliance with medication, poor nutrition and suicide (Smith and Hucker,1994; Foti et al.,2010).

Not all violence behaviour among schizophrenia patients was attributed to substance abuse though. Some patients who were schizophrenic might be violent due to hallucinations or delusions , or as a result of psychosis (Ho et al.,1998). In fact, Western studies reported that 5% to 10% of those charged with murder have a schizophrenia spectrum disorder (Mullen,2006; Fazel and Grann,2004; A. I. Simpson et al.,2004).

Schizophrenia was also related to other social problems, such as long-term unemployment, poverty and homelessness (Selten et al.,2007; Mueser and McGurk,2004).

1.7.3 Economical Burden

Schizophrenia is by far the most costly psychiatric illness because of the range of healthcare needs schizophrenia patients have. As with other major chronic diseases, schizophrenia places a great economic burden on the society (Martin,1995), in terms of :

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- Direct costs (e.g. in and outpatient care, residential care, drug therapy);

- Indirect cost (e.g. absence from work, lost productivity due to unemployment); and

- Intangible costs (e.g. suffering experienced by the patient and family).

The cost of lost productivity was especially large. In England, nearly 80% of schizophrenia patients remained unemployed. The estimated total societal cost which includes direct cost of treatment and care, and indirect costs to the society in 2004 and 2005 was 6.7 billion pounds (Mangalore and Knapp,2007).

Similarly, the indirect excess cost due to unemployment was the largest component of overall schizophrenia excess annual costs in US in 2002 (Wu et al.,2005).

1.7.4 Impact on Quality of Life

Schizophrenia was a debilitating long-term disorder that has a profound impact on patients' quality of life. The cognitive and emotional disturbances experienced in this psychiatric disorder tend to have a lasting effect on many areas of a patient's life functioning and subsequently on quality of life (Gee et al.,2003).

Several areas that affected in a schizophrenia patient's life was described by Gee (2003) include :

- Interpersonal relationships

  Patients felt isolated and were difficult to establish interpersonal relationship because of their mental health problems. They worried about what others thought of them. Friends and family might try to avoid a schizophrenia patient due to his or her psychiatric status.

- Control of behaviour and actions

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Schizophrenia patients usually avoid situations that they had previously enjoyed and choose to be isolated because of fear of they would lose control of their behaviour and actions.

- Opportunity to fulfil occupational roles

The illness of schizophrenia made them to work or fulfil occupational roles. This reduces their job choices, leaving them feeling useless, experiencing loss of respect and value in the job market, and thus loss of contact with others.

- Activities and plans

Schizophrenia patients experienced constraint in carrying out activities and plans, such as not being able to travel, go on holiday, live where they would choose, or plan anything too far ahead.

- Self-value

Low self-esteem, lowered morale, fear, feeling helpless and useless are some of the psychological responses of schizophrenia patients to their illness.

- Labelling and attitudes from others

The stigma attached to having schizophrenia or any other mental health problems result in the public to reject schizophrenia patients, causing a negative impact on their relationships, social life, work and image.

1.7.5 Mortality in Schizophrenia

Mortality rate was generally higher and life expectancy decreased among people with schizophrenia than the general population (Mortensen and Juel,1993; Harris and Barraclough,1997; Tenback et al.,2012). Taking into account of all premature deaths, people with schizophrenia usually live 9-12 years shorter than the general population (Goldman,1999; Babidge et al.,2001; Brown et al.,2000; Lawrence et al.,2000). For example, an Australian study showed that patients with schizophrenia were found to

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be 2.9 times more likely to die of natural causes than people in the general population (Ruschena et al.,1998).

Mortality was also increased because of coexisting medical illnesses, whether due to a combination of unhealthy lifestyles (e.g. lack in exercise, smoking, poor diet), side effects of medication, or decreased health care (Brown et al.,2000).

Other causes of mortality include cardiovascular disease (CVD), diabetes and its complications (e.g. kidney failure), respiratory disease (including pneumonia, influenza), and infectious disease (e.g. HIV/AIDS) (Parks et al.,2006). The rates of mortality from these diseases in schizophrenia patients were several times higher than observed in the general population (Osby et al.,2000) (Table 1.1).

Table 1.1: Prevalence of natural causes of death in schizophrenia are greater compared with general population

Cause of Death	Prevalence in Relative to General Population
Endocrine disorders (diabetes)	2.7 times
CVD	2.3 times
Respiratory disease	3.2 times
Infectious disease	3.4 times

Nevertheless, study also showed that, as a whole, a diagnosis of schizophrenia was associated with a better life expectancy than substance abuse, personality disorder, heart attack and stroke (Hannerz et al.,2001).

While 60% of premature deaths in schizophrenia patients were due to 'natural causes' (i.e. non-suicide related) (Brown and Mitchell,2011) , suicide was a well-known contributing factors to shorter life span in people with schizophrenia, accounting for about 30%-40% of excess mortality (Mortensen and Juel,1993; Erlangsen et al.,2012), A recent study showed that 30% of patients diagnosed with this condition had

attempted suicide at least once during their lifetime (Radomsky et al.,1999). Another study reported that 10% of individuals with schizophrenia die by suicide (Caldwell and Gottesman,1990).

1.7.6 Care and management barriers

There were many popular misconceptions surrounding schizophrenia, and the stigma associated with this mental disorder has been identified as a major obstacle in the treatment and recovery of patients with schizophrenia (McGorry,1999). Individuals with schizophrenia were thought to be violent by the majority of the public (Link et al.,1999). They were also believed not able to make decisions regarding their treatment and on money management (Pescosolido et al.,1999).

1.8 Prognosis

While full recovery was only attained in about one third of patients, numerous international studies have demonstrated favourable long-term outcomes for schizophrenia, even though full recovery was not achieved (Robinson et al.,2004; Harding et al.,1987). For example, a 5-year community study found that as many as 62% of people with schizophrenia showed overall improvement on a composite measure of symptomatic, clinical and functional outcomes (Harvey et al.,2007).

Multiple factors appear to influence the outcome of this disease. Symptoms during the acute illness early in the presentation of schizophrenia have some prognostic value.

Factors that predict good outcome highlighted by some studies (Davidson and McGlashan,1997; Lieberman et al.,1996) include:

- Gender

Prognosis was usually better in female patients, as they responded better to antipsychotic medications than the male patients (Canuso and Pandina,2007).

- Type of symptoms

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If schizophrenia was treated quickly and consistently with good response to treatment, the prognosis was usually very good (Cohen et al.,2008). However, this was true mainly for positive symptoms that responded fairly well to antipsychotic medication. Presence of mood symptoms and good pre-morbid functioning also help to improve disease outcome (Amminger et al.,1997).

- Onset of illness

Chances for recovery were better for acute onset compared with insidious onset of the disease (Freudenreich et al.,2007). Prognosis was also better if the first episode occurs at older age (Rajji et al.,2009).

- Family history of schizophrenia

Family history of schizophrenia was relevant (Licanin and Redzic,2010). Prognosis was better if no one in the immediate biological family of first degree relatives has schizophrenia or a related condition.

- Structural brain abnormalities

The presence of abnormal brain structure and function as indicated by a brain scan usually predicts a poor prognosis (O'Brien et al.,1996).

On the other hand, predictors of poor outcome were (Ho et al.,1998):

- Poor pre-morbid adjustment
- Longer interval from the onset to treatment
- Absence of any clear precipitating events
- Presence of negative symptoms.

1.9 Medical Co-morbidity of Schizophrenia

Schizophrenia has been described as a 'life-shortening disease' (Allebeck,1989; Goldman,1999; Babidge et al.,2001), because it was associated with excessive medical

morbidity and mortality (Druss et al.,2011). The high mortality and morbidity may generally be attributed to an environment, in which unhealthy and high-risk behaviours such as smoking, substance abuse, lack of exercise and poor diet are prevalent in a schizophrenia patient's lifestyle (Brown et al.,1999).

People diagnosed with schizophrenia were also likely to be diagnosed with co-morbid medical conditions, including clinical depression and anxiety disorders (Sim et al.,2006; Lysaker et al.,2010), metabolic disturbances (Huang et al.,2009) and cardiovascular disease (Lahti et al.,2012).

1.9.1 Prevalence of Medical Co-Morbidity in Schizophrenia

In a study by Carney et al (2006), where they examined chronic medical co-morbidity in people with schizophrenia, it was found that subjects with schizophrenia were significantly more likely to have one or more chronic conditions compared with those who had not reported of any psychiatric disorder. Adjusted odds ratio (95% CI) reported for some of the chronic conditions were:

- OR: 2.62 (95% CI: 2.09 to 3.28) for hypothyroidism
- OR:1.88 (95% CI: 1.51 to 2.32) for chronic obstructive pulmonary disease
- OR:2.11 (95% CI: 1.36 to 3.28) for diabetes with complications
- OR:7.54 (95% CI: 3.55 to 15.99) for hepatitis C
- OR:4.21 (95% CI: 3.25 to 5.44) for fluid/electrolyte disorders
- OR: 2.77 (95% CI: 2.23 to 3.44) for nicotine abuse/dependence.

Other health conditions known to be particularly problematic for schizophrenia patients also include high blood pressure, obesity and high cholesterol levels (De Hert et al.,2009).

1.9.2 Risk factors of medical co-morbidity

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Common chronic medical co-morbidity found in patients with schizophrenia was usually related to their psychiatric conditions, psychotropic medications used and lifestyle habits.

People with schizophrenia and other mental illnesses have a higher rate of lifestyle risk factors such as smoking, high alcohol consumption, poor diet and lack of exercise (Brown et al.,1999; Vancampfort et al.,2011). These unhealthy lifestyle factors increased the cardiovascular risk significantly in people with mental illness compared with the general population (Davidson,2002).

The study showed that there were more smokers or ex-smokers (70% vs. 50%) in individuals with mental illness, who also used harmful levels of alcohol more frequently than the general population (11.5% vs. 3.1%, respectively). There was also a notably high percentage of people with schizophrenia who were obese compared with the general population (40% vs. 8%) (Davidson,2002).

In terms of diet, the cognitive and social deficit symptoms of schizophrenia might predispose patients to choose unhealthy diet (e.g. easily obtainable 'fast' foods) as their major source of nutrition (Gupta and Craig,2009). Schizophrenia patients were also less motivated to keep physically active to counter the health effects of their poor diet and to maintain general fitness (Lambert et al.,2003; McCreadie,2003).

Together, these lifestyle factors increased the risk or severity of medical conditions, particularly the development of metabolic syndrome (Kilbourne et al.,2007; Meyer and Stahl,2009) and subsequently CVD (Bobes et al.,2007; Lahti et al.,2012).

1.9.3 Metabolic disturbances

People with schizophrenia were more prone to developing metabolic disturbances (Subashini et al.,2011), as metabolic risk factors tend to be more prevalent among

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patients with mental illness than in the general population. They were at increased risk of developing glucose-regulation abnormalities, insulin resistance and type 2 diabetes mellitus (Timonen et al.,2009; Dasgupta et al.,2010).

While lifestyle factors (e.g. poor diet, sedentary behaviour, smoking) evidently play a contributing role here (Vancampfort et al.,2011), treatment with psychotropic medications, including some of the second generation antipsychotic agents, were also responsible for adverse effects on the body metabolic processes (Narasimhan and Bailey,2008; Meyer et al.,2008).

Disturbances in metabolic processes result in a cluster of metabolic dysfunction, such as insulin resistance, dyslipidaemia, impaired glucose tolerance, which is known as the metabolic syndrome thereby putting patients at risk of CVD (Cho,2011).

This has been demonstrated in the Clinical Trials of Antipsychotic Intervention Effectiveness (CATIE) study involving 1,424 patients with schizophrenia. Their baseline data revealed that 20% of the patients had hypertension, 14% hyperlipidaemia, and 11% diabetes (Chwastiak et al.,2006).

While increased risk of diabetes has been attributed to lifestyle determinants and antipsychotic drugs, the association between schizophrenia and diabetes has been well aware even before lifestyle factors and pharmacological interventions were introduced (Gough and O'Donovan,2005). In fact, schizophrenia has been considered as a predisposing factor to diabetes, which was believed to be an integral part of the mental illness (Kohen,2004). A recent study showed that despite cessation of antipsychotic treatment, insulin resistance may persist (Arranz et al.,2004).

The observations suggested a possibility of a shared genetic basis between schizophrenia and diabetes, as both were common diseases with a complex mode of

inheritance and were influenced by genetic factors and environmental determinants (Gough and O'Donovan,2005).

1.9.4 Cardiovascular risk

CVD was dominated as the number one cause of death in patients with schizophrenia and in fact, in severe mental illness (Osby et al.,2000). Greater mortality rate due to ischaemic heart disease, cardiac arrhythmias and myocardial infarction has been reported in people with mental illness (Lawrence et al.,2010).

In the CATIE study, it was found that the 10-year risk for coronary heart disease was significantly raised in male (9.4% vs 7.0%) and female (6.3% vs 4.2%) patients with schizophrenia compared with the general population (*P*=.0001) (Goff et al.,2005).

The elevated CV risk in this psychiatric population was not unexpected. The high prevalence of lifestyle risk factors and metabolic syndrome in schizophrenia placed the patients at increased risk for CVD. In the CATIE study, there were 40.9% and 42.7% respectively of patients diagnosed for metabolic syndrome at baseline using the National Cholesterol Education Program (NCEP) and the American Heart Association (AHA) criteria (McEvoy et al.,2005).

Again, the use of antipsychotic medication may also partly heighten the CV risk. In the CATIE study (Daumit et al.,2008), it was found that the 10-year risk for coronary heart disease was significantly raised with olanzapine (0.5%, SE 0.3) and quetipine (0.3%, SE 0.3).

1.9.5 Other medical co-morbidity

i) Infectious disease (e.g. HIV/AIDS, hepatitis)

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Incidence of HIV/AIDS in people with schizophrenia (estimated to be 4%-23%) appeared to be higher than in the general population (Davidson et al.,2001b; Cournos and McKinnon,1997). Risk factors include unsafe sex and substance abuse. About half of schizophrenia patients tend to have co-occurring substance abuse disorder (Regier et al.,1990), they were 2-3 times more likely to become infected with HIV and hepatitis than schizophrenia patients without substance disorder.

When compared to the general population, the prevalence of HIV infection in individuals with severe mental illness including schizophrenia was reported to be about 8 times higher (29.1%) (Singh et al.,2009), while the prevalence rates of hepatitis B virus (23.4%) and hepatitis C virus (19.6%) were approximately 5 and 11 times the overall estimated population rates for these infections, respectively (Rosenberg et al.,2001).

ii) Osteoporosis

The accelerated rates of osteoporosis in schizophrenia could be attributed to several risk factors, including antipsychotic-driven decrease in oestrogen and testosterone, reduced calcium due to smoking and alcoholism, as well as polydipsia (Abraham et al.,2003; Howard et al.,2007).

iii) Hyperprolactinaemia

High doses of typical antipsychotics and the atypical antipsychotics (e.g. risperidone and amisulpride) raised prolactin levels, causing galactorrhoea, amenorrhoea, oligomenorrhoea, sexual dysfunction and contributing to CVD (Canuso et al.,2002; Rettenbacher et al.,2010).

1.9.6 Barriers to detection and treatment of schizophrenia co-morbidity

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While the excessive medical morbidity and mortality of schizophrenia were largely due to treatable medical conditions, the detection rate of the physical illness among people with schizophrenia and mental illness in general was very poor (Reeves et al.,2010).

The recognition and management of the medical co-morbidity were made more difficult by barriers related to patients themselves as well as the medical providers. Medical provider-related factors include (Goldman,1999; Jeste et al.,1996; Wright,1996; Carney et al.,2006):

- Physical complaints regarded by psychiatrists as psychosomatic symptoms.

- Reticence of non-psychiatrists to treat people with serious mental illness.

- Perception of specialist psychiatrists that physical health should be under the care of referring doctors.

- Changes of treating doctor, resulting in patients not having a longitudinal history available.

- Specialist's attention focused principally on patient's psychiatric problems, with physical examination conducted infrequently.

- Time and resources for medical examinations not available in current mental healthcare service settings.

Patient-related factors include (Goldman,1999; Jeste et al.,1996; Anath,1984):

- Poor general treatment compliance.

- Avoidance or neglect of contact with general practitioners or general healthcare services.

- Unawareness of physical problems because of cognitive deficits associated with mental illness.

- Patients' difficulty in communicating their physical needs and problems in general.

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- Reduction in pain sensitivity associated with use of antipsychotic drugs.

- Reluctance of patients to discuss problems.

It was therefore, imperative to improve the detection and treatment of co-occurring medical illness, as it will lead to significant benefits in the psychosocial functioning and overall quality of life in patients with schizophrenia.

1.10   Psychiatric Co-morbidity

Psychiatric co-morbidity was common in schizophrenia, contributing to further impairment. Researchers have documented frequent occurrence of depression (Geerts and Brune,2009; Felmet et al.,2011), panic disorder (Ulas et al.,2007; Ulas et al.,2010) and anxiety disorder (Braga et al.,2004; Achim et al.,2011), among patients who have a diagnosis of schizophrenia.

It has been reported as many as 25% of patients with schizophrenia exhibit significant symptoms of depression (Kilzieh et al.,2004), which was associated with greater overall symptom severity and a poorer quality of life (Kennedy et al.,2004). Co-morbid depression might also increase suicide risk (Montross et al.,2008), and has been associated with higher rates of relapse and rehospitalisation (Herz and Melville,1980; Johnson,1988), hopelessness (Drake and Cotton,1986), and poor psychosocial skills (Glazer et al.,1981; Kollias et al.,2008).

In a study by Ulas et al (2007), the prevalence of panic attack and panic disorder in patients with schizophrenia was rather significant. Those patients presented with panic symptoms were found to have higher scores of Positive and Negative Syndrome Scale (PANSS), Hamilton Depression Rating Scale (HDRS), Clinical Global Impression (CGI), and Extrapyramidal Symptoms Rating Scale (ESRS). These co-morbid panic

symptoms in schizophrenia were suggested to be related to positive symptoms, extrapyramidal side effects and depression.

Co-morbid psychiatric illness was also common in childhood-onset schizophrenia (Remschmidt and Theisen,2005). Study by Ross and colleague (Ross et al.,2006) reported that 99% of children and young adolescents with schizophrenia or schizoaffective disorder had at least one co-morbid psychiatric illness, with the most common co-morbid conditions being attention deficit hyperactivity disorder (84%), oppositional defiant disorder (43%), depression (36%), and separation anxiety disorder (25%).

1.11 Therapy for Schizophrenia: Pharmacological and Non-pharmacological Approaches

Pharmacological treatment: Antipsychotics

Drug therapy has been the main modality for managing schizophrenia, and antipsychotics are the mainstay of drug treatment for this psychiatric illness. The development of new antipsychotics and evaluation of their safety and efficacy is an important ongoing field of research (Tandon,2011).

1.11.1 History of antipsychotics

The first generation of antipsychotics, known as typical antipsychotics, was discovered in the 1950s. Chlorpromazine, originally developed as a surgical anaesthetic, was the first modern antipsychotic drug introduced into psychiatry in 1952 (Janicak et al.,2011). It was first used on psychiatric patients owing to its potent calming effect.

This was followed by the introduction of other antipsychotics, such as haloperidol and thioridazine, which were also referred as neuroleptic drugs. Due to their neurological side effects, particularly extrapyramidal side effects (EPS) and tardive dyskinesia

(Miyamoto et al.,2005), second generation antipsychotics or atypical antipsychotics were developed (Melnik et al.,2010).

The first atypical antipsychotic drug, clozapine was introduced into clinical practice in the 1970s. This was followed by the introduction of other atypical drugs, such as olanzapine, risperidone and quetiapine during the 1990s (Shen,1999), and ziprasidone and aripiprazole in the early 2000s. The newer atypical antipsychotic, asenapine was approved by the FDA in late 2009.

1.11.2 Classification: Typical and Atypical

Antipsychotics can be broadly divided into two groups, the typical or first generation antipsychotics and the atypical or second generation antipsychotics.

1.11.2.1   Typical antipsychotics (First generation)

Typical antipsychotics (Table 1.2) were available in different formulations, such as acute intramuscular injections, liquid form, tablets and in depot formulations. Depot injections were useful for the treatment of non-compliant or partially compliant patients (Furiak et al.,2011).

Table 1.2: Commonly used typical antipsychotics (First generation)

Chemical group	Type
Butyrophenones	Haloperidol, bromperidol, trifluperidol, etc.
Phenotiazines	Chlorpromazine, fluphenazine, perphenazine, prochlorperazine, thioridazine, trifluoperazine, promazine, promethazine, etc.
Thioxanthenes	Chlorprothixene, flupenthixol, thiothixene, zuclopenthizol
Diphenylbutylpiperidines	Fluspirilene, penfluridol, pimozide

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Typical antipsychotics effectively treat positive symptoms, but their efficacy in treating negative symptoms was limited. It has been reported that 30%-50% of patients with positive symptoms of schizophrenia were either not responsive or only partially responsive to typical antipsychotics (Kane and Correll,2010). Negative symptoms and neurocognitive deficits also tend to respond poorly to typical antipsychotics, and might even be exacerbated by them (Tandon,2011). In fact, first generation antipsychotics have been reported to cause negative symptoms, such as anhedonia. These conventional antipsychotics have little effect on the depression and suicidal behaviour in schizophrenia, leaving to a commit suicidal rate as low as 10% (Bitter,2006).

Nevertheless, the typical antipsychotics had a significant impact on the life of schizophrenia patients. Studies showed that about 20% of patients treated with typical medications had full remission, and only 30%-40% of patients relapsed during treatment, as compared with 80% among those without treatment (Bitter,2006).

1.11.2.2 Atypical antipsychotics (Second generation)

The atypical antipsychotics (Table 1.3) worked slightly differently from typical antipsychotics. This newer generation of drugs differ from each other in terms of receptor binding, efficacy and side-effect profile.

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Table 1.3: Commonly used atypical antipsychotics (Second generation)

Chemical group	Type
Diazepines/oxazepines/thiazepines	Clozapine, olanzapine, quetiapine, asenapine
Benzisoxazoles	Risperidone, ziprasidone, paliperidone
Indoles	Sertindole
Benzamides	Sulpride, remoxipride, amisulpride
Quinolinone	Aripiprazole

Atypical antipsychotics were in general more efficacious than typical antipsychotics, especially with regard to the improvement in negative, depressive and cognitive symptoms of schizophrenia (Bitter,2006). In addition, the second generation drugs decreased relapse rates and the need for hospitalisation, and were more efficacious in reducing violent behaviour than the first generation drugs (Kane and Correll,2010). The defining characteristic of atypical antipsychotics was probably the decreased tendency of these agents to cause EPS (Farah,2005) and an absence of sustained prolactin elevation (Seeman,2002).

The above mentioned reasons explained why the atypical antipsychotics were now considered to be the first-line treatment for schizophrenia, and were gradually replacing the typical antipsychotics. Table 1.4 delineated the advantages of the atypical antipsychotics compared with the typical medications.

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Table 1.4: Advantages of atypical antipsychotics (Second generation) compared with typical antipsychotics (First generation)

- Improved therapeutic effect in some treatment-resistant patients.
- Improved therapeutic effect on negative symptoms and neurocognitive deficits.
- Reduced potential to cause acute EPS (e.g. akathisia, dystonia, parkinsonism).
- Reduced potential to cause longer-term EPS (e.g. tardive dystonia, tardive dyskinesia, tardive akathisia).
- Reduced potential to elevate prolactin levels (with the exception of risperidone and amisulpride).

(Lambert and Castle,2003)

1.11.3 Mechanism of Action

Antipsychotics primarily block post-synaptic dopamine D_2 receptors in the dopamine pathways. They might also variably have activity at other receptors (e.g. serotonergic, muscarinic, alpha-adrenergic, histaminergic) to play an important role in both their beneficial and adverse effects (Tandon,2011).

Excess release of dopamine in the mesolimbic pathway has been linked to psychotic experiences (Davis et al.,1991). Blocking activity at D_2 receptors in the mesolimbic pathways was thought to underlie the therapeutic effects of antipsychotics on positive symptoms (Lambert and Castle,2003). At the same time, antipsychotic drugs acting on D_2 receptors in the basal ganglia and hypothalamus typically cause EPS and neurohormonal changes (Castle et al.,2008).

Typical antipsychotics were not particularly selective, they also blocked dopamine receptors in the mesocortical pathway, tuberoinfundibular pathway and the nigrostriatal pathway. Blocking D_2 receptors in these other pathways was thought to produce some of the unwanted side effects associated with typical antipsychotics.

Atypical antipsychotics drugs also blocked dopamine receptors, but were more loosely bound to the receptors, and also blocked or partially blocked serotonin receptors and

other neurotransmitter receptors (Bitter,2006). For example, risperidone acted vigorously on serotonin receptors, while amisulpride did not have serotonergic activity (Mortimer,2003). On the other hand, aripiprazole was a mixed dopamine agonist and antagonist (i.e. partial antagonist), as well as displaying some serotonin 5-HT$_{1A}$ partial agonism and 5-HT$_{2A}$ antagonism. The additional effects of atypical antipsychotics on serotonin receptors might explain the benefits of the newer generation drugs on the 'negative symptoms' of schizophrenia (Keck and McElroy,2003).

While there were significant pharmacodynamic differences within the atypical antipsychotics, this class of medications could generally be said to have an increased affinity for serotonergic receptors (except amisulpride) over dopaminergic receptors compared to typical antipsychotics (Mortimer,2003). In addition, the blockade of dopaminergic receptors was more pronounced in the limbic system than in the basal ganglia. As a result, the atypical antipsychotics have significantly less EPS (Olin,2001).

In a study that examined both older and newer antipsychotics, it was found that the older traditional antipsychotics, such as chlorpromazine, haloperidol, fluphenazine and flupenthixol, bind more tightly than dopamine itself to the dopamine D$_2$ receptor, with dissociation constant that were lower than that of dopamine (Seeman,2004).

On the other hand, the atypical antipsychotics, including quetiapine, clozapine, olanzapine and ziprasidone, were noted to bind more loosely than dopamine to the dopamine D$_2$ receptor and have higher dissociation constants than dopamine. By transiently occupying D$_2$ receptors and then rapidly dissociating from them, atypicals allowed normal dopamine neurotransmission that keep prolactin levels normal, spare cognition and prevent EPS (Seeman,2004).

1.11.4 Side effects

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Antipsychotics were generally associated with a range of side effects. A significant number of patients in controlled drug trials discontinued antipsychotics partly due to adverse effects.

1.11.4.1 Typical antipsychotics

Many of the typical antipsychotics, such as flupenthixol, haloperidol, perphenazine, trifluoroperazine and thiothixene were much more potent at blocking dopamine receptors than chlorpromazine. Their increased potency however, was not related to increased efficacy, but to greater incidence and prevalence of EPS (Table 1.5) caused mainly by dopamine blockade of the basal ganglia (Bitter,2006).

Table 1.5: Extrapyramidal reactions caused by typical antipsychotics

- Tardive psychosis
- Acute dystonias
- Akathisia
- Parkinsonism (rigidity and tremor)
- Tardive dyskinesia

Other common side effects of the first generation drugs include neurological syndromes hyperprolactinaemia, anhedonia, sedation, disturbances of thermoregulation, cognitive impairment, cardiac arrhythmias, weight gain, diabetes and antimuscarinic effects (e.g. dry mouth, constipation and urinary retention) (Keks,1996). For these and other reasons, typical antipsychotics were increasingly being replaced by the newer atypical antipsychotics.

1.11.4.2 Atypical antipyschotics

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The newer atypical antipsychotic drugs were usually preferred for initial treatment over the older typical antipsychotics, as they were often better tolerated and associated with fewer neurological adverse events.

Clozapine was the 'gold standard' of second generation antipsychotics. It has practically no EPS and was in fact, useful in the treatment of negative symptoms and depression in schizophrenia and in preventing suicidal behaviour in these patients (Kane and Correll,2010). However, the side effects of clozapine limit its use, especially the potentially life-threatening agranulocytosis. As such, clozapine could only be used in patients who comply with regular blood monitoring (Tandon,2011).

Atypical antipsychotics were also more likely to induce weight gain and obesity-related diseases. Diabetes, hypercholesterolaemia and the metabolic syndrome were the more frequent treatment-emergent events with second generation than with first generation antipsychotics (Bobes et al.,2007). Nevertheless, there were differences within the atypical antipsychotics. For instance, olanzapine appeared to cause decreased insulin sensitivity and weight gain more commonly than other atypical antipsychotics (McQuade et al.,2004; Lieberman et al.,2005). While amisulpride and ziprasidone caused less weight gain, they later increased the corrected QT interval on electrocardiogram (Isbister et al.,2006; Camm et al.,2012).

1.12   Non-pharmacological: Psychological Therapies

Successful treatment of schizophrenia not only depended on a life-long pharmacological treatment regimen, but also on relevant psychological therapies. While medication helped control symptoms associated with schizophrenia (e.g. delusions and hallucinations), it could not help the person find a job, learn to be effective in social relationships, increase the individual's coping skills, help them learn to communicate and work well with others.

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Educational and psychotherapeutic approaches helped in the recognition of early signs and symptoms of relapse, and compliance with drug treatment. Recognising early signs and symptoms of schizophrenia helped to prevent a relapse, and in selected high-risk populations, it helped to start treatment as soon as the symptoms of schizophrenia were present (Roder et al.,2011). There are four major and distinct psychological treatment approach identified as supplement to pharmacological treatment.

1.12.1 Social Skills Training

Social skills training was widely recommended and used in the treatment of schizophrenia. It commonly used training modules for Social and Independent Living Skills developed by Liberman el al (2002; 2007).

By practicing specific disorder-related social and instrumental skills such as basic conversation, medication management and community re-entry, individuals with schizophrenia might gradually overcome poor social competence and finally improved community integration (Bellack,2004). Recent study indicated that social skills training led to stable improvement in social functioning and decreased the hospitalisation due to relapse at follow-up (Pfammatter et al.,2006).

1.12.2 Cognitive Remediation

Majority of schizophrenia patients demonstrated poor performance of cognitive processing. The affected domains were processing speed, verbal learning, sustained attention, working memory, executive functioning and social cognition. Cognitive impairments were now recognized as important therapeutic target for schizophrenia patients (Wykes and van der Gaag,2001; Medalia and Lim,2004).

The goal of cognitive remediation was to help the patients using information from their surroundings to make adaptive coping decision. The treatment goal was not to

'cure' schizophrenia, but to improve the patient's ability to manage life problems, to function independently, and to be free of extreme distress and other psychological problems (Vita et al.,2011). Cognitive remediation was an intervention focusing on improvement of cognitive functioning by:

(i) Applying repeated practice of cognitive tasks in a computerized or paper and pencil version.

(ii) Training of strategies for compensating cognitive impairments, either in the form of organizing information, e.g. categorization or adaptive strategies, which involved other aids in the environment of the schizophrenia patients e.g. posting reminders.

One meta-analysis study findings supported the training of cognitive remediation has effects on attention, executive functioning, memory and social cognition (Pfammatter et al.,2006).

1.12.3 Cognitive-behavioural therapy (CBT) of positive symptoms

About one fourth to up to one half of all schizophrenia patients suffered from persisting both delusions and hallucinations or either one despite compliance (Bora et al.,2008).

Cognitive behaviour therapy (CBT) evolved from behavioural theory and developed to focus more on cognitive models that based on the assumption of irrational beliefs, misinterpretations or thinking errors, reality distortion which presented as visual and auditory hallucinations (Hemsley,2005). These misjudgements might hamper the discrimination between external stimuli and internal intentions (Sprong et al.,2007). It was interesting to observe psychotic experiences could be induced in healthy subjects under certain conditions e.g. sleep deprivation, severe stress or through hypnosis (Frith,2004).

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CBT for psychosis incorporated cognitive restructuring with an analysis of the quality of psychotic symptoms, their triggering events and their maintaining conditions. It would also teach patients to enhance the coping strategies in verbal challenge, empirical reality testing or reappraisal (Marcinko and Read,2004).

A meta-analysis study of 17 randomized controlled trials showed CBT led to significant decline of persistent positive symptoms especially the reduction in the severity of hallucinations (Pfammatter et al.,2006).

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1.12.4 Psychoeducational coping-oriented interventions with families and relatives' groups

Psychoeducational coping-oriented interventions with families have become a strongly supported evidence-based practice in the treatment of schizophrenia for many years (McFarlane et al.,2003; Murray-Swank and Dixon,2004). Expressed emotion (EE) was a measure of the family environment which referred to the attitudes of the family members toward the patient. The measurement reflected the quality of interaction patterns and nature of family relationships among the family caregivers and patients of schizophrenia. Patients from high EE homes have a poorer illness prognosis than the patients from low EE homes (Amaresha and Venkatasubramanian,2012; Wasserman et al.,2012).

Psychoeducational in families of patients with schizophrenia can reduced the relapse rates of these patients (Pitschel-Walz et al.,2001; Pfammatter et al.,2006), positively influenced the course of the patient's illness (Corrigan et al.,1990; Ramirez Garcia et al.,2006), and help the families and patients to better cope with the mental illness (Sherman,2003; Chien,2008).

1.12.5 Integrated psychological therapy (IPT)

Integrated psychological therapy (IPT) was a group based cognitive behaviour therapy for schizophrenia patients with the goal of improved social competence. The therapy combined neurocognitive and social cognitive interventions with social skills and problem-solving approaches (Roder et al.,2011). Studies have shown the effectiveness of IPT including as part of standard medical therapy for patients (Pfammatter et al.,2006; Briand et al.,2006).

IPT was divided into 5 subprograms. The first subprogram targeted on basic impairments in neurocognition such as attention, verbal memory, cognitive flexibility

and concept formation. The second subprogram addressed deficits in social cognition e.g. social and emotional perception, emotional expression. The third subprogram focused on neurocognitive skills that directly impact on interpersonal communication, such as verbal fluency and executive functioning. The fourth and five subprograms emphasized on building patients' social competence through practice of interpersonal skills and group based problem-solving exercises (Roder et al.,2011).

1.13   Treatment Guidelines and Recommendations

In general, internationally accepted treatment guidelines such as from American Psychiatric Association (APA,1997) and National Institute for Clinical Excellence (NICE,2010) recommended oral atypical antipsychotics as first-line medications for patients with newly diagnosed schizophrenia or in the acute phase of schizophrenia, mainly because of the decreased risk of EPS and tardive dyskinesia.

The recommended dose was aim for both effective and least cause to side effects which might difficult to tolerate. The experience of unpleasant side effects might affect long-term adherence. Treatment guidelines recommended different lengths of treatment after the first episode of schizophrenia and after repeated episodes. The usual recommendation was at least 1 year of continuous treatment after the first episode, at least 5 years after the second episode, and long-term maintenance treatment after the third episode (NICE,2010).

For those who have experienced repeated psychotic episodes, long-term (even life-long) treatment was necessary, at the lowest effective therapeutic dose (Kane et al.,2011). It was crucial not to prematurely lower treatment dose or discontinue medication during the stabilization phase, as this might lead to a recurrence of symptoms and possible relapse (APA,1997). For most patients with schizophrenia in the stable phase, psychosocial interventions were recommended as a useful adjunctive

treatment to pharmacological treatment to help improve outcomes (Pfammatter et al.,2006).

1.14 Rationale and Objectives of this study

My study will focus on few important issues related to schizophrenia patients with metabolic syndrome including:

1. Prevalence of Metabolic Syndrome in Schizophrenia Patients Receiving Antipsychotics in Malaysia. (Please refer to Chapter 2)

2. Randomized Controlled Trial of the Safety and Efficacy of Aripiprazole Vs Ziprazidone in Schizophrenic Patients with Metabolic Syndrome. (Please refer to Chapter 3)
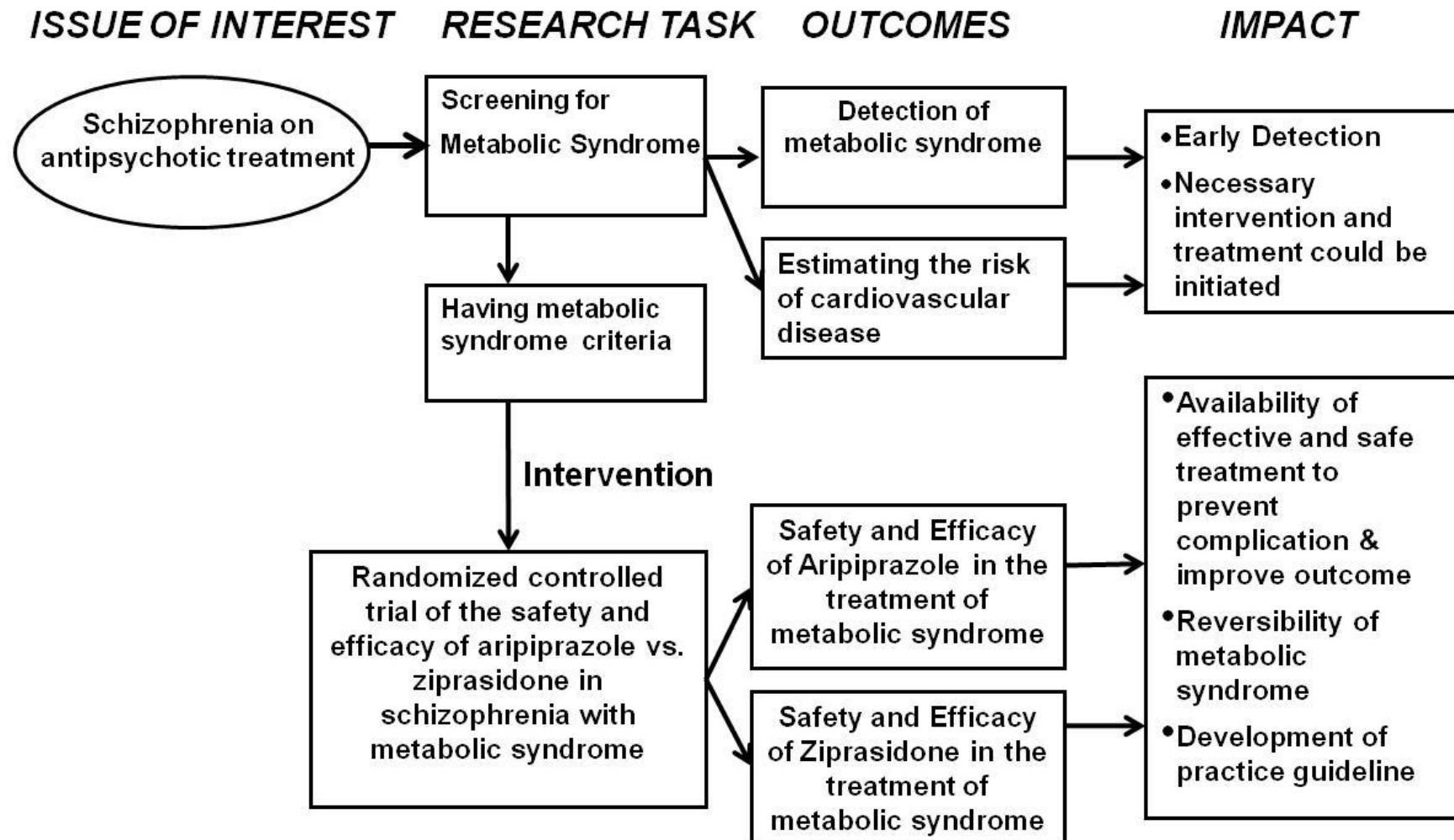
**Chapter TWO: Prevalence of Metabolic Syndrome in Schizophrenia Patients
Receiving Antipsychotics in Malaysia**

2.1   Abstract

Introduction: Metabolic syndrome comprises a spectrum of medical disorders that increase the risk of developing type-2 diabetes and cardiovascular disease. It has been shown that the association of metabolic syndrome with psychiatric disorders particularly schizophrenia, was related associated with antipsychotic used. Atypical antipsychotics were reported to be associated with increased risk of hyperglycaemia and impaired glucose level, and subsequently increase the risk of the metabolic syndrome.

Objectives: To determine the prevalence of metabolic syndrome and prevalence of coronary heart disease risk among schizophrenia patients receiving antipsychotics in Malaysia.

Methodology:

Design :   This was a cross sectional study.

Setting: The study was conducted at four mental institutions, two army hospitals and two general hospitals namely Hospital Bahagia Ulu Kinta, Perak, Hospital Permai Johor Bahru, Johor, Hospital Sentosa Kuching, Sarawak, Hospital Mesra Kota Kinabalu, Sabah, Hospital Terendak Melaka, Navy Hospital Lumut, Perak, University Malaya Medical Centre (UMMC), Kuala Lumpur and Hospital Sg. Petani, Kedah.

Patients: Study population were schizophrenia patients aged between 18 and 65 years old, who met the DSM-IV TR criteria for schizophrenia. Patients should receive antipsychotic treatment

for at least 1 year and were not on mood stabilizer or depot neuroleptics.

Measures: Metabolic syndrome was defined by using the NCEP ATP III criteria-modified for Asian waist circumference. The cardiovascular heart disease risk was assessed by using Framingham function (10-year all coronary heart disease event). A structured questionnaire to assess: (i) sociodemographic and lifestyle background (ii) medical, psychiatry and family history (iii) physical examination and blood investigation for metabolic syndrome profile.

Results: A total of 270 patients were screened for metabolic syndrome. The prevalence of metabolic syndrome was 46.7%. The mean BMI value was 29.4 ± 5.1 kg/m^2 for patients with metabolic syndrome and 25.0 ± 5.6 kg/m^2 for patient, without metabolic syndrome ($p<0.05$). The usage of commonest monotherapy atypical antipsychotics was olanzapine (42.2%) and chlorpromazine for typical antipsychotics (33.3%) in the metabolic syndrome group. The prevalence of diabetes mellitus after initiation of antipsychotics was 15.2%. There was statistically significant for all metabolic syndrome components between metabolic syndrome and non-metabolic syndrome groups i.e. Waist circumference (OR=34.8, 95% CI: 12.2, 99.4), HDL Cholesterol (OR=5.4, 95% CI: 3.2, 9.2), Triglycerides (OR= 8.6, 95% CI: 4.9, 15.2), BP (OR=5.5, 95% CI: 3.2, 9.3), FBS (OR= 11.4, 95% CI: 5.5, 23.6). Coronary heart disease 10-year risk was significantly higher in the metabolic syndrome patients. The prevalence of patients with high/very high cardiovascular event risk (Framingham $\geq$ 10%) was 31.5% in the metabolic syndrome patients vs. 11.0% in the non-metabolic syndrome patients (OR = 3.7, 95% CI: 1.9, 7.1, $p<0.0001$).

2 Prevalence of Metabolic Syndrome

Conclusion: The prevalence of metabolic syndrome in schizophrenia patients receiving antipsychotic in Malaysia was very high. It was associated with increased cardiovascular risk. Intervention measures are urgently needed to combat these problems.

Keywords: prevalence, metabolic syndrome, schizophrenia, cardiovascular risk, body mass index.

2.2 Introduction

Metabolic Syndrome

The metabolic syndrome comprises a spectrum of medical disorders that increase the risk of developing type 2 diabetes (T2D) and cardiovascular disease (CVD). The metabolic syndrome is also commonly known as 'syndrome X' and 'insulin resistance syndrome' (Cho,2011).

2.2.1 History

The term 'metabolic syndrome' was introduced in the late 1950s. However it only became more commonly used in the late 1970s to explain the various risk factors associated with diabetes that had been described as early as the 1920s (Joslin,1921; Kylin,1923). In 1977, the term was used by Haller to describe the additive effects of a cluster of risk factors on atherosclerosis (Haller,1977). The risk factors were obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia and hepatic steatosis. The term was also used by Singer (1977) to describe the associations of obesity, gout, diabetes mellitus and hypertension with hyperlipoproteinemia.

In 1977 and 1978, Gerald B. Phillips developed the concept that risk factors for myocardial infarction overlap to form a "constellation of abnormalities" (i.e. glucose intolerance, hyperinsulinemia and hypertension) that was associated not only with heart disease, but also with aging, obesity and other clinical states (Phillips,1977; Phillips,1978). A decade later, Gerald Reaven proposed insulin resistance as the underlying factor, and named the cluster of abnormalities Syndrome X. However, abdominal obesity was not included as part of the syndrome at that time (Reaven,1988).

2   Prevalence of Metabolic Syndrome

Today, the metabolic syndrome was used to define a group of metabolic abnormalities (i.e. diabetes or prediabetes, abdominal obesity, elevated lipid levels and blood pressure) associated with increased risks of T2D and CVD.

2.2.2 Prevalence

The metabolic syndrome affects a great number of people. It was estimated that around 20%-25% of the world's adult population have the metabolic syndrome (Alberti et al.,2006). In the recent National Health Survey in US, it was found that 34.3% adults suffering from the metabolic syndrome, which was about 71.8 million adults (Ford et al.,2010). While most European studies found the prevalence of the metabolic syndrome to be within the range of 12%-38% (Pannier et al.,2006; Bernal-Lopez et al.,2011; Mokáň et al.,2008; Fernández-Bergés et al.,2012; Szigethy et al.,2012).

Study by Lee et al (2008) reported the prevalence of the metabolic syndrome in four Asia-Pacific populations using different definitions from the World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR), National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), and International Diabetes Federation (IDF). It was found that Japanese had the lowest metabolic syndrome rates (3%-11%), followed by Korea (7%-29%), Australia (16%-42%) and Samoa (17%-60%).

Asians have a lower prevalence of the metabolic syndrome (5%-17.8%) (Lao et al.,2012; Kim et al.,2012; DECODA,2007; Lee et al.,2004). In Koreans, the reported prevalence rates of the metabolic syndrome, using the Asia Pacific criteria for obesity, were 13.1% (13.2% male, 13.1% female) (Lee et al.,2004). In addition, the odds ratio of the metabolic syndrome in those aged over 70 years against those aged 20-29 years was 13.8 (95% CI 8.2-23.2), and in women vs. men 1.4 (95% CI 1.2-1.5). In Thailand,

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a prevalence of 15.2% was reported among Thai professional and office workers, and it was three times more common in men than in women (25.8% vs. 8.2%) (Lohsoonthorn et al.,2007).

However, Malaysia has a much higher prevalence of metabolic syndrome compared to other Asian countries. Based on the WHO, ATP III, IDF and Harmonized definitions, the overall crude prevalence of metabolic syndrome in Malaysia was 32.1%, 34.3%, 37.1% and 42.5%, respectively (Mohamud et al.,2011).

Despite the generally lower incidence of metabolic syndrome in Asians, it should be noted that current evidence has shown a heightened risk for diabetes mellitus among Asian populations (Craig et al.,2007; Gupta and Kumar,2008).

2.2.3   Impact of the metabolic syndrome

While the metabolic syndrome itself poses serious health complications, it also places individuals at an increased risk for other serious medical conditions, such as cardiovascular mortality (Simons et al.,2011; Kondo et al.,2011).

The clustering of various metabolic abnormalities occurring in the same individual confers a significant additional cardiovascular risk, over and above the sum of the risk associated with each abnormality (Shin et al.,2009; Protopsaltis et al.,2007). Studies showed that the more components of the metabolic syndrome that were evident, the higher was the cardiovascular mortality rate (Hu et al.,2004). For instance, the 4-year risk of incident myocardial infarction among men ages 40-65 in the Prospective Cardiovascular Munster (PROCAM) study was increased 2.5 times in the presence of either T2D or hypertension, 8 times in the presence of both factors, and 19 times in the presence of both factors plus an abnormal lipid profile (Assmann et al.,2002).

2 Prevalence of Metabolic Syndrome

In a 10-year follow-up study of PROCAM (Assmann et al.,2002), based on 325 acute coronary events among 5,389 men aged 35-65 years at recruitment into the study, a COX proportional hazards model was developed. Based on this model, eight independent risk predictors of coronary events were found. Among the risk variables, diabetes (HR=1.491, 95% CI: 1.095 -2.030), elevated systolic blood pressure (HR=1.010, 95% CI: 1.005 - 1.016), reduction in HDL-cholesterol level (HR=0.968, 95% CI: 0.957 - 0.980) and triglycerides (HR=1.373, 95% CI: 11.056 - 1.785) were components of the metabolic syndrome.

Individuals with the metabolic syndrome were twice as likely to die from and three times as likely to have a myocardial infarction or stroke compared with people without the syndrome. In addition, people with the syndrome had a five-fold greater risk of developing T2D (Stern et al.,2004). The cardiovascular complications of diabetes, which was also a leading cause of blindness, amputation and kidney failure, account for much of the social and financial burden of the disease (WHO,1994b).

When comparing type 2 diabetic (T2D) patients with and without the metabolic syndrome, those with the syndrome (about 19.2%%) have a much greater risk for CVD than those without (about 7.5%) (Alexander et al.,2003). It has been shown in the US Third National Health and Nutrition Examination Survey (NHANES III) that the age-adjusted prevalence of coronary heart disease (CHD) was highest in patients with both T2D and the metabolic syndrome (19.2%), followed by patients with the syndrome but not T2D (13.9%) (Alexander et al.,2003). Among the risk variables, diabetes (OR=1.55, 95% CI: 1.07 –2.25), elevated blood pressure (OR=1.87, 95% CI: 1.37 –2.56) and reduction in HDL-cholesterol level (OR=1.74, 95% CI: 1.18 - 2.58) were components of the metabolic syndrome.

In a follow-up by Isomaa and colleagues (2001), the risk of CHD and stroke was found to be tripled among subjects with the metabolic syndrome aged 35 to 70 years as compared with those who did not have the syndrome (p<0.001). Compared with subjects without the metabolic syndrome, total mortality (18.0 vs. 4.6%, p<0.001) and cardiovascular mortality (12.0 vs. 2.2%; p<0.001) were increased in subjects with the metabolic syndrome. Further analysis with a multiple regression analysis, Isomaa and colleagues reported metabolic syndrome (RR=1.81, 95% CI: 1.24 - 2.65) and microalbuminuria (RR=2.80, 95% CI: 1.62 - 4.83) as an indication of diabetic nephropathy were the strongest risk factor for cardiovascular death.

2.2.4   Risk factors and underlying factors

While the pathophysiology of the metabolic syndrome was extremely complex and remained to be fully elucidated, currently both insulin resistance and central obesity were considered to be the significant underlying causes of this syndrome (Anderson et al.,2001; Nesto,2003).

Insulin resistance

Insulin resistance occured when body cells become less sensitive and eventually resistant to insulin. It resulted from inherited and acquired influences, and has been linked to increased risk of CHD (Meshkani and Adeli,2009; Miranda et al.,2005).

Hereditary causes of insulin resistance include mutations of insulin receptors, glucose transporters and signalling proteins, although the common forms were largely unidentified. Acquired causes include physical inactivity, diet, medications, hyperglycaemia, increased free fatty acids and the aging process (Cho,2011). Insulin resistance played a major pathogenic role in the development of the metabolic syndrome, including: (Meshkani and Adeli,2009; Alberti et al.,2006)

- Hyperinsulinaemia

- T2D or glucose intolerance

- Central obesity

- Hypertension

- Dyslipidaemia, chiefly manifested as a triad of low high-density lipoprotein-cholesterol (HDL-C) together with increases in triglycerides and small, dense low-density lipoprotein (sLDL) particles

- Hypercoagulability characterized by an increased plasminogen activator inhibitor 1 (PAI-1) level

- A proinflammatory state, with increases in acute-phase reactants, such as C-reactive protein (CRP)

- A prothrombotic state, with increases in plasminogen activator inhibitor (PAI-1) and fibrinogen.

Central obesity

Obesity was associated with the metabolic syndrome, and was the most common cause of insulin resistance (Shand et al.,2009). Obesity contributed to hypertension, high serum cholesterol, low high-density lipoprotein-cholesterol and hyperglycaemia, and was independently associated with higher CVD risk (Kurukulasuriya et al.,2011; Zalesin et al.,2011).

The risk of serious health consequences in the form of T2D, CHD and a range of other conditions had been shown to rise with an increase in body mass index (BMI) (Flint et al.,2010; Chung et al.,2012). A BMI greater than 25 kg/m^2 increased the risk of metabolic syndrome (Lohsoonthorn et al.,2007). However, the waist circumference in people with central obesity was considered to be more indicative of the metabolic syndrome profile (Parikh et al.,2009).

2.2.5 Other risk factors

Besides insulin resistance and obesity, various factors, including age, gender, family history, lifestyle and medications, play important roles in the development of the metabolic syndrome. The effect of the risk factors however, might vary depending on ethnic group (Tan et al.,2011).

Age

The prevalence of metabolic syndrome increases with age, affecting less than 20% of people in their 20s and more than 50% of people in their 60s (Ford et al.,2010). However, it had been noted that the features of the metabolic syndrome were becoming evident in young children, where three or more components of the syndrome being present (Xu et al.,2012).

Gender

Metabolic syndrome was more evident in middle-aged men (Novak et al.,2011) but later women tend to assume increased cardiovascular risk after menopause (Pérez-López et al.,2009). A study in US reported prevalence of the metabolic syndrome was more common in African American women than in African American men and in Mexican American women than in Mexican American men. However the metabolic syndrome affects more White men than White women (Salsberry et al.,2007).

Genetic factors

People with a sibling or parent with diabetes or with a personal history of diabetes, were at greater risk of developing the metabolic syndrome (Magnusson et al.,2012; Efstathiou et al.,2012).

Ethnicity

Members of certain ethnic groups were at increased risk for the metabolic syndrome. Hispanics seem to be at greater risk for the syndrome than other races (Kolovou et al.,2007). For example, in the US, Mexican Americans have the highest rate of metabolic syndrome (44.5%), followed by Caucasians (43.2%) and African Americans (32.5%) (Ford et al.,2010).

Lifestyle

Sedentary lifestyle and excess caloric intake predispose individuals to various medical disorders, including hypertension, hypercholesterolaemia and obesity, thereby contributing to the development of the metabolic syndrome (Cho,2011).

Medications

Some people were at risk for the metabolic syndrome due to medications that might cause gain in weight or changes in the blood pressure, cholesterol and blood sugar level. These medicines were most often used for inflammation and allergies (e.g. glucocorticoids) (Schacke et al.,2002) , HIV (e.g. protease inhibitors) (Boesecke and Cooper,2008), depression and other types of psychiatric diseases (e.g. atypical antipsychotics) (Fenton and Chavez,2006).

Atypical antipsychotics were reported to be associated with increased risk of impaired glucose level and hyperglycaemia, and subsequently increase the risk of the metabolic syndrome (Newcomer et al.,2002). Nevertheless, it has been shown that psychiatric disorders including schizophrenia, were associated with an elevated risk of developing diabetes regardless of antipsychotic use (Henderson,2002).

Patients with schizophrenia were at greater risk for metabolic dysfunctions than other individuals due to a number of reasons, including inactive lifestyle, poor dietary choices, and side effects of antipsychotic medications (Cohn,2009).

2　Prevalence of Metabolic Syndrome

In a study conducted by Cohn and colleagues (2004) involving 240 subjects with schizophrenia or schizoaffective disorder, a prevalence of 42.6% and 48.5% were found in the male and female patients respectively, using the NCEP criteria. Cohn also reported equal prevalence for those under age 45 years (43.8%) and those ages 45 years and over (45.8%). Using the same metabolic syndrome definition, studies of inpatients with schizophrenia have described the prevalence of metabolic syndrome ranging from 27% to 29 % (Teixeira and Rocha,2007; Rezaei et al.,2009) while in outpatients ranging from 25% to 35% (Bobes et al.,2007; Huang et al.,2009).

2.2.6　Diagnostic criteria and classification

There were a number of diagnostic criteria developed for the metabolic syndrome by different expert organizations. The most widely accepted ones were produced by the World Health Organization (WHO) (1999) (Table 2.1), the European Group for the Study of Insulin Resistance (EGIR) (Balkau and Charles,1999) (Table 2.2) and the National Cholesterol Education Program - Third Adult Treatment Panel (NCEP ATP III) (2001) (Table 2.3). NCEP ATP III definition was most commonly used in the US.

Although all these existing guidelines agreed on the core components of the metabolic syndrome e.g. obesity, insulin resistance, dyslipidaemia and hypertension, they were difficult to use or sometimes produced conflicting results in the attempt to identify individuals with the metabolic syndrome in clinical practice (Alberti et al.,2006). Therefore, it has made direct comparisons of data difficult between studies because different definitions have been used to identify the metabolic syndrome.

Although there was no single and universally accepted diagnostic tool for metabolic syndrome, NCEP ATP III and International Diabetes Federation (IDF) more favours and easier to use in clinical practice. The latest International Diabetes Federation (IDF) definition of the metabolic syndrome addressed both clinical and research needs,

providing an accessible, diagnostic tool suitable for worldwide use (Table 2.4) (Alberti et al.,2006). Furthermore, The latest NCEP ATP III criteria (Grundy et al.,2005) and the IDF criteria provide different obesity cut-points for different ethnic groups (Table 2.5) (Alberti et al.,2006).

2 Prevalence of Metabolic Syndrome

Table 2.1: WHO Diagnostic Criteria

For a person to be defined as having the metabolic syndrome, they must have:	
• **Diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance** • <u>**Plus**</u> **at least two of the following:**	
Elevated blood pressure	• ≥140/90 mmHg • **Or** on antihypertensive drugs
Dyslipidaemia	• Triglycerides ≥1.7 mmol/L • **Or** HDL-C ≤0.9 mmol/L in males, ≤1.0 mmol/L in females
Central obesity	• Waist:hip ratio >0.90 in males, >0.85 in females, • **And/or** body mass index >30 kg/m^2
Microalbuminuria	• Urinary albumin excretion level of 20 mcg/min • **Or** albumin:creatinine ratio (ACR) ≥30 mg/g

(WHO,1999)

Table 2.2: EGIR Diagnostic Criteria

For a person to be defined as having the metabolic syndrome, they must have:	
• **Insulin resistance, defined as the top 25% of the fasting insulin values among non-diabetic individuals** • <u>**Plus**</u> **at least two of the following:**	
Elevated blood pressure	• ≥140/90 mmHg • **Or** on antihypertensive drugs
Dyslipidaemia	• Triglycerides ≥2.0 mmol/L • **And/or** HDL-C ≤1.0 mmol/L, or treated for dyslipidaemia
Central obesity	Waist circumference ≥94 cm in males, ≥80 cm in females
Raised fasting plasma glucose (FPG)	FPG ≥6.1 mmol/L

(Balkau and Charles,1999)

Table 2.3: NCEP ATP III Diagnostic Criteria

For a person to be defined as having the metabolic syndrome, they must have: • **At least three of the following:**	
Elevated blood pressure	• ≥130/85 mmHg
Dyslipidaemia	• Triglycerides ≥1.695 mmol/L (150 mg/dL) • **Or** HDL-C <40 mg/dL in males, <50 mg/dL in females
Central obesity	Waist circumference ≥102 cm (40 inches) in males, ≥88 cm (36 inches) in females
Raised fasting plasma glucose (FPG)	FPG ≥6.1 mmol/L (110 mg/dL)

(NCEP,2001)

Table 2.4: The IDF Diagnostic Criteria

For a person to be defined as having the metabolic syndrome, they must have: • **Central obesity (defined as waist circumference* with ethnicity specific values)** • **Plus at least two of the following:**	
Raised triglycerides	≥150 mg/dL (1.7 mmol/L) **or specific treatment for this lipid abnormality**
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in males <50 mg/dL (1.29 mmol/L) in females **or specific treatment for this lipid abnormality**
Raised blood pressure	Systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg **or treatment of previously diagnosed hypertension**
Raised fasting plasma glucose (FPG)	FPG ≥100 mg/dL (5.6 mmol/L), **or previously diagnosed type 2 diabetes** If above 5.6 mmol/L (100 mg/dL), oral glucose tolerance test is strongly recommended, but is not necessary to define presence of the syndrome

If BMI is >30 kg/m^2, central obesity can be assumed and waist circumference does not need to be measured.(Alberti et al.,2006)

Table 2.5: Country-/ethnic-specific values for waist circumference

Country/ethnic group	Waist circumference (as measure of central obesity)
Europids	Male: ≥94 cm; Female: ≥80 cm
South Asians	Male: ≥90 cm; Female: ≥80 cm
Chinese	Male: ≥90 cm; Female: ≥80 cm
Japanese	Male: ≥90 cm; Female: ≥80 cm

These are pragmatic cut-points and better data are required to link them to risk. Ethnicity should be the basis for classification, not country of residence.(Alberti et al.,2006)

2.2.7   Antipsychotics and Metabolic Syndrome

While physicians today were familiar with the risk of diabetes amongst patients, there were still many physicians unaware those psychiatric disorders such as schizophrenia, also place patients at an increased risk for other serious medical comorbidities (Lieberman,2004; Subashini et al.,2011).

The development of the metabolic syndrome in patients suffering from schizophrenia was indeed a serious concern today. Patients with schizophrenia were at greater risk for metabolic dysfunctions than other individuals due to a number of reasons, including inactive lifestyle, poor dietary choices and side effects of antipsychotic medications (Meyer et al.,2008; Vancampfort et al.,2011).

2.2.8   Prevalence of Metabolic Syndrome with Antipsychotics Treatment

The metabolic adverse effects of atypical antipsychotics have received particular attention in the recent years. Certain atypical antipsychotics were recognised to be associated with greater incidence of metabolic syndrome than others (ADA-APA-AACE,2004; Picchioni and Murray,2007). While the metabolic syndrome itself was a serious health risk and medical complication, some studies suggested that the

syndrome might place patients at an increased risk of cardiovascular disease (Isomaa et al.,2001; Goff et al.,2005).

Emerging data indicated that the metabolic syndrome was much more prevalent among schizophrenia patients (Heiskanen et al.,2003; Basu et al.,2004; Cohn et al.,2004). Heiskanen and colleagues (2003) were amongst the earliest study quantify the prevalence of the metabolic syndrome among the mentally ill using the National Cholesterol Education Program (NCEP) criteria. Their data was drawn from a sample of 35 Finnish schizophrenic outpatients, and showed a prevalence of 37%, which was 2-4 times higher than the prevalence reported for the general population in eastern Finland (Table 2.6).

Basu and colleagues (2004) also noted a prevalence of 42.4% out of 33 outpatients with schizoaffective disorder enrolled in a clinical trial (mean age 44.5 years). That rate was almost two times the prevalence for the cohort ages 40-49 years in the Third National Health and Nutrition Examination Survey (NHANES III) (Table 2.6).

In a larger study by conducted by Cohn and colleagues (2004) involving 240 subjects with schizophrenia and schizoaffective disorder, a prevalence of 42.6% was found in the male patients and 48.5% female patients using the NCEP criteria. Cohn also reported equal prevalence for those under age 45 years (43.8%) and those ages 45 years and over (45.8%). Their findings were a complete contrast to that observed in the general population that shown the prevalence of metabolic syndrome increased with age (Table 2.6).

2 Prevalence of Metabolic Syndrome

Table 2.6 Prevalence of Metabolic Syndrome in Schizophrenia Patients with ATP NCEP III definition

Study	Study description	N	Mean Age, Years	Prevalence
Heiskanen (2003)	35 Finnish outpatients with schizophrenia.	Female:16 Male : 19	44.5	37.1%
Basu (2004)	33 outpatients with schizophrenia or schizoaffective disorder	Female: 19 Male:14	44.5	42.4%
Cohn (2004)	240 Canadian subjects with schizophrenia or schizoaffective disorder, two thirds outpatients.	Female: 84 Male: 156	43.3	44.7%

Heiskanen et al.,2003 ;Basu et al.,2004 ;Cohn et al.,2004

In recent studies, the prevalence of metabolic syndrome among schizophrenia with antipsychotics treatment has not much change from the earliest studies, ranging from 34.4% to 49.6% (Kraemer et al.,2011; Subashini et al.,2011; Grover et al.,2012), except for Japan 27.5% (Sugawara et al.,2010). Low prevalence was also noted for schizophrenia patients who never received antipsychotic drug, ranging from 3.9% to 24.7% (Padmavati et al.,2010; Kraemer et al.,2011; Mitchell et al.,2011).

A meta-analysis has included 77 publications shown the overall rate of metabolic syndrome was 32.5% (95%CI: 30.1%, 35.0%). Waist circumference was the most useful in predicting high rate of metabolic syndrome with a sensitivity of 79.4% and a specificity of 78.8% (Mitchell et al.,2011).

2.2.9 Metabolic side effects of antipsychotic medication

The onset of either one or all of the metabolic side effects associated with the second generation antipsychotics such as obesity, impaired glucose tolerance or diabetes and dyslipidaemia would increase the probability of patients developing the metabolic syndrome and also cardiovascular disease (Goff et al.,2005).

2.2.10 Weight Gain and Obesity

Atypical antipsychotics have been frequently reported as causing a higher increase in weight gain than conventional antipsychotics (Bustillo et al.,1996; Citrome et al.,2011). There was considerable evidence, particularly in patients with schizophrenia, that treatment with the atypical antipsychotics could cause a rapid increase in body weight in the first few months of therapy (Zhang et al.,2004).

There was however, considerable variability in weight gain caused by the various atypical antipsychotics (Wirshing et al.,1999). In a study conducted by Allison et al (1999), patients were on standard doses of 5 atypical antipsychotics for 10 weeks and weight gain for each drug was calculated. Weight gain associated with ziprasidone (0.04 kg), risperidone (2.10 kg), sertindole (2.92 kg), olanzapine (4.15 kg) and clozapine (4.45 kg). Subjects receiving placebo has mean lost weight of 0.74 kg.

Another prospective study by Meyer el al (2001) reported mean weight increased during the first year of therapy with clozapine 5.3-6.3 kg, olanzapine 6.8-11.8 kg, risperidone 2.0-2.3 kg, quetiapine 2.8-5.6 kg, ziprasidone and aripiprazole less than 0.9 kg.

The mechanisms responsible in weight gain associated with atypical antipsychotic were not fully understood. It is suspected to be related to the changes in leptin and insulin level (Zhang et al.,2004), which might alter hunger and satiety in people taking atypical antipsychotics, from the result through binding of atypical drugs to serotonin, norepinephrine, dopamine and particularly histamine-H_1 receptors. All of these receptors have been implicated in the control of body weight (ADA-APA-AACE,2004).

2   Prevalence of Metabolic Syndrome

Weight gain and changes in body composition might account for many of the metabolic complications associated with atypical antipsychotic therapy, such as insulin resistance, pre-diabetes, diabetes and dyslipidaemia (ADA-APA-AACE,2004). Even without the development of the metabolic syndrome or diabetes, significant weight gain associated with antipsychotic treatment might compromise a patient's health by contributing to comorbid conditions, such as hypertension and coronary artery disease (Daumit et al.,2008).

2.2.11 Hyperglycaemia and Impaired Glucose Tolerance

Atypical antipsychotics could increase the risk of hyperglycaemia and impaired glucose levels, and subsequently lead to the risk of metabolic syndrome. Abnormalities in glucose regulation were first reported in patients with schizophrenia and bipolar disorder prior to the introduction of antipsychotic medications, with early reports indicating a pattern of insulin resistance in untreated patients (Meduna et al.,1942). Ryan et al (2003) also reported impaired fasting glucose tolerance in first-episode, drug-naïve patients with schizophrenia. These patients were also more insulin resistant and have higher levels of plasma glucose, insulin and cortisol than healthy comparison subjects.

Patients treated with olanzapine and clozapine have higher fasting and postprandial insulin levels than patients treated with conventional antipsychotics, even after adjusting for body weight (ADA-APA-AACE,2004). Individual cases have shown marked hyperglycaemia in patients taking clozapine and olanzapine (Koro et al.,2002; Sernyak et al.,2003).

One possible mechanism for hyperglycaemia was effect on pancreatic β- cell function that lead to impairment of insulin action and insulin resistance (Best et al.,2005).

Drug-induced insulin resistance might occur because of weight gain or a change in body fat distribution, or by a direct effect on insulin sensitive target tissues (ADA-APA-AACE,2004).

2.2.12   Diabetes

Treatment with antipsychotic medications was also associated with exacerbation of existing type 1 and type 2 diabetes, new onset of type 2 diabetes mellitus, as well as diabetic ketoacidosis (Henderson,2001; Cohen and Correll,2009). Numerous case reports have documented the onset of exacerbation of diabetes, including the occurrence of hyperglycaemia crises, following initiation of therapy with many of the atypical antipsychotics (ADA-APA-AACE,2004).

The onset of diabetes tended to occur within the first few months of the treatment. A meta-analysis of 45 published cases of new-onset diabetes and diabetic ketoacidosis over a 21-year period found the highest increase of new diabetes cases within the first 1 to 3 months after the initiation of atypical antipsychotic treatment (Jin et al.,2002).

Despite limitations in study design, data consistently showed an elevated risk for diabetes in patients treated with clozapine or olanzapine compared with patients receiving treatment with the first generation antipyschotics or with other atypical antipsychotics (ADA-APA-AACE,2004). The risk of new onset type 2 diabetes associated with use taking risperidone and quetiapine was also noted by Lambert et al (2006). Aripiprazole and ziprasidone have relatively limited epidemiological data, but clinical trial experience with these drugs thus far has not shown an increased risk for diabetes (Blonde et al.,2008; Yood et al.,2009).

The concern about glucose intolerance, diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotic therapy has culminated in Food and Drug

Administration (FDA) mandating changes in the drug labelling, which contains warnings for hyperglycaemia and diabetes for all atypical antipsychotics (FDA,2004).

2.2.13 Dyslipidaemia

An additional related consequence of atypical antipsychotic use was their effect on serum lipids. The available evidence suggested that changes in serum lipids were in accordance with body weight changes. Clozapine and olanzapine, which produces the greatest weight gain, were associated with the greatest increases in total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides, and with decreased high-density lipoprotein (HDL) cholesterol (ADA-APA-AACE,2004).

Aripiprazole and ziprasidone, which were associated with the least amount of weight gain, did not appear to be associated with a worsening of serum lipids, while risperidone and quetiapine have intermediate effects on lipids (Casey,2004).

Table 2.7 Atypical Antipsychotics and Metabolic Effects

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/-	-	-
Ziprasidone*	+/-	-	-

*+ = increase effect; - = no effect; D = discrepant results., *Newer drugs with limited long-term data*
(ADA-APA-AACE,2004)

2.2.14 Management of antipsychotic-related metabolic syndrome

Simple monitoring and management tips could aid physicians in managing obese schizophrenia patients, or those with the metabolic syndrome. Some guidance about this issue was provided in the consensus statement developed by a panel consisting of the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity (ADA-APA-AACE,2004).

In summary, the panel recommended the following:

1. Risk-benefit assessment when starting atypical antipsychotics

2. Patient, family and caregiver education.

3. Baseline screening.

4. Regular monitoring.

5. Referral to specialised services, when appropriate.

2.2.15 Risk-benefit assessment

The choice of atypical antipsychotics for a specific patient depended on many factors. The implications of developing treatment-induced metabolic disease should be an important consideration (ADA-APA-AACE,2004).

Amongst the currently available atypical antipsychotics, clozapine was clearly the most effective antipsychotic. However, clozapine was only indicated after other medication have failed or in patients at high risk for suicidal behaviour, largely because it can cause agranulocytosis (Agid et al.,2007; Meltzer,2005).

A number of factors should be considered when selecting among the antipsychotic medications (ADA-APA-AACE,2004). These include:

- The nature of the patient's psychiatric conditions

- The specific target signs and symptoms

- Past history of drug response

- Patient preference

- History of treatment adherence

- Medication effectiveness

- Psychiatric and medical comorbidities

- The availability of appropriate formulations

- The need for special monitoring

- The cost of and access to medications.

Given the serious health risks, patients taking atypical antipsychotics should receive appropriate baseline screening and ongoing monitoring (De Hert et al.,2011).

2.2.16 Patient, family and caregiver education

Patients, family members and caregivers need to know that treatment with some atypical antipsychotics might be associated with significant weight gain and a heightened risk of developing diabetes and dyslipidaemia. Healthcare professionals, patients, family members and caregivers should also be aware of the signs and symptoms of diabetes, and especially those associated with the acute decompensation of diabetes, such as diabetic ketoacidosis (Li and Arthur,2005).

2.2.17 Baseline screening

When prescribing an atypical antipsychotic, baseline screening and follow-up monitoring was essential in order to lower the possibility of developing CVD, diabetes or other diabetes complications (De Hert et al.,2011).

The ADA-APA panel recommended that baseline screening measures (Table 2.8) be obtained before, or as soon as clinically feasible right after the initiation of any antipsychotic medication (ADA-APA-AACE,2004):

1. Personal and family history of obesity, diabetes, dyslipidaemia, hypertension, or CVD

2. Weight and height

3. Waist circumference

4. Blood pressure;

5. Fasting plasma glucose

6. Fasting lipid profile.

These assessments could determine if the patient was overweight (BMI 25.0-19.9) or obese BMI ($\geq$30), has pre-diabetes (fasting plasma glucose 100-125 mg/dl) or diabetes

(FBS ≥ 126 mg/dl), hypertension (BP >140/90mmHg) or dyslipidaemia. If any of these conditions were identified, appropriate treatment should be initiated.

For patients with or at higher risk for diabetes and in those treated with other medications that might increase these risks, it might be preferable to initiate treatment with an atypical antipsychotics that have a lower propensity for weight gain and glucose intolerance (Freudenreich et al.,2007).

2.2.18 Regular monitoring

Careful monitoring of at-risk patients might aid in the prevention of metabolic syndrome as well as the management of any potential symptoms should they occur. The patient's weight should be reassessed at 4, 8 and 12 weeks after initiating or changing atypical antipsychotic therapy, and quarterly thereafter at the time of routine visits (ADA-APA-AACE,2004) (Table 2.8).

Fasting plasma glucose, lipid levels and blood pressure should also be assessed 3 months after initiation of antipsychotic medications. Thereafter, blood pressure and plasma glucose values should be obtained annually or more frequently in those who have a higher baseline risk for the development of diabetes or hypertension. In those with a normal lipid profile, repeat testing should be performed at 5-year intervals or more frequently if clinically indicated (ADA-APA-AACE,2004) (Table 2.8).

If a patient gains ≥5% of his or her initial weight at any time during therapy, one should consider switching to more weight-neutral antipsychotic medications (ADA-APA-AACE,2004). When switching from one antipsychotic drug to another, it was preferable to discontinue the current medication gradually.

2 Prevalence of Metabolic Syndrome

For people who developed worsening glycaemia or dyslipidaemia while on antipsychotic therapy, the panel recommended considering switching to an atypical agent that has not been associated with significant weight gain or diabetes. The blood pressure, lipid and glycaemic goals of therapy for people with diabetes applied equally to those who also have psychiatric disorders. However, all goals need to be individualised (ADA-APA-AACE,2004).

Table 2.8 Monitoring Protocol for Patients on Atypical Antipsychotics*

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	✓					✓	
Weight (BMI)	✓	✓	✓	✓	✓		
Waist circumference	✓					✓	
Blood pressure	✓			✓		✓	
Fasting plasma glucose	✓			✓		✓	
Fasting lipid profile	✓			✓			✓

*More frequent assessments may be warranted based on clinical status, (ADA-APA-AACE,2004)

2.2.19 Referral to specialised services

The ADA-APA panel recommended that nutrition and physical activity counselling have to be provided for all patients who are overweight or obese, particularly if they were starting treatment with a second-generation antipsychotic that was associated with significant weight gain. Referral to a healthcare professional or program with expertise in weight management might also be necessary (ADA-APA-AACE,2004).

All patients with abnormal glucose or lipid levels should be referred to specialised clinicians. Immediate care or consultation was required for patients with symptomatic

or severe hyperglycaemia, symptomatic hypoglycaemia, or glucose levels ≤ 60 mg/dl, even in the absence of symptoms. In short, treatment with atypical antipsychotics might increase the patient's risk of metabolic syndrome and diabetes. Therefore, physicians needed to be proactive when treating patients with schizophrenia.

In South East Asia, especially in Malaysia, there was paucity of data on the prevalence of metabolic syndrome and cardiovascular risk among schizophrenia patients. A study performed by Rahman et al (2009) among 51 patients with primary psychotic and mood disorder found that the prevalence of metabolic syndrome was 37.2%.

The objective of the present study was to determine the prevalence of metabolic syndrome among schizophrenia patients receiving antipsychotics in Malaysia. The present study also sought to determine the prevalence of coronary heart-disease risk among these patients.

2.2.20 RESEARCH QUESTION

What was the prevalence of metabolic syndrome among schizophrenia patient?

2.2.21 STUDY OBJECTIVES

(i) **Primary Objective**

To determine the prevalence of metabolic syndrome among schizophrenia patients in Malaysia.

(ii) **Secondary objective**

(a) To describe the demographic, lifestyle, medical and psychiatric history according to the metabolic syndrome status among schizophrenia patients.

(b) To describe the characteristics of antipsychotic treatment and other medication according to the metabolic syndrome status among schizophrenia patients.

(c) To determine the prevalence of hypertension, diabetes mellitus and hyperlipidemia among schizophrenia patients after initiation of monotherapy antipsychotics.

(d) To determine the prevalence of metabolic syndrome and its component among schizophrenia patients treated with monotherapy atypical antipsychotics.

(e) To determine the prevalence of metabolic syndrome and its component among schizophrenia patients treated with monotherapy typical antipsychotics.

(f) To determine the prevalence of metabolic syndrome component according to metabolic syndrome status among schizophrenia patients.

(g) To determine the prevalence of cardiovascular risk factors (CVRFs), coronary heart disease (CHD) risk according to metabolic syndrome status among schizophrenia patients.

2.3 Methodology

2.3.1. Study design

This study was a descriptive cross sectional study.

2.3.2. Setting and study period

The study was conducted at four mental institutions, two army hospitals and two general hospitals namely Hospital Bahagia Ulu Kinta, Perak, Hospital Permai Johor Bahru, Johor, Hospital Sentosa Kuching, Sarawak, Hospital Mesra Kota Kinabalu, Sabah, Hospital Terendak Melaka, Navy Hospital Lumut, Perak, University Malaya Medical Centre (UMMC), Kuala Lumpur and Hospital Sg. Petani, Kedah from June 2008 until September 2011.

2.3.3. Study population

Study population were schizophrenia patients aged between 18 and 65 years old, who met the DSM-IV TR criteria for schizophrenia.

i). Inclusion criteria

Patients received antipsychotic treatment for at least 1 year.

ii). Exclusion criteria

- Patient with history of diabetes mellitus and hypertension prior to the treatment of schizophrenia.

- Patients who were on mood stabilizer.

2.3.4. Sample size and sampling procedure

This study was used as a screening for randomised controlled trial study in Chapter 3. Therefore universal sampling was used for the recruitment of this study subjects.

Out of 527 patients that were screened during study period, 485 patients fulfilled the DSM-IV TR criteria for schizophrenia. Three hundred and twenty five schizophrenia patients agreed to be interviewed and part of metabolic syndrome parameters were taken but only 270 consented for fasting blood investigations and full metabolic syndrome profile. The socidemographic characterictic of patients with fasting blood taking (n=270) and with no fasting taking (n=55) is in Table 2.15.

2.3.5. Study variables

(a) Dependent variable

Metabolic syndrome

(b) Independent variables

Sociodemographic variables

i). Age

ii). Sex

iii). Ethnicity

iv). Occupation

v). Educational level

vi). Marital status

vii). Body mass index (BMI)

viii). Care setting

Lifestyle, medical and psychiatric history

  i).   Smoking status

  ii).   Duration of quit smoking

  iii).   Physical activity

  iv).   Medical history

  v).   Family history

  vi).   Psychiatric history

Characteristic of treatment

  i).   Current antipsychotic

  ii).   Typical antipsychotics (monotherapy)

  iii).   Atypical antipsychotics (monotherapy)

  iv).   Concomitant medication

  v).   Other medication

Metabolic syndrome criteria

  i).   Waist circumference

  ii).   HDL cholesterol

  iii).   Triglyceride

  iv).   Blood pressure

  v).   Fasting glucose

Cardiovascular risk factors

  i).   Age

  ii).   Smoking status

  iii).   Diabetes mellitus

  iv).   HDL cholesterol

v).   Systolic blood pressure

vi).   Diastolic blood pressure

2.3.6. Operational definitions

There were two definitions for metabolic syndrome. The first one was Modified

National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) with

Asian values for waist circumference (Grundy et al.,2005) and second one was

modified IDF with South Asian values for waist circumference (Alberti et al.,2006)

(Table 2.6).

The operational definitions for variables and scale were described in detail in ANNEX

"A".

Table 2.6: Definitions of Metabolic Syndrome

	NCEP ATP III*	IDF**
Waist circumference (cm)	Male ≥ 90, female ≥ 80	Male ≥ 90, female ≥ 80
Blood pressure (mmHg)	≥ 130/85 or on drug treatment for hypertension	≥ 130/85 or treatment of previous diagnosed hypertension
HDL (mg/dL)	< 40 mg/dL(1.03 mmol/L) in males < 50 mg/dL(1.29 mmol/L) in females or on drug treatment for reduced HDL-C	< 40 mg/dL(1.03 mmol/L) in males < 50 mg/dL(1.29 mmol/L) in females or specific treatment for this lipid abnormality
TG (mg/dL)	≥ 150 mg/dL(1.7 mmol/L) or on drug treatment for elevated triglyceride	≥ 150 mg/dL(1.7 mmol/L) or specific treatment for this lipid abnormality
Glucose (mg/dL)	≥ 100 mg/dL(5.6 mmol/L) Or on drug treatment for elevated glucose	≥ 100 mg/dL(5.6 mmol/L) or previous diagnosed type 2 diabetes

*NCEP ATP III - Modified National Cholesterol Education Program Adult Treatment Panel
- Metabolic Syndrome is any 3 of 5 criteria, Asian values for waist circumference
**IDF - International Diabetes Federation, South Asian values for waist circumference
- Metabolic Syndrome is central obesity plus any 2 of 5 criteria
- If BMI is > 30kg/m^2, central obesity can be assumed and waist circumference does not need to be measured

2.3.7. Study instrument

The Mini International Neuropsychiatric Interview (M.I.N.I.) is a short structured diagnostic interview for DSM-IV TR for the Major Axis I psychiatric disorder (D.V. Sheehan et al.,1998).The M.I.N.I. was available in local language (D.V. Sheehan et al.,1998).

Framingham Coronary Heart Disease (CHD) 10-year risk score was developed by National Heart, Lung and Blood Institute (NHLBI) in U.S. through Framingham Heart Study (Wilson et al.,1998). The CHD 10-year risk was calculated separately for men and women using CHD score sheet. Variables required were age, total cholesterol or LDL cholesterol, HDL cholesterol, blood pressure, diabetes and smoking status. The risk score was given in percentage. The interpretation of CHD 10-year risk was the number of people out of 100 people probably has a heart attack in the next 10 years.

2.3.8. Data collection methods

All patients with schizophrenia were approached during the study period. Patients who fulfilled study criteria were briefed on the study and written consent was obtained. A face-to-face interviewed was conducted using a screening structured questionnaire and the Mini International Neuropsychiatric Interview (M.I.N.I.).

The screening structured questionnaire consisted of three sections: (i) sociodemographic and lifestyle background (ii) medical, psychiatry and family history (iii) physical examination and blood investigation for metabolic syndrome profile.

Patient was given an appointment date and were asked for minimum of 8 hours fasting since last meal for the blood investigation. Secondary data pertaining to date onset of

illness, patient's treatment and medication, diagnosis of hypertension, diabetes mellitus and hyperlipidemia were obtained from patient's case note.

2.3.9. Data Management

The data were checked before ending each interview session and before compilation to ensure completeness. Raw data obtained were coded and entered into Statistical Package for Social Sciences (SPSS) Version 16.0. Cleaning for wrong entry and outliers were done before the analysis.

2.3.10. Pre-test

A pre-test of the questionnaires was done on 5 patients who were attending the psychiatric clinic, UMMC. These respondents were excluded from the study. Some corrections were made after the pre-test to facilitate patients' understanding of the questionnaires.

2.3.11. Ethical consideration

Ethical approval was obtained from Medical Ethics Committee of UMMC and Medical Research and Ethics Committee, Ministry of Health. Before any interview, patients were informed regarding the nature and purpose of the study and the respondents were given the assurance that all information given will be treated with confidentiality. A written consent was obtained from the patients prior the interviews.

2.3.12.   DATA ANALYSIS

i).   Univariate analyses

For categorical variables, they were described in the form of frequencies and percentages. For continuous independent variables, they were summarized and described as means, standard deviations, median and interquartile range.

ii).   Bivariate analysis

Pearson's Chi-square test and Fisher's exact test were used to determine the possible association of significant variables to the occurrence of metabolic syndrome. Continuous data and comparison of two means were analyzed using the t-test. Skewed continous data and comparison of median was analysed using non parametric test. Subsequently the continuous variables were recategorised and further tested by Pearson's Chi-square test. For bivariate analysis of BMI, only normal, overweight and obese categories were considered in the analysis. Normal category was chosen as reference group and underweight category was excluded for the analysis. The individual prevalence of the cardiovascular risk factors and the prevalence of metabolic syndrome components were estimated by calculating the corresponding 95% confidence interval (95% CI). Framingham risk score in the metabolic syndrome and non-metabolic syndrome groups were compared using parametric tests (Student's t test) or non-parametric test (Mann-Whitney U test), according to the distribution of the variables. The risk score of the patients were further classified according to the category "low" CHD risk (Framingham < 10%) and "high/ very high" CHD risk (Framingham ≥ 10%) within 10 years.

In addition, the mean of Framingham risk score was also compared according to patients' age group with and without metabolic syndrome. The multiple comparisons

2 Prevalence of Metabolic Syndrome

were analyzed using Two-Way Interaction in Three-Way Anova with Bonferroni correction and adjusting for sex. The SPSS version 16.0 statistical package was used throughout. An alpha level of significance p< 0.05 was set for all analyses.

2 Prevalence of Metabolic Syndrome

2.4 Results

Study population and socio demographic characteristics

For the study, 527 patients were screened, of whom 485 patients fulfilled the DSM-IV TR criteria for schizophrenia. Three hundred and twenty five schizophrenia patients agreed to be interviewed and metabolic syndrome parameters were taken except for blood investigation. Only 270 patients consented for fasting blood investigations and full metabolic syndrome profile.

The prevalence of metabolic syndrome among the recruited patients based on modified NCEP ATP III definition (Grundy et al.,2005) and modified IDF (Alberti et al.,2006) were 46.7% and 45.9% respectively. Table 2.7 displayed the socio demographic characteristics of the study population. The metabolic syndrome group had higher mean age, a larger proportion of female, unemployed individual and patients from psychiatric institution. Among schizophrenia patients, an association between BMI and metabolic syndrome was significant based on modified NCEP ATP III definition. There was statistically significant difference of the mean BMI between metabolic syndrome and non-metabolic syndrome among schizophrenia patients on antipsychotics. The mean BMI for metabolic syndrome was higher than non-metabolic syndrome groups (29.4 ± 5.1 vs. 25.0 ± 5.6). Majority of the patients with metabolic syndrome had significantly higher prevalence of overweight (39.7% vs. 24.3%) and obesity (40.5% vs. 17.4%) compared to the non-metabolic syndrome group.

2 Prevalence of Metabolic Syndrome

Table 2.7: Demographics and Characteristics of Schizophrenia Patient

Characteristics	Patients with metabolic syndrome (n=126) n (%)	Patients without metabolic syndrome (n=144) n (%)	p value
Age(year)mean ± SD	40.7 ± 11.3	39.5± 11.8	P=0.472*
Age group (n =270)			
< 20[‡]	2(1.6)	2(1.4)	P=0.500
20 – 29	18(14.3)	34(23.6)	
30 – 39	44(34.9)	40(27.8)	
40 – 49	29(23.0)	32(22.2)	
50 – 59	26(20.6)	27(18.8)	
> 60	7(5.6)	9(6.2)	
BMI(kg/m^2) mean ± SD	29.4 ± 5.1	25.0± 5.6	**p<0.001***
BMI[¶](n =256)			
Underweight(<18.5)	0(0)	14(9.7)	**p<0.001**
Normal(18.5 – 24.9)	25(19.8)	70(48.6)	
Overweight(25 – < 30)	50(39.7)	35(24.3)	
Obese(≥ 30)	51(40.5)	25(17.4)	
Sex (n =270)			
Male[‡]	74(58.7)	100(69.4)	p=0.670
Female	52(41.3)	44(30.6)	
Race (n = 270)			
Malay[‡]	53(42.1)	53(36.8)	P=0.747
Chinese	44(34.9)	58(40.3)	
Indian	15(11.9)	15(10.4)	
others	14(11.1)	18(12.5)	
Marital status (n=259)			
Married[‡]	42(33.9)	35(25.9)	P=0.398
Single	70(56.4)	90(66.7)	
Divorced	8(6.5)	6(4.4)	
widowed	4(3.2)	4(3.0)	
Education level(n=234)			
No formal education[‡]	2(1.7)	5(4.3)	P=0.683
Primary	21(17.8)	20(17.3)	
Secondary	86(72.9)	81(69.8)	
Tertiary	9(7.6)	10(8.6)	
Occupation (n=249)			
Employed[‡]	33(27.0)	55(43.3)	**P=0.003**
Unemployed	83(68.0)	67(52.8)	
Housewife	6(4.9)	5(3.9)	
Care setting (n=270)			
General hospital[‡]	68(54.0)	92(63.9)	P=0.098
Institution	58(46.0)	52(36.1)	

Chi square test, *t-test, ‡ Reference group, BMI[¶] excluded underweight- Chi square test based on category normal (reference group), overweight and obese. Metabolic syndrome status was based on modified NCEP ATP III definition.

Lifestyle

Most of the schizophrenia patients in this study did not practice healthy lifestyle habits. The prevalence of current smokers was higher than former smokers in the metabolic syndrome group (24.8% vs. 20.5%). Very small proportion of former smokers admitted the duration of quit smoking. Among the current and former smokers, majority smoked less than 20 sticks cigarettes/day and majority of the patients have sedentary lifestyle with hardly any physical activity for both groups (Table 2.8).

Medical and Psychiatric History

Among the screened patient, 8 patients had history of hypertension and 3 patients had history of diabetes mellitus before antipsychotics treatment. These patients were excluded from the analysis of this study.

The metabolic syndrome group had a larger proportion of patients developed hypertension and diabetes mellitus after initiation of antipsychotics, female patients with history of gestational diabetes and family history of diabetes. Among schizophrenia patients, there was association between the occurrence of diabetes mellitus after initiation of antipsychotics and metabolic syndrome. There was also statistically significant difference between metabolic syndrome and non-metabolic syndrome patients in the mean age of onset of illness. The age of onset for schizophrenia in metabolic syndrome patients was slightly older than non-metabolic syndrome patients (28.7 ± 9.3 vs. 25.5 ± 7.4).

There were no statistically significant differences between metabolic syndrome and non-metabolic syndrome patients with respect to mean year duration of illness, mean number of relapse and history of relapse (Table 2.8).

2 Prevalence of Metabolic Syndrome

Table 2.8: Lifestyle, medical and psychiatric history according to the metabolic syndrome status

Characteristics	Patients with metabolic syndrome (n=126) n (%)	Patients without metabolic syndrome (n=144) n (%)	P value
Smoking	**n=117**	**n=130**	
Never[‡]	64(54.7)	62(47.7)	P=0.211
Former smoker < 20 sticks/day	20(17.1)	18(13.8)	
Former smoker ≥ 20 sticks/day	4(3.4)	3(2.3)	
Current smoker < 20 sticks/day	17(14.5)	35(27.0)	
Current smoker ≥ 20 sticks/day	12(10.3)	12(9.2)	
Duration of quitting smoking	**n=8**	**n=4**	
≥ 10 years[‡]	7(87.5)	2(50.0)	P=0.082
5 - 9 years	0(0.0)	2(50.0)	
1 – 4 years	1(12.5)	0(0.0)	
< 1 year	0(0.0)	0(0.0)	
Physical activity	**n=118**	**n=131**	
Never[‡]	56(47.5)	58(44.3)	P=0.840
Rarely	28(23.7)	25(19.1)	
1 -3 times/month	4(3.4)	5(3.8)	
1-2 times /week	9(7.6)	12(9.2)	
3 -4 times /week	8(6.8)	13(9.9)	
≥ 5 times /week	13(11.0)	18(13.7)	
Medical and family history			
Hypertension after initiation of antipsychotics(n=233)	14/115(12.2)	6/118(5.1)	P=0.053
Diabetes mellitus after initiation of antipsychotics(n=231)	17/112(15.2)	6/119(5.0)	**P=0.010**
History of gestational diabetes (female)(n=38)	2/25(8.0)	1/13(7.7)	P=0.973
Family history of hypertension(n=219)	39/107(36.4)	45/112(40.2)	P=0.570
Family history of diabetes(n=219)	31/109(28.4)	27/110(24.5)	P=0.514
Parent obese(n=225)	13/111(11.7)	15/114(13.2)	P=0.742
Siblings obese(n=225)	13/111(11.7)	14/114(12.3)	P=0.896
Psychiatric history			
Age of onset(year),mean ± SD(n=177)	28.7(9.3)	25.5(7.4)	**P=0.014***
Duration of illness (year) ,mean ± SD (n=260)	10.9(9.3)	10.0(7.8)	P=0.403*
History of relapse(n=264)	42(33.9)	51(36.4)	P=0.763
No of relapse, mean ± SD (n=263) Median (interquatile range)	0.9(1.6) 0.0(0.0 -1.0)	0.8(1.5) 0.0(0.0 -1.0)	P=0.522**

Chi square test, *t-test, **Mann-Whitney U test, ‡ Reference group. Metabolic syndrome status was based on modified NCEP ATP III definition

2 Prevalence of Metabolic Syndrome

Characteristics of treatment with antipsychotics and other medications

Table 2.9 showed the characteristics of treatment with antipsychotics and other concomitant medications. The majority of patients were treated with only one antipsychotic (75.9%). For the overall use of antipsychotic, the proportion of atypical antipsychotics monotherapy used was the highest in both metabolic syndrome and non-metabolic syndrome groups (50.8% vs. 58.3%). Followed by typical antipsychotics monotherapy used in both groups (21.4% vs. 20.8).

With respect to patients with typical monotherapy antipsychotic treatment in the metabolic syndrome group, chlorpromazine had the highest proportion (33.3%) of followed by sulpiride and perphenazine (18.5%). While in patients received atypical monotherapy antipsychotic treatment, olanzapine had the highest proportion followed by risperidone (42.2% vs. 32.8%). None of the patients prescribed on amisulpride has metabolic syndrome.

For the overall schizophrenia patients, antipsychotics were combined with anticholinergics (31.5%), benzodiazepines (15.9%), antidepressants (13.0%). In addition, 4.8% was being treated for diabetes, 4.4% of patient took antihypertensive medication and 5.9% of patients took lipid-lowering medication. There was no significantly difference in the distribution of concomitant and other medications between metabolic syndrome and non-metabolic syndrome group.

2 Prevalence of Metabolic Syndrome

Table 2.9: Characteristics of treatment with antipsychotic and other medication

Characteristics	Patients with metabolic syndrome (n=126) N (%)	Patients without metabolic syndrome (n=144) N (%)	P value
Current antipsychotic			
Atypical antipsychotics (monotherapy) [‡]	64(50.8)	84(58.3)	P=0.339
Typical antipsychotics (monotherapy)	27(21.4)	30(20.8)	
Combination of Typical and Atypical Antipsychotics	15(11.9)	11(7.7)	
Combination of Typical Antipsychotics	14(11.1)	9(6.2)	
Combination of Atypical Antipsychotics	6(4.8)	10(7.0)	
Typical antipsychotics(monotherapy)			
Chlorpromazine	9(33.3)	10(33.3)	
Sulpiride	5(18.5)	6(20.0)	
Perphenazine	5(18.5)	5(16.7)	P=0.960
Haloperidol[‡]	3(11.2)	5(16.7)	
Trifluoperazine	2(7.4)	1(3.3)	
Flupenthixol decanoate	2(7.4)	1(3.3)	
Fluphenazine decanoate	1(3.7)	2(6.7)	
Atypical antipsychotics(monotherapy)			
Olanzapine[‡]	27(42.2)	26(31.0)	P=0.390
Risperidone	21(32.8)	29(34.5)	
Paliperidone	11(17.2)	16(19.0)	
Clozapine	2(3.1)	1(1.2)	
Quetiapine	1(1.6)	2(2.4)	
Aripiprazole	2(3.1)	6(7.1)	
Amisulpride	0(0)	4(4.8)	
Concomitant medication			
Anticholinergic	41(32.5)	44(30.6)	P=0.726
Benzodiazepine	25(19.8)	22(15.3)	P=0.324
antidepressants	16(12.7)	19(13.2)	P=0.904
Other medication			
Anti diabetic medication	8(6.3)	5(3.5)	P=0.271
Blood pressure lowering	6(4.8)	6(4.2)	P=0.813
Lipid-lowering medication	6(4.8)	10(6.9)	P=0.449

Chi square test, ‡ Reference group, Metabolic syndrome status was based on modified NCEP ATP III definition.

Prevalence of hypertension, diabetes mellitus and hyperlipidemia after initiation of monotherapy antipsychotic

For the prevalence of hypertension, diabetes mellitus and hyperlipidemia among schizophrenia patients after initiation of monotherapy antipsychotic, the denominator includes patient without blood investigation for metabolic syndrome parameters. Among the typical antipsychotics, sulpiride has the highest prevalence of hypertension, diabetes mellitus and hyperlipidemia after initiation of monotherapy antipsychotic (9.1% for all prevalence respectively). As for the intra muscular injection antipsychotics, fluphenazine decanoate has the highest prevalence of hyperlipidemia (3.3%).

For schizophrenia patients on atypical antipsychotics, the highest prevalence of hypertension and hyperlipidemia after initiation of monotherapy antipsychotic was aripiprazole (12.5% for both respectively), whereas paliperidone has the highest prevalence of diabetes mellitus (3.4%) (Table 2.10).

Table 2.10: Prevalence of hypertension, diabetes mellitus and hyperlipidemia after initiation of monotherapy antipsychotic among schizophrenia patients

	Typical antipsychotics													
	Haloperidol(n=8)		Perphenazine(n=13)		Sulpiride(n=11)		Trifluoperazine (n=3)		Chlorpromazine(n=19)		Flupenthixol decanoate (n=3)		Fluphenazine decanoate (n=3)	
Prevalence	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI
Hypertension	0(0.0)	0.0-32.4	1(7.7)	1.4-33.3	1(9.1)	1.6-37.7	0(0.0)	0.0-56.2	0(0.0)	0.0-16.8	0(0.0)	0.0-56.2	0(0.0)	0.0-56.2
Diabetes mellitus	0(0.0)	0.0-32.4	1(7.7)	1.4-33.3	1(9.1)	1.6-37.7	0(0.0)	0.0-56.2	0(0.0)	0.0-16.8	0(0.0)	0.0-56.2	0(0.0)	0.0-56.2
Hyperlipidemia	0(0.0)	0.0-32.4	1(7.7)	1.4-33.3	1(9.1)	1.6-37.7	0(0.0)	0.0-56.2	0(0.0)	0.0-16.8	1(3.3)	6.2-79.2	0(0.0)	0.0-56.2

	Atypical antipsychotics													
	Olanzapine (n=61)		Clozapine (n=14)		Risperidone (n=64)		Quetiapine (n=7)		Amisulpride (n=4)		Paliperidone (n=29)		Aripiprazole (n=8)	
Prevalence	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI
Hypertension	2(3.3)	0.9-11.2	0(0.0)	0.0-21.5	3(4.7)	1.6-12.9	0(0.0)	0.0-35.4	0(0.0)	0.0-49.0	2(6.9)	1.9-22.0	1(12.5)	2.2-47.1
Diabetes mellitus	2(3.3)	0.9-11.2	0(0.0)	0.0-21.5	2(3.1)	0.86-10.7	0(0.0)	0.0-35.4	0(0.0)	0.0-49.0	1(3.4)	0.6-17.2	0(0.0)	0.0-32.4
Hyperlipidemia	1(1.6)	0.29-8.7	0(0.0)	0.0-21.5	5(7.8)	3.4-17.0	0(0.0)	0.0-35.4	0(0.0)	0.0-49.0	2(6.9)	1.9-22.0	1(12.5)	2.2-47.1

The denominator for hypertension, diabetes mellitus and hyperlipidemia include patients without blood investigation for metabolic syndrome components

2 Prevalence of Metabolic Syndrome

Table 2.11 showed the prevalence of metabolic syndrome and its components among schizophrenia patients treated with monotherapy atypical antipsychotics. Among the metabolic syndrome component, waist circumference has the highest proportion compare to other components for all atypical antipsychotics except for aripiprazole. All patients with monotherapy clozapine (n=3) and quetiapine (n=3) had metabolic syndrome components for waist circumference and blood pressure. Olanzapine had the highest prevalence of triglyceride and HDL cholesterol (37.7% vs. 58.5%).

For patients treated with monotherapy typical antipsychotics, waist circumference was the highest proportion among the metabolic syndrome components for all typical antipsychotics except for haloperidol. Perphenazine has the highest prevalence of blood pressure and triglyceride (70.0% vs. 50.0%). Flupenthixol decanoate has the highest prevalence of HDL cholesterol (66.7%) and Trifluoperazine has the highest prevalence of fasting blood sugar (66.7%) (Table 2.12).

2 Prevalence of Metabolic Syndrome

Table 2.11: Prevalence of metabolic syndrome(MetS) and its components among schizophrenia patients treated with monotherapy atypical antipsychotics

| | Atypical antipsychotics | | | | | | | | | | | | | |
| | Olanzapine (n=53) | | Clozapine (n=3) | | Risperidone (n=50) | | Quetiapine (n=3) | | Amisulpride (n=4) | | Paliperidone (n=27) | | Aripiprazole (n=8) | |
MetS Prevalence	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI
NCEP ATP III*	27(50.9)	37.9-63.9	2(66.7)	20.8-93.9	21(42.0)	29.4-55.8	1(33.3)	6.2-79.2	0(0.0)	0.0-49.0	11(40.7)	24.5-59.3	2(25.0)	7.2-59.1
MetS components prevalence														
Waist circumference Male ≥90 cm , female ≥80 cm	44(83.0)	70.8-90.8	3(100)	43.9-100	46(92.0)	81.2-96.9	3(100)	43.9-100	1(25.0)	4.6-69.9	23(85.2)	67.5-94.1	1(12.5)	2.2-47.1
BP(≥130/85 mmHg)	25(47.2)	34.4-60.3	3(100)	43.9-100	22(44.0)	31.2-57.7	3(100)	43.9-100	1(25.0)	4.6-69.9	11(40.7)	24.5-59.3	3(37.5)	13.7-69.4
HDL(male< 40 mg/dL ,female< 50mg/dL)	31(58.5)	45.1-70.7	1(33.3)	6.2-79.2	23(46.0)	33.0-59.6	1(33.3)	6.2-79.2	0(0.0)	0.0-49.0	10(37.0)	21.5-55.8	3(37.5)	13.7-69.4
Triglyceride (≥150mg/dL)	20(37.7)	25.9-51.2	1(33.3)	6.2-79.2	18(36.0)	24.1-49.9	1(33.3)	6.2-79.2	0(0.0)	0.0-49.0	9(33.3)	18.6-52.2	4(50.0)	21.5-78.5
Glucose(100 mg/dL)	15(28.3)	18.0-41.6	1(33.3)	6.2-79.2	12(24.0)	14.3-37.4	1(33.3)	6.2-79.2	0(0.0)	0.0-49.0	9(33.3)	18.6-52.2	1(12.5)	2.2-47.1

NCEP ATP-III* has Asian values for waist circumference

Table 2.12: Prevalence of metabolic syndrome(MetS) and its components among schizophrenic patients treated with monotherapy typical antipsychotics

	Haloperidol(n=8)		Perphenazine(n=10)		Sulpiride(n=11)		Trifluoperazine (n=3)		Chlorpromazine(n=19)		Flupenthixol decanoate (n=3)		Fluphenazine decanoate (n=3)	
							Typical antipsychotics							
MetS Prevalence	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI
NCEP ATP III*	3(37.5)	13.7-69.4	5(50.0)	23.7-76.3	5(45.5)	21.3-72.0	2(66.7)	20.8-93.9	9(47.4)	27.3-68.3	1(33.3)	6.2-79.2	2(66.7)	20.8-93.9
MetS components prevalence														
Waist circumference Male ≥90 cm , female ≥80 cm	4(50.0)	21.5-78.5	10(100)	72.3-100	10(90.9)	62.3-98.4	3(100.0)	43.9-100	12(63.2)	41.0-80.9	3(100.0)	43.9-100	3(100.0)	43.9-100
BP(≥130/85 mmHg)	1(12.5)	2.2-47.1	7(70.0)	39.7-89.2	3(27.3)	9.8-56.6	2(66.7)	20.8-93.9	6(31.6)	15.4-54.0	2 (66.7)	20.8-93.9	2(66.7)	20.8-93.9
HDL(male< 40 mg/dL ,female< 50mg/dL)	4(50.0)	21.5-78.5	6(60.0)	31.3-83.2	6(54.5)	28.0-78.7	1(33.3)	6.2-79.2	10(52.6)	31.7-72.7	1(33.3)	6.2-79.2	2(66.7)	20.8-93.9
Triglyceride (≥150mg/dL)	3(37.5)	13.7-69.4	5(50.0)	23.7-76.3	4(36.4)	15.2-64.6	1(33.3)	6.2-79.2	8(42.1)	23.1-63.7	1(33.3)	6.2-79.2	1(33.3)	6.2-79.2
Glucose(100 mg/dL)	2(25.0)	7.2-59.1	1(10.0)	1.8-40.4	3(27.3)	9.8-56.6	2(66.7)	20.8-93.9	6(31.6)	15.4-54.0	0(0.0)	0.0-56.2	1(33.3)	6.2-79.2

NCEP ATP-III* has Asian values for waist circumference

2 Prevalence of Metabolic Syndrome

In Table 2.13, there was statistically significant for all metabolic syndrome components between metabolic syndrome and non-metabolic syndrome groups (Waist circumference OR=34.8 (95% CI: 12.2, 99.4), HDL Cholesterol OR=5.4 (95% CI: 3.2, 9.2), TG OR= 8.6 (95% CI: 4.9, 15.2), BP- OR=5.5 (95% CI: 3.2, 9.3), FBS OR= 11.4 (95% CI: 5.5, 23.6).

Among the metabolic syndrome components, the prevalence of waist circumference was the highest in both metabolic syndrome and non-metabolic syndrome groups (98.4% vs. 50.7%) followed by HDL cholesterol (72.6% vs. 30.9%). The prevalence of fasting blood glucose was the lowest in both the metabolic syndrome and non-metabolic syndrome groups (51.6% vs. 6.2%).

There was statistically significant difference for median (Mann-Whitney U test) of fasting blood glucose, triglycerides and HbA1c between metabolic syndrome and non-metabolic syndrome groups. In addition, there was statistically significant difference for mean of waist circumference and HDL Cholesterol by gender. The mean waist circumference for male was higher than female in metabolic syndrome group (102.4 ± 9.8 cm vs. 96.7 ± 10.8 cm). There was also significant difference for mean for total cholesterol, systolic and diastolic blood pressure between metabolic syndrome and non-metabolic syndrome groups.

2 Prevalence of Metabolic Syndrome

Table 2.13: Prevalence of Metabolic Syndrome components according metabolic syndrome status

Metabolic Syndrome Component	Metabolic Syndrome(n=126)		Non Metabolic Syndrome(n=144)		Overall (n=270)		*p*
	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	
Waist circumference (Male ≥90 cm , female ≥80 cm)	124(98.4)	94.4-99.6	73(50.7)	42.6-58.7	197(73.0)	67.4-77.9	**p<0.001**
HDL[#] (Male< 40 mg/dL ,female < 50mg/dL)	90(72.6)	64.1-79.7	42(30.9)	23.7-39.1	132(50.8)	44.7-56.8	**p<0.001**
Triglyceride [#](≥150mg/dL)	84(67.7)	59.1-75.3	21(15.4)	10.3-22.5	105(40.4)	44.7-56.8	**p<0.001**
BP(≥130/85 mmHg)	77(61.1)	52.4-69.2	36(25.0)	18.6-32.7	113(41.9)	36.1-47.8	**p<0.001**
Fasting glucose(≥100 mg/dL)	65(51.6)	42.9-60.1	9(6.2)	3.3-11.5	74(27.4)	22.4-33.0	**p<0.001**
Laboratory test parameters		95% CI		95% CI		95% CI	
Fasting blood glucose(mg/dL)							
Mean(SD)	110.5(37.9)	103.9-117.2	89.2(21.3)	85.7-92.7	99.2(31.9)	95.3-103.0	
Median (Interquartile range)	100.8 (88.2-113.4)		86.4 (81.0-91.8)		90.0 (82.8-100.8)		**p<0.001****
Triglycerides (mg/dL)							
Mean(SD)	214.1(57.0)	185.5-242.6	116.9(57.0)	107.2-126.6	163.2(127.9)	147.6-178.9	
Median (Interquartile range)	171.8 (125.8-245.3)		113.8 (81.5-138.2)		132.9 (97.4-186)		**p<0.001****
HbA1c(%)							
Mean(SD)	6.4(1.7)	6.1-6.7	5.5(0.7)	5.4-5.6	5.9(1.3)	5.8-6.1	
Median (Interquartile range)	5.9 (5.6-6.5)		5.4 (5.2-5.8)		5.6(5.3-6.1)		**p<0.001****
	Mean(SD)	95% CI	Mean(SD)	95% CI	Mean(SD)	95% CI	
Total Cholesterol (mg/dL)	216.1(46.5)	207.8-224.3	202.2(41.3)	195.2-209.2	208.8(44.3)	203.4-214.2	**p<0.001***
LDL Cholesterol (mg/dL)	136.6(40.4)	129.1-144.0	131.1(40.4)	124.2-138.0	133.6(40.4)	128.6-138.6	P=0.287*
HDL Cholesterol(mg/dL)							
Male	37.9(6.8)	36.3-39.5	46.0(13.0)	43.3-48.6	42.5(11.5)	40.7-44.2	**p<0.001***
Female	44.5(10.7)	41.5-47.5	52.8(13.6)	48.5-57.1	48.2(12.7)	45.5-50.8	**P=0.001***
Other parameters	Mean(SD)	95% CI	Mean(SD)	95% CI	Mean(SD)	95% CI	
Waist circumference							
Male	102.4(9.8)	100.1-104.7	87.5(13.8)	84.7-90.2	93.9(13.9)	91.9-95.8	**p<0.001***
Female	96.7(10.8)	93.7-99.7	88.6(13.7)	84.4-92.8	91.7(13.1)	89.4-94.0	**P=0.002***
Systolic BP(mm Hg)	127.0(16.7)	124.0-130.0	117.4(17.4)	114.5-120.2	121.6(18.2)	119.7-123.6	**p<0.001***
Diastolic BP(mm Hg)	83.8(12.7)	81.6-86.1	77.1(11.9)	75.1-79.1	80.7(13.0)	79.3-82.1	**p<0.001***

Chi square test, *t-test ,** Mann-Whitney U test, [#]the denominator for Triglycerides and HDL Cholesterol N=260

2   Prevalence of Metabolic Syndrome

In Table 2.14 showed the prevalence of cardiovascular risk factors. The individual prevalences of each cardiovascular risk factor differed significantly between metabolic syndrome and non-metabolic syndrome groups were present of diabetes mellitus (OR=5.9, 95% CI: 2.4, 15.1), raised of total cholesterol (OR=1.8, 95% CI: 1.1, 3.0), reduction in HDL cholesterol (OR=2.9, 95% CI: 1.7, 5.1) and increased in diastolic blood pressure (OR=3.1, 95% CI: 1.7, 5.7).

Prevalence of patients with high and very high risk of CHD in 10 years (Framingham) in the metabolic syndrome group was 31.5% and 11.0% in the non-metabolic syndrome group. The difference was statistically significant. There was also statistically significant difference in the Framingham risk median score for metabolic syndrome and non-metabolic syndrome groups (6.5% vs. 4.0%, respectively). In the metabolic syndrome group, the mean of Framingham risk score was 7.6, which meant that about 7.6 of 100 people with this level of risk may have a heart attack in the next 10 years. In the non-metabolic syndrome group, the mean of Framingham risk score was 5.0, which meant about 5 of 100 people with this level of risk may have a heart attack in the following 10 years (Table 2.14).

2 Prevalence of Metabolic Syndrome

Table 2.14: Prevalence of CVRFs and CHD risk (Framingham) according to metabolic syndrome status

	Metabolic Syndrome(n=126)		Non Metabolic Syndrome(n=144)		Overall (n=270)		*p*
	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	
Cardiovascular risk factors(CVRFs)							
Age≥40(male) or≥45(female) years	58(46.0)	37.6-54.7	64(44.4)	36.6-52.6	122(45.2)	39.4-51.2	P=0.794
Smoker	29(23.0)	16.5-31.1	47(32.6)	25.5-40.7	76(28.1)	23.1-33.8	P=0.079
Diabetes (known diagnosis or glucose ≥126 mg/dL)	26(20.6)	14.5-28.5	6(4.2)	1.9-8.8	32(11.9)	8.5-16.3	**p<0.001**
Total cholesterol[#] ≥ 200 mg/dL	80(64.5)	55.8-72.4	68(50.0)	41.7-58.3	148(56.9)	50.9-62.8	**P=0.018**
HDL cholesterol[#] (male< 45 or female< 50mg/dL)	99(79.8)	71.9-86.0	78(57.4)	49.0-65.4	177(68.1)	62.2-73.4	**p<0.001**
SBP ≥140 or ≥ 130 mmHg (Diabetes ,prior cardiovascular or kidney disease)	28(22.2)	15.9-30.2	22(15.3)	10.3-22.1	50(18.5)	14.3-23.6	P=0.143
DBP ≥90 or ≥ 80 mmHg (Diabetes,prior cardiovascular or kidney disease)	42(33.3)	25.7-42.0	20(13.9)	9.2-20.5	62(23.0)	18.4-28.3	**p<0.001**
Risk of CHD in 10 years(Framingham)							
Mean (SD)	7.6(6.4)	6.5-8.8	5.0(4.4)	4.3-5.8	6.3(5.6)	5.6-7.0	
Median (Interquartile range)	6.5(2.5-11.0)		4.0 (1.0-7.0)		4.0 (1.0-9.0)		**p<0.001****
	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	
Patients with high & very high risk (≥10%) of CHD in 10 years (Framingham)	39(31.5)	23.9-40.1	15(11.0)	6.8-17.4	54(20.8)	16.3-26.1	**p<0.001**

Chi square test, *t-test,** Mann-Whitney U test, [#]the denominator for Total and HDL Cholesterol N=260

2 Prevalence of Metabolic Syndrome

Table 2.15: Demographics and Characteristics of Schizophrenia Patient with and without fasting blood investigation

Characteristics	Patients with Blood taken (n=270) n (%)	Patients without blood taken (n=55) n (%)	p value
Age(year)mean ± SD	39.9 ± 11.6	42.0± 11.5	P=0.225*
Age group (n =270)			
< 20[‡]	4(1.5)	0(0)	P=0.899
20 – 29	52(19.3)	9(16.4)	
30 – 39	84(31.1)	16(29.1)	
40 – 49	61(22.6)	14(25.5)	
50 – 59	53(19.6)	13(23.5)	
> 60	16(5.9)	3(5.5)	
BMI(kg/m^2) mean ± SD	27.0 ± 5.8	24.7± 5.1	**P=0.006***
BMI[¶](n =256)			
Underweight(<18.5)	14(5.2)	6(10.9)	P=0.083
Normal(18.5 – 24.9)	95(35.2)	23(41.8)	
Overweight(25 – < 30)	85(31.5)	19(34.6)	
Obese(≥ 30)	76(28.1)	7(12.7)	
Sex (n =270)			
Male[‡]	174(64.4)	23(41.8)	p=0.002
Female	96(35.6)	32(58.2)	
Race (n = 270)			
Malay[‡]	106(39.3)	9(16.4)	**P<0.001**
Chinese	102(37.8)	32(58.2)	
Indian	30(11.1)	12(21.8)	
others	32(11.8)	2(3.6)	
Marital status (n=259)			
Married[‡]	77(29.7)	17(30.9)	P=0.790
Single	160(61.8)	33(60.0)	
Divorced	14(5.4)	2(3.6)	
widowed	8(3.1)	3(5.5)	
Education level(n=234)			
No formal education[‡]	7(3.0)	1(2.3)	**P<0.001**
Primary	41(17.5)	6(14.0)	
Secondary	167(71.4)	21(48.8)	
Tertiary	19(8.1)	15(34.9)	
Occupation (n=249)			
Employed[‡]	88(35.4)	18(36.7)	P=0.843
Unemployed	150(60.2)	28(57.1)	
Housewife	11(4.4)	3(6.2)	
Care setting (n=270)			
General hospital[‡]	160(59.3)	54(98.2)	**P<0.001**
Institution	110(40.7)	1(1.8)	

Chi square test, *t-test, ‡ Reference group, BMI[¶] excluded underweight- Chi square test based on category normal (reference group), overweight and obese. Metabolic syndrome status was based on modified NCEP ATP III definition.
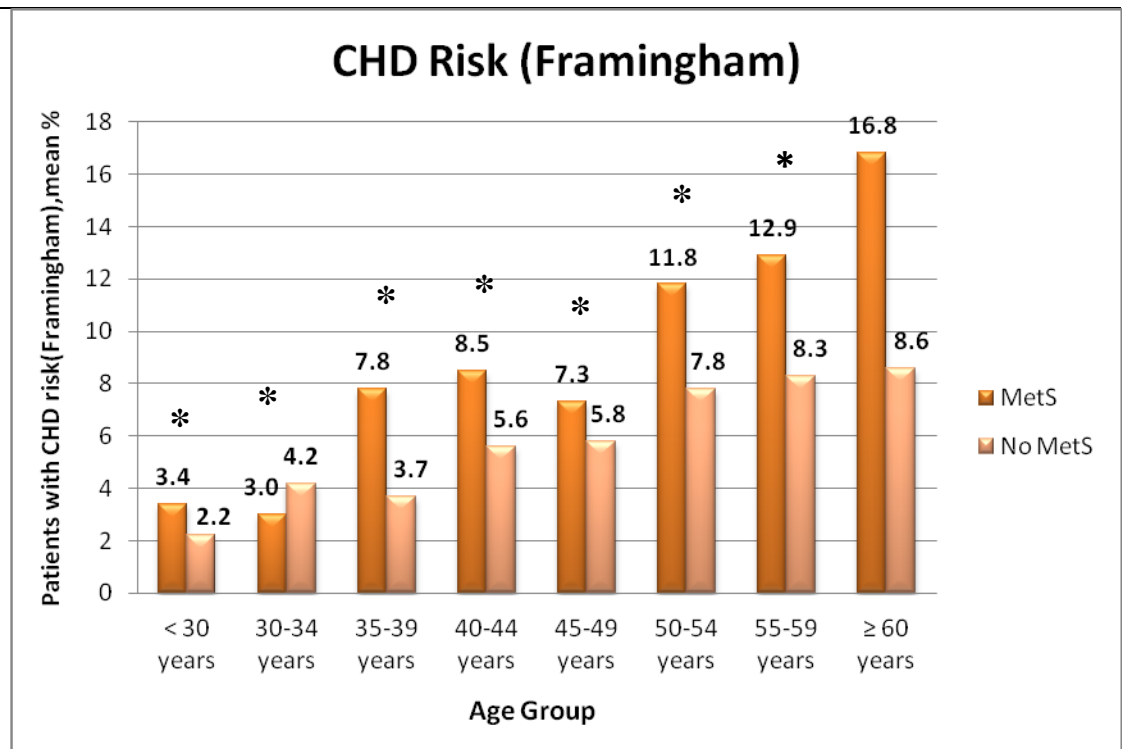
Figure 2.1 Risk score of CHD (Framingham) according to patients age group and metabolic syndrome status
*corrected by Bonferroni formula (p<0.008) for multiple comparisons and adjusted for sex, CHD - coronary heart disease, MetS – metabolic syndrome

There was greater increased of mean score of CHD risk for all age groups in the metabolic syndrome as compared to non-metabolic syndrome groups. The significant difference of mean score CHD risk was for all age group except for more than 60 years old (Figure 2.1).

2.5   Discussion

Prevalence of Metabolic Syndrome Treated with Antipsychotics

The main aim of this study was to estimate the prevalence of metabolic syndrome in schizophrenia patients who were treated with antipsychotic medications for at least one year. The results of the present study showed that 46.7% of the patients met the criteria for metabolic syndrome as defined by NCEP ATP III guidelines. This rate was considerably greater than the 34.3% prevalence found in the general Malaysian population (Mohamud et al.,2011) and the 10-20% prevalence reported among Asian population (Nestel et al.,2007).

The higher prevalence of metabolic syndrome among schizophrenia patients has been frequently reported in other studies. Study conducted by Cohn and colleagues (2004) found prevalence of 42.6% in the male patients and 48.5% female patients using the same criteria. A Japanese study reported the prevalence of 48.1% of metabolic syndrome in outpatient with schizophrenia (Sugawara et al.,2011).

There were several reasons why schizophrenia was associated with higher rate of the metabolic syndrome. Certain lifestyles, such as sedentary habits, high-fat and high-carbohydrate diets, were common in people with severe mental illness and were associated with the metabolic syndrome (Brown et al.,1999; Davidson et al.,2001a). Schizophrenia might also predispose individuals to physiological changes that increased the risk of developing metabolic syndrome, e.g. abnormalities in glucose regulation with a pattern of insulin resistance, which have been described in schizophrenic patients even before the development of the illness and the use of antipsychotic agents (Kasanin,1926; Meduna et al.,1942). Some antipsychotics were also associated with higher rates of developing metabolic syndrome. These medications may cause weight gain or changes in the blood pressure, cholesterol and

blood sugar level (Fenton and Chavez,2006). Atypical antipsychotics had been associated with increased risk of hyperglycaemia and impaired glucose level, and subsequently increased the risk of metabolic syndrome (Kamran et al.,1994; Ober et al.,1999; Newcomer et al.,2002). In the present study 42.2% of the olanzapine patients, 32.8% of the patients on risperidone and 17.2% of the patients on paliperidone had metabolic syndrome.

Cardiovascular Risk

The results of the present study showed that the presence of metabolic syndrome was associated with high coronary heart disease risk. We found a significant difference in the cardiovascular risk between patients with and without metabolic syndrome. The data obtained in our study appeared to be consistent with that to the Cardiovascular, Lipid and Metabolic Outcomes Research in Schizophrenia Study in Spain (Bobes et al.,2007), which reported high cardiovascular risk in patients treated with antipsychotic drugs as defined by the Framingham score. Further, in a study of 367 adults treated with atypical antipsychotics, Correll et al (2006) reported that the metabolic syndrome was present in 137 (37.3%) of patients and was significantly associated with the 10-year risk of CHD events. In addition, Holt el al (2010) found 12% of the study patients had a greater than 20% risk of a CHD event within the next 10 years.

Metabolic Syndrome Component

In our study, we observed statistically significant difference for all metabolic syndrome components between metabolic syndrome and no-metabolic syndrome groups. Notably, the mean fasting blood sugar level in the metabolic syndrome group was clearly impaired while the mean fasting blood sugar for the non-metabolic syndrome group was normal (110.5 mg/dL vs. 89.2 mg/dL). The male patients in the

non-metabolic syndrome group had normal mean HDL cholesterol level compared to those in the metabolic syndrome group. Further, the mean triglyceride level in the metabolic syndrome group almost doubled that of the non-metabolic syndrome group (214.1 mg/dL vs. 116.9 mg/dL).

The most common findings in our patients with metabolic syndrome were abnormal waist circumference (98.4%), followed by low HDL cholesterol level (72.6%), raised triglyceride level (67.7%) and elevated blood pressure (61.1%).While elevated fasting blood glucose was the least frequent abnormality. Our data substantiates the findings from study by Kato and colleagues (2004), where the most common metabolic syndrome criteria reported in their study population were abnormal waist circumference, followed by dyslipidemia and elevated blood pressure, while the least prevalent metabolic component was elevated fasting blood glucose.

Mental health professionals should consistently measure and monitor waist circumference and blood pressure, two components of metabolic syndrome, which are easily assessed in clinic setting. In our sample, 98.4% of patients with metabolic syndrome had abnormal waist circumference and 61.1% had elevated blood pressure. Abnormalities of either waist circumference or blood pressure warrant screening for other components of the syndrome.

Body Mass Index (BMI)

The mean BMI was significantly higher in patients with metabolic syndrome compared to those without metabolic syndrome (p<0.05), with the mean BMI value of 29.4 ± 5.1 kg/m^2 in patients with metabolic syndrome. When our patients were categorised according to weight status, there was statistically significant higher proportion of overweight (39.7% vs. 24.3%) and obese patients (40.5% vs. 17.4%) in the metabolic syndrome groups than in the non-metabolic syndrome groups. These results concurred with the findings from the Cardiovascular, Lipid and Metabolic Outcomes Research in Schizophrenia Study (CLAMORS) (Bobes et al.,2007) in which the prevalence of general obesity and abdominal adiposity was also high in their schizophrenia outpatients with metabolic syndrome. The study recorded a two-fold higher rate of obesity in metabolic syndrome subjects compared to non-metabolic syndrome subjects (55.2% vs. 22.7%). The high prevalence of obesity and abdominal adiposity in our study also corroborates the data from the CATIE study (McEvoy et al.,2005).

Limitations

The current study has few limitations. Firstly, it was a cross sectional study. Although the metabolic syndrome was frequent in this group of patients, causal pathway could not be inferred. Secondly, there was no reference population without psychopathology. However, there were national rates available from the nationwide survey (Mohamud et al.,2011). Thirdly, the prevalence of hypertension, diabetes mellitus and hyperlipidemia after initiation of antipsychotics were described with current antipsychotics used, however this might be not true as the mean duration of schizophrenia about 10 years, and patients were on several antipsychotics before current antipsychotics. Nevertheless, if the current antipsychotics have property of

metabolic syndrome neutral and the duration of treatment for at least one year, it should be sufficient to observe the reversibility of the metabolic syndrome parameters causing by previous antipsychotics.

Despite these limitations, our findings were consistent with higher rate of the metabolic syndrome found in the schizophrenia population.

2.6 Conclusions

The prevalence of metabolic syndrome in schizophrenia patients receiving antipsychotic in Malaysia was very high. Our data adds to the mounting evidence that schizophrenia patients are at increased risk for developing metabolic syndrome. The high prevalence of the syndrome underscores an urgent need to formulate a comprehensive intervention measures to combat these problems.

Chapter THREE: Randomized Controlled Trial of the Safety and Efficacy of Aripiprazole Vs Ziprazidone in Schizophrenic Patients with Metabolic Syndrome

3.1 Abstract

Introduction: Atypical antipsychotics were reported to be associated with increased risk of hyperglycaemia and hyperlipidemia, and subsequently increase the risk of the metabolic syndrome. However, aripiprazole and ziprasidone have a favourable metabolic profile.

Objectives: i) To determine the improvement and reversibility of metabolic syndrome, its components and lipid profiles after switching to aripiprazole or ziprasidone. ii) To determine the safety and efficacy of aripiprazole and ziprasidone in the treatment of schizophrenia patients with metabolic syndrome.

Methodology:

Design: This was a double blind randomized controlled trial.

Setting: The study was conducted at four mental institutions and four general hospitals.

Patients: Study population were patients aged between 18 and 65 years old, with a current Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision (DSM-IV TR) diagnosis of schizophrenia.

Intervention: Eligible patients were randomised either to aripiprazole or ziprasidone. The dose of aripiprazole and ziprasidone, can be either increased or reduced based on clinical assessment. The total daily dosage of ziprasidone ranges from 80mg - 160mg.The total daily dosage of aripiprazole ranges from 10mg - 30 mg.

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Measures: Metabolic syndrome was defined by using the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria-modified for Asian waist circumference. For baseline and follow-up evaluation, the outcome measures included body mass index (BMI), waist circumference, blood pressure (BP), fasting blood sugar (FBS), lipid profile, adverse effects monitoring and clinical rating scale such as Positive and Negative Symptoms Scale (PANSS), Clinical Global Impression Scale (CGI), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathasia Scale (BAS) and Simpson Angus Scale (SAS). Intention-to-treat was used for the data analysis. Generalized Estimating Equation (GEE) and Mixed-Effects Model Repeated-Measures (MMRM) analysis was utilized to examine changes in outcome measures over time with the treatment of aripiprazole and ziprasidone.

Results: A total of 527 schizophrenia patients were screened, 175 patients were recruited for the study. 51.4% (90/175) of patients was randomized to aripiprazole and 48.6% (85/175) to ziprasidone. There was improvement in the prevalence of metabolic syndrome from baseline to 6-month after switching to aripiprazole or ziprasidone; (aripiprazole 58.9% vs. 30.0%, ziprasizone 51.8% vs. 15.3%, p<0.05), 14.4% of patients had resolved metabolic syndrome after switching to aripiprazole and 18.8% of patients had resolved metabolic syndrome after switching to ziprasidone. There was improvement in the prevalence of all metabolic syndrome component from baseline to 6-month after switching to aripiprazole or ziprasidone; waist circumference (aripiprazole 84.4% vs. 44.4%, ziprasizone 87.1% vs. 35.3%), HDL cholesterol (aripiprazole 54.4% vs. 33.3%, ziprasizone 52.9% vs. 23.5%), triglycerides (aripiprazole 50.0% vs. 21.1%, ziprasizone 37.6% vs. 12.9%), BP (aripiprazole 41.1%

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vs. 25.6%, ziprasizone 32.9% vs. 20.0%) , FBS (aripiprazole 42.2% vs. 20.0%, ziprasizone 25.9% vs. 8.2%, p<0.05). There was statistically significant improvement in PANSS, CGI, BARS and SAS after switching to aripiprazole or ziprasidone. The commonest side effects reported were EPS and insomnia for both treatment groups.

Conclusion: Switching to aripiprazole or ziprazidone was effective in reversing the metabolic syndrome and its components among schizophrenia patients who had metabolic syndrome. Aripiprazole and ziprasidone were efficacious and safe in the treatment of schizophrenia patients with metabolic syndrome.

Keywords: Randomized controlled trial, schizophrenia, aripiprazole, ziprasidone, safety, efficacy.

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3.2 Introduction

It has been known that patients with schizophrenia were at greater risk for type 2 diabetes, cardiovascular disease (CVD) and early mortality associated with CVD, as compared to the general population (Osborn et al.,2008; Hennekens,2007; Roshanaei-Moghaddam and Katon,2009). Numerous reports have also associated the development of insulin resistance (Houseknecht et al.,2007; Chintoh et al.,2009) and type 2 diabetes (Jin et al.,2004; Smith et al.,2008) with long-term treatment with certain atypical antipsychotic drugs.

Not all antipsychotic agents carry the same adverse metabolic risk. Of the atypical antipsychotics, aripiprazole and ziprasidone were associated with a lower metabolic risk (ADA-APA-AACE,2004; Newcomer,2005). Both ziprasidone and aripiprazole were known to be the second generation atypical antipsychotics that were least likely to cause dyslipidaemia, and in fact might improve the lipid profile of patients switched from another antipsychotic drug to one of these agents (Spurling et al.,2007; Greenberg and Citrome,2007).

Therefore, switching patients with schizophrenia who require long-term treatment with antipsychotic drugs to either aripiprazole or ziprasidone appeared to be a rational choice to lessen the metabolic effects (e.g. obesity, hyperglycaemia, dyslipidaemia) induced by the antipsychotics. The evidence for supporting this strategy has mostly come from small observational studies (Alptekin et al.,2009; Schorr et al.,2008; Takeuchi et al.,2010), short-term randomised studies (Pae et al.,2009), retrospective chart review (Spurling et al.,2007), or post-hoc analysis of pooled data from randomised efficacy trials (Weiden et al.,2003; Weiden et al.,2008).

In particular, switching to aripiprazole or ziprasidone from antipsychotics with greater tendency to cause weight gain and metabolic dysregulation (e.g. olanzapine, clozapine,

quetiapine) has been shown to reduce body weight, triglyceride and LDL-cholesterol levels (Weiden et al.,2008; Casey et al.,2003; Cetin and Karagozoglu,2007; Montes et al.,2007; Newcomer et al.,2008). More recently, the results from a 12-month, prospective, randomised, open-label study by Chen et al (2012) suggested that, switching existing antipsychotic treatment to either aripiprazole or ziprasidone in stable patients with schizophrenia, schizoaffective disorder or bipolar disorder improved the metabolic profile of those patients over the long-term.

3.2.1 Atypical Antipyschotics: Aripiprazole and Ziprasidone

3.2.2. Aripiprazole

Aripiprazole, the sixth atypical antipsychotic of its kind, was approved by the Food and Drug Administration (FDA) in 2002 for the treatment of schizophrenia. It later also received FDA approval for the treatment of acute manic and mixed episodes associated with bipolar disorder, as well as treatment of depression (BMS,2007). The introduction of aripiprazole, which was classified as a D_2 partial agonist, was an interesting development in this area of schizophrenia treatment.

3.2.3 Pharmacology

Aripiprazole was chemically characterised as a quinolinone derivative. The clinical benefits of aripiprazole in treating schizophrenia could be attributed partly to the drug's unique mechanism of action on dopamine and serotonergic receptors. While all previously available antipsychotics were antagonists at D_2 receptors, aripiprazole was said to be a partial agonist at these receptors (Burris et al.,2002), exhibiting both pre-synaptic dopamine autoreceptor agonistic activity and post-synaptic D_2 antagonistic activity (Kikuchi et al.,1995). When dopamine levels were high (e.g. in the limbic regions in schizophrenia), aripiprazole acted as an antagonist, while at the same time

worked as an agonist in other regions where dopamine levels were low (e.g. in the prefrontal cortex in schizophrenia). For this reason, aripiprazole was also claimed to be a 'dopamine stabilizer' (Stahl,2001).

Although it was commonly believed that aripiprazole mediates its antipsychotic through partial agonism at the D_2 dopamine receptor, it was more likely that its primary mechanism of action was functional selectivity at the D_2 receptor (Urban et al.,2007). Studies have shown that aripiprazole has an affinity about 100 times higher for D_2 than D_1 receptors in rat stratium *in vitro* (Inoue et al.,1997), and has a high affinity for the D_2 receptor (Burris et al.,2002). Some type of differential modulation of dopaminergic activity might also occur in the mesolimbic, mesocortical, and basal ganglia target fields in the brain (Tanahashi et al.,2012).

Besides its functional selectivity at the D_2 receptor, aripiprazole was also an antagonist at the serotonin $5\text{-}HT_{2A}$ receptors (Burris et al.,2002), a common trait of all atypical antipsychotics, as well as a partial agonist at the serotonin $5\text{-}HT_{1A}$ receptors (Jordan et al.,2002). The $5\text{-}HT_{2A}$ antagonism was one potential mechanism by which aripiprazole (and all atypical antipsychotic agents) helped alleviate negative symptoms associated with schizophrenia (e.g. flattened affect, alogia, anhedonia, emotional and social withdrawal). It has also been reported that $5\text{-}HT_{2A}$ blockade might offer certain amount of protection from the extrapyramidal symptoms associated with extensive D_2 blockade (Kapur and Remington,1996; Meltzer et al.,1989). High-affinity blockade of D_2 receptors and increased in D_2 receptor density were thought to be associated not only with undesirable extrapyramidal symptoms (EPS), but also with the development of tardive dyskinesia (Blanchet et al.,2012).

The $5\text{-}HT_{1A}$ agonistic action of aripiprazole, on the other hand, might offer extra help in mediating EPS when D_2 blockade was complete. This was accomplished through

the inhibitory actions on serotonergic neurons, which lead to an increased in dopaminergic transmission in the stratium, thus reducing EPS (Jordan et al.,2002). This pharmacological action of aripiprazole has led some specialists to describe this drug as the first of a new class of atypical antipsychotic agents, termed 'dopamine-serotonin system stabilizer' (McQuade et al.,2004). As for other neuroreceptors, aripiprazole exhibited moderate affinity for histamine and alpha-adrenergic receptors, and no appreciable affinity for cholinergic muscarinic receptors (Green,2004).

3.2.4 Pharmacokinetics

i) Absorption and distribution

Aripiprazole displayed linear kinetics, with its steady-state plasma concentrations achieved after 2 weeks with once-daily dosing. After multiple oral doses, maximum plasma concentration (C_{max}) occurs 3-5 hours after administration without food (Molden et al.,2006).

The bioavailability of aripiprazole oral tablets was about 90%. Administration with food does not significantly affect C_{max} or area under the curve (AUC), but delay the time to reach C_{max} by 3 hours for the parent compound, and by 12 hours for dehydroaripiprazole, its major metabolite (Bristol-Myers,2002).

Aripiprazole and dehydroaripiprazole were 99% protein-bound at therapeutic concentrations (Molden et al.,2006). No clinically relevant effects of aripiprazole on the pharmacokinetics of warfarin (a highly protein-bound drug) have been reported when the two agents were administered concurrently (Bristol-Myers,2002).

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ii) Metabolism and Elimination

Aripiprazole has undergone extensive hepatic metabolisation, with a mean terminal half-life of 60 hours (range 48-68 hours) 14 days after administration. Aripiprazole has an elimination half-life of approximately 75 hours (Winans,2003). The active major metabolite of aripiprazole was dehydroaripiprazole, with elimination half-life of about 94 hours. The parent compound was excreted only in traces – less than 1% and 18% eliminated in the urine and faeces, respectively (Winans,2003; Molden et al.,2006).

Aripiprazole was metabolised via three pathways: dehydrogenation, hydroxylation and N-dealkylation. Cytochrome P450 (CYP) enzymes 3A4 and 2D6 were responsible for the dehydrogenation and hydroxylation processes, while N-dealkylation appears to be catalyzed solely by CYP3A4. At steady state, dehydroaripiprazole, the major metabolite, represents about 40% of the AUC and has an affinity similar to that of aripiprazole for D_2 receptors (Bristol-Myers,2002).

In poor metabolisers of CYP2D6, aripiprazole plasma concentration increased by about 80%, while dehydroaripiprazole decreased by 30%. In patients with mild and moderate hepatic insufficiency, AUC of aripiprazole increased by 31% and 8%, respectively. However, AUC of aripiprazole decreased by 20% in those with severe hepatic insufficiency. In patients with severe renal impairment (creatinine clearance <30 ml/min), the AUC for aripiprazole was decreased by 15%, and for dehydroaripiprazole was increased by 7%. These differences observed in patients with renal or hepatic impairment, however, did not warrant dosage adjustments (Bristol-Myers,2002).

iii) Drug Interactions

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Results from *in vivo* studies support *in vitro* findings that aripiprazole did not affect pharmacokinetic parameters of drugs metabolized by CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dosages of aripiprazole 10-30 mg/day showed no significant effects on metabolism of dextromethorphan (CYP2D6 and CYP3A4 substrate), warfarin (CYP2C19 and CYP2C9 substrate) or omeprazole (CYP2C19 substrate) (Bristol-Myers,2002).

Administration of aripiprazole after 13 days of administration of the potent CYP2D6 inhibitor quinidine (166mg/day) increased the AUC of aripiprazole by 112% and of dehydroaripiprazole by 52%. The AUC also increased by 63% and 77% for aripiprazole and dehydroaripiprazole, respectively, after administration of ketoconazole (200 mg/day), a potent CYP3A4 inhibitor (Bristol-Myers,2002).

Population pharmacokinetic analysis of data from several phase II and III studies did not demonstrate any clinically relevant effects from co-administration of substrates and inhibitors of CYP2D6 and CYP3A4 on aripiprazole pharmacokinetics. However, the manufacturer recommended reducing the dosage of aripiprazole to half the normal dosage when administered concomitantly with ketoconazole or quinidine (Bristol-Myers,2002).

Co-administration of carbamazepine, a potent CYP3A4 inducer, with aripiprazole resulted in decreased of approximately 70% in C_{max} and AUC of both aripiprazole and dehydroaripiprazole. Adding carbamazepine to aripiprazole would necessitate doubling the aripiprazole dosage; further dosage adjustments should be based on clinical evaluation (Bristol-Myers,2002).

Co-administration of aripiprazole with valproate at steady state resulted in a 25% decrease in C_{max} and AUC of aripiprazole. Lithium did not show any substantial effects on aripiprazole pharmacokinetics (Citrome et al.,2005).

iv) Dosage and administration

The recommended dosage of aripiprazole for an acute exacerbation of schizophrenia was 10-30 mg/day administered as a single daily dose, with or without food (Bristol-Myers,2002).

3.2.5. Side effects

Standard dosages of aripiprazole 10-30 mg/day were generally well tolerated. The tolerability profile of aripiprazole was broadly similar to that observed with placebo in short-term trials in patients with acute relapse of schizophrenia or schizoaffective disorder, as well as in a 26-week trial in patients with chronic stable schizophrenia (Swainston Harrison and Perry,2004).

The most common side effects of aripiprazole reported in patients with schizophrenia and schizoaffective disorder include:

- Headache
- Agitation
- Anxiety
- Insomnia
- Dyspepsia
- Nausea
- Light headedness
- Blurred vision
- Akathisia

i) EPS

Aripiprazole was generally associated with a placebo-level incidence of EPS and EPS-related adverse events. In a 52-week trial, there were significantly fewer aripiprazole recipients experiencing EPS-related adverse events compared with haloperidol recipients. Changes in severity of EPS were minimal and usually no different from those observed with placebo.

There was also less severe EPS in aripiprazole-treated patients than in haloperidol-treated patients in a long-term trial. In short-term trials, treatment-emergent tardive dyskinesia was reported in only 0.2% of patients receiving aripiprazole, an incidence comparable to that seen in placebo recipients (0.2%) (de Oliveira et al.,2009).

ii) Cardiovascular and metabolic effects

Studies have shown that aripiprazole has a low propensity to cause clinically significant weight gain, prolactin elevation or corrected QT (QTc) interval prolongation in patients with schizophrenia or schizoaffective disorder. There were also no clinically marked differences in mean changes from baseline in diabetes and dyslipidaemia parameters between aripiprazole-treated patients or placebo recipients in a 26-week, placebo-controlled trial (Swainston Harrison and Perry,2004).

3.2.6 Clinical trials on efficacy and tolerability

The efficacy and tolerability of aripiprazole has been demonstrated in patients with schizophrenia or schizoaffective disorder. Multicentre clinical trials indicated aripiprazole to be well tolerated and significantly more efficacious than placebo and comparable with other atypical antipsychotics (Kane et al.,2002; Bowles and Levin,2003; Potkin et al.,2003).

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i)   Short-term studies

Short-term clinical trials showed that, when compared with placebo, treatment with aripiprazole (10-30 mg/day) led to significant improvement in positive and negative symptom scores, as well as in Clinical Global Impression Severity of Illness (CGI-S) scores, in patients with acute relapse of chronic schizophrenia or schizoaffective disorder.   Aripiprazole has also been shown to significantly more effective than placebo in reducing relapse rate in patients with stable chronic schizophrenia in a 26-week, randomised trial (Swainston Harrison and Perry,2004).

A 4-week, double-blind, randomised study comparing aripiprazole (15 mg/day) and risperidone (6 mg/day) was conducted in Chinese patients with schizophrenia or schizoaffective disorder in Taiwan. Results showed that both the aripiprazole and risperidone groups showed statistical improvement from baseline in Positive and Negative Syndrome Scale (PANSS) total, PANSS positive, PANSS negative and CGI-S scores at study endpoint ($p < 0.001$). However aripiprazole was associated with significantly less EPS liability ($p < 0.005$) and less serum prolactin level elevation than risperidone ($p < 0.001$) (Chan et al.,2007).

ii)   Long-term studies

A 26-week, multicentre, randomised, double-blind study was conducted to compare aripiprazole and olanzapine in patients with schizophrenia who were in acute relapse and required hospitalisation. While both treatment groups achieved comparable clinically meaningful improvements on efficacy measures, a greater proportion of patients in the olanzapine group exhibited clinically significant weight gain as compared with the aripiprazole group. By end of study, 37% of olanzapine recipients had experienced significant weight gain compared with 14% of aripiprazole recipients

(p<0.001). In fact at week 26, there was a mean weight loss of 1.37 kg with aripiprazole compared with a mean increase of 4.23 kg with olanzapine among patients who remained on therapy (p<0.001). Changes in fasting plasma levels of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were also significantly different between the two treatment groups, with worsening of the lipid profile among olanzapine-treated patients. The observed effects on weight and lipids indicate a potentially lower metabolic and cardiovascular risk in patients treated with aripiprazole compared with those treated with olanzapine (McQuade et al.,2004).

When compared with olanzapine (10-15 mg/day) in a non-blind, 26-week trial, patients with chronic schizophrenia receiving aripiprazole (30mg/day) experienced similar (general cognitive function) or better (verbal learning) changes from baseline in the neurocognitive parameters as compared with olanzapine-treated patients (Swainston Harrison and Perry,2004).

When compared with haloperidol in a 52-week trial involving patients with acute relapse of schizophrenia, the response rates at study end was higher in the aripiprazole group (77%) than in the haloperidol group (73%) (Swainston Harrison and Perry,2004).

Clearly, aripiprazole has an apparent advantage over existing antipsychotics in terms of safety and tolerability (Bowles and Levin,2003; Marder et al.,2003; Crismon et al.,2003), given its beneficial profile in terms of a low potential for body weight gain and changes in metabolic indices.

3.2.7 Ziprasidone

Ziprasidone was the fifth atypical antipsychotic to gain FDA approval in February 2001. In the United States, ziprasidone was approved for the treatment of

schizophrenia. The intramuscular injection form of ziprasidone was approved for acute agitation in schizophrenic patients. Ziprasidone has also received approval for acute treatment of mania and mixed states associated with bipolar disorder (FDA,2001).

3.2.8 Pharmacology

Ziprasidone was an antipsychotic with combined dopamine and serotonin receptor antagonist activity. It also has a high affinity for alpha-adrenergic receptors and a medium affinity for histamine receptors. The exact mechanism of action of ziprasidone was unknown. However, it was believed that the drug's antipsychotic activity was mediated primarily by antagonism at dopamine receptors, specifically D_2 (Seeger et al.,1995).

The most potent action of ziprasidone was at the 5-HT_{2A} site. This atypical antipsychotic has perhaps the most selective affinity for 5-HT_{2A} receptors compared with most clinically available antipsychotic agents. This powerful antagonism of 5-HT_{2A} receptors in the brain might limit the EPS associated with dopamine receptor blockade and also improved efficacy against negative symptoms of schizophrenia (Seeger et al.,1995).

On the other hand, antagonism at histaminic and alpha-adrenergic receptors was likely to explain some of the side effects of ziprasidone (e.g. sedation, orthostasis) (Green,2001). Ziprasidone has weak anticholinergic activity, suggesting a low potential for impairing cognitive abilities (Byerly et al.,2001). This might indicate an advantage in the elderly who were prone to anticholinergic cognitive effects.

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3.2.9 Pharmacokinetics

i)   Absorption and distribution

Ziprasidone tended to show linear pharmacokinetics. The mean C_{max} and AUC increased with increasing dose, with apparent dose-proportionality between the 20 mg and 60 mg dose levels (Miceli et al.,2000).

The systemic bioavailability of ziprasidone was 100% when administered intramuscularly. Ziprasidone was well absorbed after oral administration, reaching peak plasma concentrations in 6 to 8 hours. The absolute bioavailability of a 20 mg dose under fed conditions was approximately 60%. In the presence of food, the absorption of ziprasidone was increased up to two-fold. The mean terminal half-life of ziprasidone was about 7 hours within the proposed clinical dose range (FDA,2006).

After a single dose intramuscular administration, the peak serum concentration typically occurred at about 60 minutes or earlier. Steady-state plasma concentrations were achieved within 1-3 days. Exposure increased in a dose-related manner and following 3 days of intramuscular dosing, little accumulation was observed (FDA,2006).

Ziprasidone absorption was not optimally achieved when administered without food. The bioavailability of the drug was only 50%-60% when administered without food. At lower doses, ziprasidone might have a higher affinity for the serotonin and norepinephrine transmitter systems. This might be a risk factor for mania when used in patients with bipolar disorder. No dose adjustment was required in patients with mild-to-moderate renal impairment or mild-to-moderate hepatic impairment (FDA,2006).

ii)   Metabolism and elimination

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Ziprasidone was highly protein-bound (> 99%) and was hepatically metabolised by aldehyde oxidase. The drug was thoroughly metabolised with <1% being excreted unchanged in faeces or urine. Ziprasidone did not change into active metabolites. Ziprasidone was primarily metabolised by CYP3A4 in human liver microsomes and did not, at clinically effective doses, appeared to mediate drug interactions with simultaneously administered CYP substrates (FDA,2006).

One study on extensive metaboliser subjects found that ziprasidone did not inhibit the clearance of drugs metabolised by the 2D6 isoenzyme of cytochrome P450 (CYP2D6). Unlike clozapine and olanzapine, ziprasidone was not metabolised by CYP1A2, and cigarette smoking (a CYP1A2 inducer) was unlikely to affect its metabolism (Wilner et al.,2000).

iii)   Drug interactions

Medications that induced (e.g. carbamazepine) or inhibited (e.g. ketoconazole) CYP3A4 have been shown to decrease and increase, respectively, blood levels of ziprasidone (FDA,2006). There were no significant interactions with lithium in healthy subjects taking a moderate dose of lithium and ziprasidone.(Apseloff et al.,2000) The drug has also no interaction with aluminium and magnesium hydroxide antacids or cimetidine (FDA,2006).

iv)   Dosage and administration

Ziprasidone was available in oral and intramuscular forms for administration. The oral form of ziprasidone was the hydrochloride salt, ziprasidone hydrochloride, while the intramuscular form was the mesylate salt, ziprasidone mesylate trihydrate, which was provided as a lyophilized powder (FDA,2006).

3 RCT Aripirazole vs. Ziprasidone

Initial evidence suggested an effective dosage range of ziprasidone at 80-160 mg/day (Daniel et al.,1999). Rapid-acting intramuscular fixed doses of ziprasidone at 5-20 mg have also been well tolerated , and not associated with EPS, dystonia or excessive sedation (Green,2001).

3.2.10 Side effects

Ziprasidone was generally well tolerated. The most frequent side-effects associated with ziprasidone were (Daniel et al.,1999):

- Mild or moderate headache

- Mild dyspepsia

- Nausea

- Dizziness

- Transient somnolence

Ziprasidone was shown to have a very low liability for inducing movement disorders and weight gain (Daniel et al.,1999). According to a meta-analysis study, weight gain attributable to ziprasidone therapy was only 0.44 kg on average (Allison et al.,1999). Another systematic review also concluded that ziprasidone did not appear to be linked to weight gain (Taylor and McAskill,2000). A Cochrane review for ziprasidone by Bagnall et al (2000) concluded that ziprasidone might be an effective antipsychotic with less EPS than haloperidol, but it also might cause more nausea and vomiting.

Ziprasidone also has important advantages in the sense that it was not associated with clinically significant adverse changes in cholesterol, triglycerides or glycemic control. In fact, patients might experience moderate improvement in these measures when switching to ziprasidone from a different antipsychotic agent. The tolerability profile

of ziprasidone might thus be quite valuable in the treatment of some patients (Greenberg and Citrome,2007).

Ziprasidone was associated with transient prolactin elevation, which was not dose related, and which attenuates as treatment continues (Miceli et al.,2000). Ziprasidone was not anticholinergic, and therefore only infrequently causes EPS or postural hypotension (Greenberg and Citrome,2007).

Nevertheless, ziprasidone has been associated with an increased mortality in elderly patients with dementia-related psychosis. It might also prolong the electrocardiogram QTc interval in some patients, and increases the risk of a type of heart arrhythmia known as torsades de pointes. As such, it has been advised that ziprasidone should be used cautiously in patients simultaneously taking medication that were likely to interact with ziprasidone or increase the QTc interval (FDA,2006).

3.2.11 Clinical trials on tolerability and efficacy

The efficacy and tolerability of ziprasidone has been demonstrated in a number of studies involving patients with schizophrenia or schizoaffective disorder. When compared with chlorpromazine and haloperidol, ziprasidone appeared to have some limited clinical advantages over the two typical antipsychotics in ameliorating negative symptoms of schizophrenia (Greenberg and Citrome,2007).

Ziprasidone has also demonstrated comparable antipsychotic efficacy to other atypical antipsychotics, but exhibited a more favourable metabolic parameter profile (Greenberg and Citrome,2007; G. M. Simpson et al.,2004; Bartko et al.,2006).

i)   Short-term studies

3 RCT Aripirazole vs. Ziprasidone

Ziprasidone was compared with olanzapine in a 6-week, multicentre, double-blind, parallel-design and flexible-dose trial. The study results showed that, while both antipsychotics were efficacious in improving symptoms and global illness severity, and were well tolerated, ziprasidone was less associated with changes in the metabolic parameters compared with olanzapine. Body weight, total cholesterol, triglycerides and low-density lipoprotein cholesterol were noted to significantly increase in the olanzapine group, but not in the ziprasidone group. Olanzapine, but not ziprasidone, was also associated with significant increased in fasting insulin level (G. M. Simpson et al.,2004).

Another short-term 8 weeks randomised, double-blind study compared ziprasidone (40-80 mg b.i.d) with risperidone (3-5 mg b.i.d) in patients with acute exacerbation of schizophrenia and schizoaffective disorder. Again, both agents were comparable in terms of improving psychotic symptoms and tolerability. However, ziprasidone demonstrated a lower Movement Disorder Burden score and fewer incidence of prolactin elevation and clinically relevant weight gain compared with risperidone (Addington et al.,2004).

ii)   Long-term studies

Ziprasidone has been shown to be well tolerated and beneficial for long-term treatment in terms of improving severity of symptoms and general functioning in patients undergoing usual care.

In an open-label, large-scale, naturalistic trial conducted by Ratner et al(2007) unstable schizophrenia patients with persistent symptoms or troublesome side effects were treated with ziprasidone (40-160 mg/day) for 12 months. Improvement in PANSS factors and global functioning was observed among patients who had

completed the study. The response rate remained high at 43.8% when a cut-off of 20% improvement of PANSS total scores was used. The most common side effects of ziprasidone were fatigue, sleep disturbances and headache, but the treatment did not appear to be associated with weight gain.

In Phase 2 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) for schizophrenia, ziprasidone did not match the clinical performance of olanzapine and risperidone, but appeared to be comparable to quetiapine in overall effectiveness. The researchers suggested that the rate of dose titration and the dose achieved might have an important influence on the efficacy profile of ziprasidone (Greenberg and Citrome,2007).

iii)   Switch studies

Studies looking at switching from other antipsychotics to ziprasidone have also demonstrated improvements of psychopathology and negative symptoms in schizophrenia patients.

A study by Daniel et al(1999) looked at switching from olanzapine to ziprasidone in 58 outpatients over a short period. They found that ziprasidone was associated with improvements in attention, vigilance, verbal learning and memory after 6 weeks of therapy with ziprasidone.

 In patients with schizophrenia who were already treated with conventional or other atypical antipsychotics, but had to be switched due to unsatisfactory efficacy or poor tolerance, a 12-week therapy with ziprasidone resulted in significant improvements on all major symptoms measures and subscales. At least 50% of patients were rated much or very much improved on CGI-I 12 weeks later. The mean SAS score was also significantly reduced during the ziprasidone treatment period. In addition, during the

12-week treatment, the body weight of the patients was significantly reduced by an average of 1.2 kg (p=0.002) (Bartko et al.,2006).

Therefore, ziprasidone might be considered a first-line drug option in the treatment of schizophrenia. Nevertheless, in view of the differences among antipsychotic medications, drug selection should be guided by the patient's individual characteristics and situation.

3.3 Systematic review on efficacy and safety of aripiprazole and ziprasidone as treatment of metabolic syndrome components and metabolic syndrome among schizophrenia patients

3.3.1. Methods

3.3.2. Search strategy

This systematic review included literature published between January 2000 and October 2012. An electronic search on the following databases was carried out: PUBMED, Web of Science, OVID Medline (R), the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Review, using the search terms:

   i). Aripiprazole

   ii). Ziprasidone

   iii). Schizophrenia

   iv). Metabolic

Where Medical Subject Headings (MeSH) terms were available, they were exploded and combined. Reference lists from retrieved papers were also searched. Reference lists of the all papers were checked for the potential publications.

3.3.3. Type of studies

Only publications in English for randomized clinical trials were included if:

    (a) Aripiprazole at any dose compared with any other antipsychotics or placebo

    (b) ziprasidone at any dose compared with any other antipsychotics or placebo

    (c) aripiprazole compared with ziprasidone

Types of participant

Male or female patients, age $\geq$ 18 years old, any ethnic origin, who was diagnosed schizophrenia and other form of schizophrenia without mood stabilizer .e.g. schizoaffective disorder.

3.3.4. Types of interventions

    (a) The treatment group was aripiprazole or ziprasidone and the comparison groups were either any antipsychotic drugs or placebo or non-drug treatment.

    (b) The treatment group was between aripiprazole and ziprasidone

3.3.5. Types of outcome measures

    (a) Efficacy findings using clinical rating scales – PANSS total, positive, negative subscale and Brief Psychiatry Rating Scale (BPRS), CGI-I and CGI-S

    (b) Metabolic syndrome rate

    (c) Parameters included mean or median changes in lipids(mg/dL), Fbs (mg/dL), SBP and DBP (mmHg), waist circumference (cm), weight(kg)

3.3.6. Data extraction

Two reviewers were involved in identifing potentially relevant abstracts and assessment of full papers for inclusion and methodological quality. Any disagreement was discussed and resolved the discrepancy.

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Information was extracted on data source such as study design, participants, interventions, summary results at the endpoint. Publication reported on efficacy using rating scales without reporting any of these parameters were excluded from the systematic review: mean or median changes in lipids (mg/dL), Fbs (mg/dL), SBP & DBP (mmHg), waist circumference (cm), weight (kg), metabolic syndrome rate.

The data were summarized into three systematic review tables:

i). Aripiprazole versus other antipsychotics

ii). Ziprasidone versus other antipsychotics

iii). Aripiprazole versus ziprasidone

3 RCT Aripirazole vs. Ziprasidone

3.3.7. Results

A total of 15 RCT studies for aripiprazole, 17 RCT studies for ziprasidone and 2 RCT

studies for aripiprazole and ziprasidone were identified by the search and cross-

referencing strategies.

Figure 3.1   Flow chart showing the article-identification process for aripiprazole as treatment in schizophrenia patients

```
+----------------------------------+
|   Total number of potential      |
|    relevant papers = 15          |
+----------------------------------+
                 |
                 |------------------->  +------------------------------------------+
                 |                      | Papers not meeting inclusion criteria =5 |
                 |                      | 4 include schizoaffective disorder with  |
                 |                      | mood stabilizer(Potkin et al.,2003;      |
                 |                      | Casey et al.,2003; Kinon et al.,2008;    |
                 |                      | Newcomer et al.,2008) and 1              |
                 |                      | results not clearly stated(Sarin et al., |
                 |                      | 2004)                                    |
                 |                      +------------------------------------------+
                 v
+----------------------------------+
|   Final number of paper          |
|   included in the study = 10     |
+----------------------------------+
```
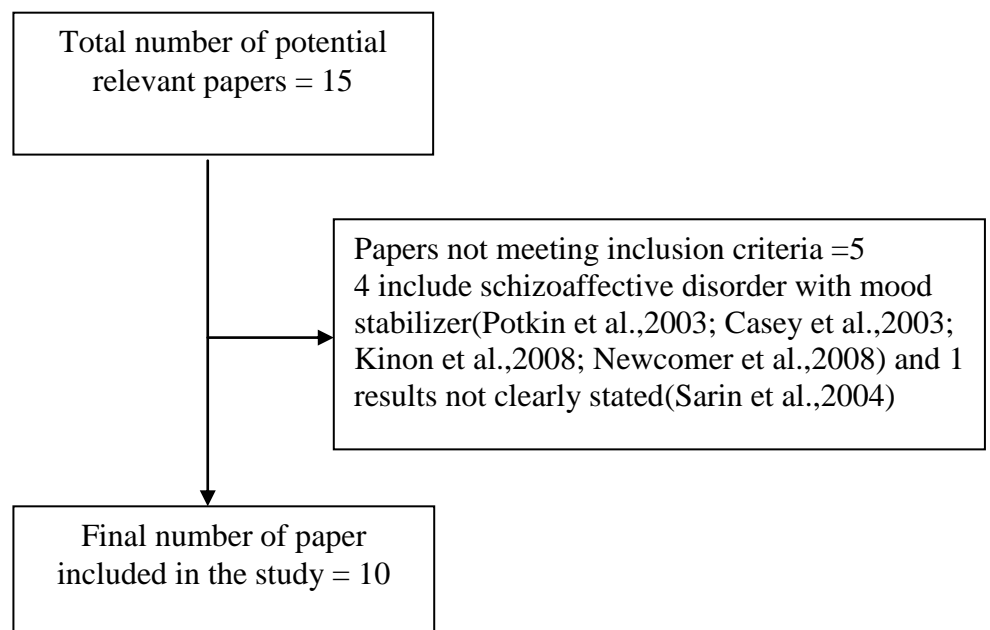
Figure 3.2   Flow chart showing the article-identification process for ziprasidone as treatment in schizophrenia patients

```
+----------------------------------+
|   Total number of potential      |
|    relevant papers = 17          |
+----------------------------------+
                 |
                 v
+----------------------------------+
|   Final number of paper          |
|   included in the study = 17     |
+----------------------------------+
```
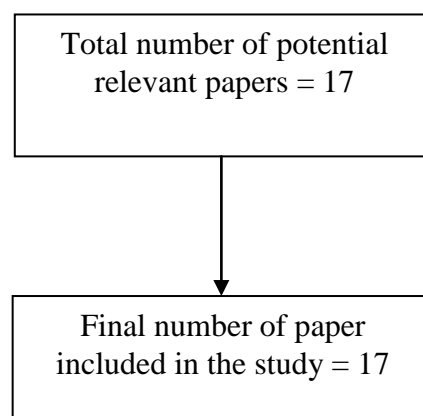
3 RCT Aripirazole vs. Ziprasidone

Figure 3.3   Flow chart showing the article-identification process for aripiprazole and ziprasidone as treatment in schizophrenia patients

Table 3.1   Systematic review on the aripiprazole as treatment in schizophrenia patients

Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
Pigott et al.(2003) 26-week, Randomized,double-blind	Schizophrenia on antipsychotic age≥18 years old 310 patients	Aripiprazole15mg/day(n=155) Placebo(n=155)	Discontinuation rate Aripiprazole 54.2%,Placebo 71% PANSS total, positive subscale and BPRS, CGI-I and CGI-S (p<0.05) PANSS negative subscale(p>0.05)	TG: aripipzazole -37.2, placebo -2.9 HDL-C: aripiprazole +2.0 ,placebo +0.89 LDL-C: aripiprazole -5.1,placebo -2.9 Fbs: aripiprazole +0.13,placebo +2.1 (p=NS) Weight : aripipzazole -1.26,placebo -0.87 (p<0.05) Reported by L'Italien et al,(2007) Metabolic syndrome rate: Placebo 26.9%, Aripiprazole 22.1%(p=NS) Incidence Metabolic syndrome : Placebo 10.4%, Aripiprazole 3.2%(p<0.05)
Marder et al.(2003) Pooled of 4-6-week, five randomized,double-blind	Schizophrenia on antipsychotic except clozapine, Schizoaffective disorder not on mood stabilizer age≥18 years old 1539 patients	Aripiprazole 2-30mg/day(n=926) Haloperidol 5 - 20mg/day(n=200) Placebo(N=413)	Discontinuation rate Aripiprazole 46%,Haloperidol 42%, placebo 56% BARS,SAS and AIMS(p>0.05 aripiprazole vs. placebo)	TC(median): aripiprazole +1.0, haloperidol +8.0,placebo +3.0(p=NS) Fbs(median): aripiprazole +0.13,placebo +2.1 (p=NS) Weight : aripiprazole +0.71,haloperidol +0.56, placebo -0.1 (p<0.05 aripiprazole vs. placebo)
McQuade et al.(2004) 26-week,	Schizophrenia on antipsychotic except clozapine	Aripiprazole15-30mg/day(n=156) Olanzapine 10-	Discontinuation rate Aripiprazole 75%,Olanzapine 70% Mean CGI and PANSS total -both	TG: olanzapine +79.4,aripipzazole+6.5 (p<0.05) HDL-C: olanzapine -3.39, aripiprazole

3 RCT Aripiprazole vs. Ziprasidone

Table 3.1 Systematic review on the aripiprazole as treatment in schizophrenia patients

Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
Randomized,double-blind	age≥18 years old 317 patients	20mg/day(n=161)	treatment arms improved	+3.61(p<0.05) TC: olanzapine +16.3, aripiprazole -1.13(p=NS) LDL-C: olanzapine +2.27, aripiprazole -3.86(p=NS) Weight :olanzapine +4.23,aripipzazole -1.37 (p<0.001)
Chrzanowski et al.(2006) 52-week, Randomized,open-label extension study(Pigott et al.,2003)	Schizophrenia previously from RCT aripiprazole vs. placebo age≥18 years old 214 patients	Aripiprazole15-30mg/day(n=104) Olanzapine 5-20mg/day(n=110)	Discontinuation rate Aripiprazole 37%,Olanzapine 26% PANSS total, positive and negative subscales, CGI-I and CGI-S -both treatment arms improved(p=NS)	TG: (p=NS) between groups HDL-C: a slight worsening with olanzapine versus a small improvement with aripiprazole (p<0.05) TC: greater increase with olanzapine versus aripiprazole (p<0.001) LDL-C: worsening with olanzapine versus improvement with aripiprazole(p<0.001) Fbs: aripiprazole -1.4,olanzapine +12.0 (p=NS) Weight: aripiprazole +0.04,olanzapine +2.54(p<0 Reported by L'Italien et al(2007) Metabolic syndrome rate: olanzapine 36.7%, Aripiprazole 25.3%(p<0.05)

3 RCT Aripiprazole vs. Ziprasidone

Table 3.1 Systematic review on the aripiprazole as treatment in schizophrenia patients

Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
				Incidence Metabolic syndrome : olanzapine 20.6%, Aripiprazole 8.9%(p=NS)
Kerwin et al.(2007) 26-week, Randomized,open-label	Schizophrenia on antipsychotic except clozapine age≥18 years old 555 patients	Aripiprazole10-30mg/day(n=284) versus standard of care(SOC-atypical antipsychotics n=271) -Risperidone 2-16mg/day -Olanzapine 5-20mg/day -Quetiapine 100-800mg/day	Discontinuation rate Aripiprazole 42.3%,SOC 38.7% CGI-I and CGI-S -both treatment arms improved(p=NS)	*presented as proportion of patients with potentially clinically relevant TG: aripipzazole(47.8%),SOC(59.7%) (p<0.05) HDL-C: aripipzazole(30.4%),SOC(35.1%) (p=NS) TC: aripipzazole(52.9%),SOC(70.2%) (p<0.05) LDL-C: aripipzazole(39.1%),SOC(60.0%) (p<0.05) Fbs: aripipzazole(25.2%),SOC(26.5%) (p=NS) Weight : aripipzazole -1.3, SOC+-1.4(p=NS)
Chan et al.(2007) 4-week, Randomized,double-blind	Schizophrenia on antipsychotic except clozapine, Schizoaffective disorder not on mood stabilizer age≥18 years old 83 patients	Aripiprazole15mg/day(n=49) Risperidone 6mg/day(n=34)	Discontinuation rate Aripiprazole 22%,Risperidone 29% PANSS total, positive and negative subscales, CGI-I and CGI-S -both treatment arms improved(p=NS)	TC: aripiprazole -3.1,risperidone +19.2, (p=NS) Fbs: aripiprazole +4.1,risperidone -2.7 (p=NS) Weight: aripipzazole +0.9,risperidone +1.5 (p=NS)

3 RCT Aripiprazole vs. Ziprasidone

Table 3.1 Systematic review on the aripiprazole as treatment in schizophrenia patients

Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
McEvoy et al.(2007) 6-week, Randomized,double-blind, discontinued RCT, entered open-label	Schizophrenia on antpsychotic age≥18 years old 420 patients	Aripiprazole10mg/day(n=106) Aripiprazole15mg/day(n=106) Aripiprazole20mg/day(n=106) Placebo (n=108)	Discontinuation rate Placebo 72.2%, Aripiprazole10mg 59.4% Aripiprazole15mg 69.8%, Aripiprazole 20mg 63.0% PANSS total, positive,negative subscale and BPRS, CGI-I and CGI-S (p<0.05)	Weight : Placebo -0.64, Aripiprazole10mg +0.46, Aripiprazole15mg -0.17, Aripiprazole 20mg +0.31(p=NS) Repoted by L'Italien et al,(2007)Metabolic syndrome rate: Placebo 23.4%, Aripiprazole 18.2%(p=NS) Incidence Metabolic syndrome : Placebo 25.0%, Aripiprazole 6.7%(p<0.05)
Kane et al.(2009) 28-week, Randomized,double-blind	Schizophrenia on antipsychotic age≥18 years old 566 patients	Aripiprazole10-30mg/day(n=285) Olanzapine 10-20mg/day(n=281)	Discontinuation rate Aripiprazole 50.2%,Olanzapine 42.7% PANSS total, positive subscales (p<0.05) Olanzapine superior than aripiprazole PANSS negative subscales, CGI-I and CGI-S -both treatment arms improved(p=NS)	*Least-squares mean change TG: olanzapine +25.66,aripipzazole -17.52 (p<0.001) HDL-C: olanzapine -1.70, aripiprazole +1.43(p=0.006) TC: olanzapine +4.09, aripiprazole -9.85 (p<0.001) LDL-C: olanzapine +1.74, aripiprazole -6.72 (p=0.003) Fbs: olanzapine +4.87, aripiprazole +0.90 (p=0.045) Weight :olanzapine +3.4,aripipzazole +0.3

Table 3.1 Systematic review on the aripiprazole as treatment in schizophrenia patients

Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
				(p<0.001)
Fleischhacker et al.(2009) 52-week, Randomized,double-blind	Schizophrenia on antipsychotic except clozapine age≥18 years old 703 patients	Aripiprazole15-30mg/day(n=355) Olanzapine 10-20mg/day(n=348)	Discontinuation rate Aripiprazole 61%,Olanzapine 53% PANSS total,CGI-I and CGI-S and -both treatment arms improved (p<0.05). Olanzapine superior than aripiprazole	TG: olanzapine +10.5,aripipzazole -25.2 (p<0.05) HDL-C: olanzapine +4.8, aripiprazole +5.4 (p=NS) TC: olanzapine +5.8, aripiprazole -17.0 (p<0.001) LDL-C: olanzapine +2.2, aripiprazole -17.0 (p<0.001) Fbs: (p=NS) between groups Weight(adjusted mean change):olanzapine +4.74,aripipzazole +0.32 (p<0.001)
Macfadden et al.(2010) 104-week, Randomized,rater-blinded, open label	Schizophrenia on antipsychotic except clozapine age≥18 years old 349 patients	Aripiprazole10-30mg/day(n=172) IM Risperidone 25-50/biweekly(n=177)	Discontinuation rate Aripiprazole 28.4%,IM Risperidone 29.6% PANSS total -both treatment arms improved(p=NS)	TG: aripiprazole -0.1,risperidone +0.03, (p=NS) TC: aripiprazole -0.3,risperidone -0.1, (p=NS) Rbs(not fasting): aripipzazole -0.2, risperidone +0.3 (p=NS) Weight: aripipzazole +1.6,risperidone +2.6 (p=NS)

3   RCT Aripiprazole vs. Ziprasidone

Table 3.2 Systematic review on the ziprasidone as treatment in schizophrenia patients				
Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
Arato et al.(2002) 52-week, Randomized,double-blind	Schizophrenia on antipsychotic age≥18 years old 294 patients	Ziprasidone 40mg/day (n=72) Ziprasidone 80mg/day (n=68) Ziprasidone 160mg/day (n=67) Placebo (n=71)	Discontinuation rate Ziprasidone 40mg/day 58%, Ziprasidone 80mg/day 57%, Ziprasidone 160mg/day 55%, Placebo 86% PANSS total,positive and negative subscales, CGI-S (p<0.05) for ziprasidone different doses compared with placebo	Weight: Ziprasidone 40mg/day -2.7, Ziprasidone 80mg/day -3.2, Ziprasidone 160mg/day -2.9, Placebo -3.6(p=NS)
Simpson et al.(2004) 6-week, Randomized,double-blind	Schizophrenia on antipsychotic , Schizoaffective disorder not on mood stabilizer age≥18 years old 269 patients	Ziprasidone 80-160mg/day (n=136) Olanzapine 5-20mg/day (n=133)	Discontinuation rate Ziprasidone 48.5%, Olanzapine 36.8% PANSS total,positive and negative subscales, CGI-S and CGI-I- both treatment arms improved(p=NS)	TG(median): Ziprasidone -2.0, Olanzapine +26.0, (p<0.05) HDL-C: ziprasidone vs. olanzapine (p=NS) TC(median): Ziprasidone -1.0, Olanzapine +19.5, (p<0.05) LDL-C(median): ziprasidone -1.0, olanzapine +13.0 (p<0.05) Fbs(median): Ziprasidone +1.0, Olanzapine +1.0 , (p=NS) weight : Ziprasidone vs. Olanzapine (p<0.001) olanzapine weight change greater than ziprasidone

Table 3.2   Systematic review on the ziprasidone as treatment in schizophrenia patients

Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
Simpson et al.(2005) 52-week, Randomized,double-blind extension study(G. M. Simpson et al.,2004)	Schizophrenia on antipsychotic , Schizoaffective disorder not on mood stabilizer age≥18 years old 126 patients	Ziprasidone 80-160mg/day (n=55) Olanzapine 5-20mg/day (n=71)	Discontinuation rate Ziprasidone 69.1%, Olanzapine 70.4% PANSS total,positive and negative subscales, CGI-S and CGI-I- both treatment arms improved(p=NS)	TC(median): Ziprasidone -1.0, Olanzapine +13.0, (p=NS) LDL-C(median): ziprasidone +9.0, olanzapine +17.0 (p=NS) weight : Ziprasidone -0.82 , Olanzapine +4.97 (p<0.001)
Addington et al.(2004) 8-week, Randomized,double-blind	Schizophrenia on antipsychotic , Schizoaffective disorder not on mood stabilizer age≥18 years old 296 patients	Ziprasidone 80-160mg/day (n=149) Risperidone 2-6mg/day (n=147)	Discontinuation rate Ziprasidone 36.9%, Risperidone 29.3% PANSS total and negative subscales, CGI-S and CGI-I - both treatment arms improved(p=NS)	Weight increase (≥7% of body weight)(p<0.05) Risperidone 16.0%, ziprasidone 8.2% Weight decrease (≥7% of body weight)(p<0.05) Risperidone 2.4%, ziprasidone 7.4%
Breier et al.(2005) 28-week, Randomized,double-blind	Schizophrenia on antipsychotic except clozapine age≥18 years old 548 patients	Ziprasidone 80-160mg/day (n=271) Olanzapine 10-20mg/day (n=277)	Discontinuation rate Ziprasidone 57.6%, Olanzapine 40.4% PANSS total, general psychopathology ,positive and negative subscales, CGI-S (p<0.001) olanzapine better than ziprasidone	TG: olanzapine +34.5,ziprasidone -21.3 (p<0.05) HDL-C: olanzapine -2.3, ziprasidone +0.8 (p<0.001) TC: olanzapine +3.1, ziprasidone -12.8 (p<0.001) LDL-C: olanzapine +0.8, ziprasidone -10.4 (p<0.001) Fbs: olanzapine +5.0, ziprasidone -0.18

Table 3.2   Systematic review on the ziprasidone as treatment in schizophrenia patients

Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
				(p<0.001)
				Weight:olanzapine +3.06, ziprasidone -1.12 (p<0.001)
Lieberman et al.(2005) 72-week, Randomized,double-blind (CATIE phase 1)	Schizophrenia on antipsychotic except clozapine age≥18 years old 1493 patients	Ziprasidone 80-160mg/day (n=185) Olanzapine 7.5-30mg/day (n=336) Quetiapine 200-800mg/day (n=337) Risperidone 1.5-6mg/day (n=341) Perphenazine 8-24mg/day (n=261)	Discontinuation rate Ziprasidone 79%, Olanzapine 64%, Quetiapine 82%, Risperidone 74%, Perphenazine 75% PANSS total and CGI (p<0.05)	*Exposure-adjusted mean *TG: Ziprasidone -16.5, Olanzapine +40.5, Quetiapine +21.2, Risperidone -2.4, Perphenazine +9.2(p<0.001) *TC: Ziprasidone -8.2, Olanzapine +9.4, Quetiapine +6.6, Risperidone -1.3, Perphenazine +1.5(p<0.001) *Fbs: Ziprasidone +2.9, Olanzapine +13.7 , Quetiapine +7.5 , Risperidone +6.6, Perphenazine +5.4(p=NS) Weight : Ziprasidone -0.7, Olanzapine +4.3, Quetiapine +0.5, Risperidone +0.4, Perphenazine -0.9(p<0.001)
Brook et al.(2005) 6-week, Randomized,single-blinded	Schizophrenia or schizoaffective not on mood stabilizer Aged 18-70 years 572 patients	IM Ziprasidone 10-40mg for initial 3 days followed by oral Ziprasidone 80-160mg/day (n=429) IM Haloperidol 2.5-10mg for initial 3 days followed by oral Haloperidol 5-20mg/day	Discontinuation rate IM Phase:Ziprasidone 0.9%, Haloperidol 2.2% Oral Phase:Ziprasidone 31.0%, Haloperidol 31.9% BPRS, BPRS-derived measures and	Weight: Ziprasidone +0.25, Haloperidol -0.15

Table 3.2   Systematic review on the ziprasidone as treatment in schizophrenia patients

Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
		(n=138)	COVI Anxiety Scale -Ziprasidone better than haloperidol (p<0.05) CGI-S and CGI-I(P=NS)	
Stroup et al.(2006) 24-week, Randomized, double –blind (CATIE phase 2)	Schizophrenia on antipsychotic except clozapine age≥18 years old 444 patients	Ziprasidone 80-160mg/day (n=137) Olanzapine 7.5-30mg/day (n=68) Quetiapine 200-800mg/day (n=63) Risperidone 1.5-6mg/day (n=70)	Discontinuation rate Ziprasidone 77%, Olanzapine 67%, Quetiapine 84%, Risperidone 64% PANSS total (p=0.005) except risperidone(p=NS) PANSS positive subscale (p<0.05) PANSS negative and psychopathology subscale, CGI(p=NS)	*Exposure-adjusted mean *TG: Ziprasidone -3.5, Olanzapine +94.1, Quetiapine +39.3, Risperidone -5.2, (p<0.001) *TC: Ziprasidone -10.7, Olanzapine +17.5, Quetiapine +6.5, Risperidone -3.1, (p<0.001) *Fbs: Ziprasidone +0.8, Olanzapine +13.8 , Quetiapine +1.2 , Risperidone +6.9, (p=NS) Average weight change/month : Ziprasidone -0.8, Olanzapine +0.6, Quetiapine +0.3, Risperidone -0.1 (p<0.001)
Olie et al.(2006) 12-week, Randomized,double-blind	Schizophrenia on antipsychotic age≥18 years old 123 patients	Ziprasidone 80-160mg/day (n=60) Amisulpride 50-200mg/day (n=63)	Discontinuation rate Ziprasidone 14.6%, amisulpride 10.6% PANSS total, negative subscale and BPRS,CGI-S (p<0.001) overall amisulpride better than ziprasidone	Weight increase (>7% of body weight)(p<0.05) Amisulpride 17.9%, ziprasidone 8.8% Weight decrease (>7% of body weight)(p<0.05) Amisulpride 5.4%, ziprasidone 7.0%

Table 3.2   Systematic review on the ziprasidone as treatment in schizophrenia patients

Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
Kinon et al.(2006) 24-week, Randomized,double-blind	Schizophrenia on antipsychotic , Schizoaffective disorder not on mood stabilizer age≥18 years old 394 patients	Ziprasidone 80-160mg/day (n=192) Olanzapine 10-20mg/day (n=202)	Discontinuation rate Ziprasidone 70%, Olanzapine 55% PANSS total - both treatment arms improved(MMRM,p=NS) CDSS, MADRS and GAF -olanzapine better than ziprasidone(p<0.05) .	TG: Ziprasidone -9.47, Olanzapine +13.6, (p<0.05) HDL-C: ziprasidone -0.5 ,olanzapine -1.8 (p=NS) TC: Ziprasidone -11.7, Olanzapine -2.27, (p=NS) LDL-C: ziprasidone -7.3, olanzapine -4.41 (p=NS) Fbs: Ziprasidone +0.14, Olanzapine +2.85 , (p=NS) weight : Ziprasidone -1.65, Olanzapine +2.53, (p<0.001)
Kane et al.(2006) 12-week, Randomized,double-blind	Schizophrenia , treatment resistant with haloperidol age≥18 years old 306 patients	Ziprasidone up to160mg/day (n=152) Chlorpromazine up to1200mg/day (n=154)	Discontinuation rate Ziprasidone 10.5%, Chlorpromazine 12.3% PANSS total - both treatment arms improved(p=NS) PANSS negative subscale and CGI-S (p<0.05) Ziprasidone superior than Chlorpromazine	Weight increase (≥7% of body weight)(p<0.05) Chlorpromazine 13.8%, ziprasidone 5.1% Weight decrease (≥7% of body weight)(p<0.05) Chlorpromazine 1.8%, ziprasidone 10.2%

3 RCT Aripiprazole vs. Ziprasidone

Table 3.2 Systematic review on the ziprasidone as treatment in schizophrenia patients				
Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
Meyer et al.(2008) 12-week, Randomized, double –blind (CATIE prospective data from phase 1)	Schizophrenia on antipsychotic except clozapine age≥18 years old 281 patients	Ziprasidone 80-160mg/day (n=31) Olanzapine 7.5-30mg/day (n=74) Quetiapine 200-800mg/day (n=67) Risperidone 1.5-6mg/day (n=54) Perphenazine 8-24mg/day (n=52)	To demonstrate the rate of metabolic syndrome and metabolic effect comparing baseline and 3-month study visit	MetS　　Baseline, 3-month Olanzapine: 41.9%, 51.4% 　MetS　　Baseline, 3-month Risperidone: 37.0%, 42.6% Quetiapine : 38.8%,43.3% Ziprasidone: 48.4%,38.7% Perphenazine: 42.3%,38.5% waist : Ziprasidone 0.0, Olanzapine +1.8, Quetiapine +1.8, Risperidone +1.0, Perphenazine -1.0(p<0.001) systolic: Ziprasidone -0.5, Olanzapine -0.9, Quetiapine -1.7, Risperidone -1.4, Perphenazine -2.9(p=NS) Diastolic: Ziprasidone -0.6, Olanzapine +0.1, Quetiapine -0.3, Risperidone -1.4, Perphenazine -1.3(p=NS) HDL-C: ziprasidone -0.1 ,olanzapine -2.3, Quetiapine -1.0, Risperidone -0.7, Perphenazine -0.1 (p=NS) Fbs: Ziprasidone -1.1, Olanzapine +0.5 , Quetiapine +2.7, Risperidone +4.7,

3 RCT Aripiprazole vs. Ziprasidone

Table 3.2 Systematic review on the ziprasidone as treatment in schizophrenia patients

Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
				Perphenazine +1.4 (p=NS) TG: Ziprasidone -32.1, Olanzapine +21.5, Quetiapine +11.9, Risperidone -18.4, Perphenazine +11.5 (p=0.016)
Cutler et al.(2008) 4-week, Randomized,double-blind	Schizophrenia on antipsychotic. age18-65 years old 606 patients	Ziprasidone 160mg/day (n=151) Iloperidone 24mg/day (n=303) Placebo (n=152)	Discontinuation rate Ziprasidone 34%, Iloperidone 35%, placebo 40% PANSS positive, negative subscale and general psychopathology, CGI-S and BPRS Ziprasidone and Iloperidone were improved when compared to placebo except for PANSS general psychopathology	TG: Ziprasidone +4.6, Iloperidone +0.8, placebo +19.5 TC: Ziprasidone +4.1, Iloperidone +8.1, placebo -0.5 Fbs: Ziprasidone +4.7,Iloperidone +7.9,placebo +3.2 Weight : Ziprasidone +1.1, Iloperidone +2.8, placebo +0.5 Weight increase (≥7% of body weight) Ziprasidone 7%,Iloperidone 21%,placebo 3%
Lawson et al.(2009) Pooled of 4-6-week, four randomized, double-blind	Schizophrenia and schizoaffective disorder not on mood stabilizer(comparing Black and White patients) age≥18 years old	Ziprasidone 10-200mg/day (n=702) Haloperidol (n=85) Placebo(n=273)	Discontinuation rate Ziprasidone 49.4%,Haloperidol 48.2%, Placebo 63.7% PANSS total and negative subscale, BPRS,CGI-S and CGI-I : Ziprasidone better than placebo, Black patients	TG: Ziprasidone -8.82, placebo -15.52 TC : Ziprasidone -7.79, placebo -7.57 Random glucose: Ziprasidone +0.68, placebo +0.65

Table 3.2   Systematic review on the ziprasidone as treatment in schizophrenia patients

Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
	1060 patients		significantly improve than White patients p<0.05	Weight: Ziprasidone +0.96, placebo -0.4
Sacchetti et al.(2009) 18-week, Randomized,double-blind	Schizophrenia on antipsychotic. age≥18 years old 147 patients	Ziprasidone 80-160mg/day (n=73) Clozapine 250-600mg/day (n=74)	Discontinuation rate Ziprasidone 38.4%, Clozapine 38.4% PANSS positive, negative and general psychopathology subscales, CGI-S and CGI-I scale, CDSS,GAF scale and DAI-10 scale - Clinical scales for both treatment arms improved when compared to each other(p=NS),the difference for CGI-I was not significant for both arms	TC(median):Ziprasidone -5.0, Clozapine +2.0(p<0.05) HDL(median):Ziprasidone +8.0, Clozapine +2.0 LDL(median):Ziprasidone -6.0, Clozapine +4.0(p<0.05) TG(median):Ziprasidone -15.0, Clozapine +10.0(p<0.05) Fbs(median):Ziprasidone 0.0, Clozapine +6.0(p<0.05) Weight : Ziprasidone -2.6 ± 4.7, Clozapine +0.8 ±4.6kg
Potkin et al.(2011) 3-week, Randomized,double-blind	Schizophrenia on antipsychotic , Schizoaffective disorder not on mood stabilizer age≥18 years old 307 patients	Ziprasidone 160mg/day (n=153) Lurasidone 120mg/day (n=154)	Discontinuation rate Ziprasidone 30.7%, Lurasidone 32.5% PANSS total, positive and negative subscale, general psychopathology and CGI-S : both treatment arms improved(p=NS)	TG(median): Ziprasidone 0.0, lurasidone 0.0, (p=NS) TC(median): Ziprasidone -5.0, lurasidone -6.0, (p=NS) Fbs(mean): Ziprasidone +4.8,lurasidone +4.7 ,(p=NS)

Table 3.2 Systematic review on the ziprasidone as treatment in schizophrenia patients

Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
				Weight(median) : Ziprasidone -0.29, lurasidone -0.16 (p=NS)
Grootens et al.(2011) 8-week, Randomized, double-blind	Schizophrenia on antipsychotics, schizoaffective and schizophreniform disorder not on mood stabilizer age≥18 years old 74 patients	Ziprasidone 80-160mg/day (n=39) Olanzapine 10-20mg/day (n=35)	Discontinuation rate Ziprasidone 28.2%,Olanzapine 17.1% PANSS total, positive, negative subscale and general psychopathology, CGI-S and CGI-I, CDSS, HQLS both treatment arms improved(p=NS)	TC:Olanzapine+18.5, Ziprasidone-9.3 TG: Olanzapine +36.0, Ziprasidone -18.4 Systolic: Olanzapine+0.7, Ziprasidone-0.9 Diastolic: Olanzapine+0.7, Ziprasidone+3.1 Fbs: Olanzapine+1.08, Ziprasidone 1.8 Weight:Olanzapine +6.8,Ziprasidone +0.1 Weight increase (≥7% of body weight) Olanzapine 64.5%,Ziprasidone 3.3%

Table 3.3 Systematic review on the aripiprazole and ziprasidone as treatment in schizophrenia patients

Study design	Study Subjects	Intervention	Summary of results at endpoint	
			Efficacy	Changes in lipids(mg/dL), Fbs(mg/dL), SBP&DBP(mmHg),waist circumference(cm), weight(kg),metabolic syndrome
Zimbroff et al.(2007) 4-week, Randomized,double-blind	Schizophrenia on antpsychotic , Schizoaffective disorder not on mood stabilizer age≥18 years old 256 patients	aripiprazole 10-30mg/day (n=129) Ziprasidone 80-160mg/day (n=127)	Discontinuation rate Aripiprazole 30.5%, Ziprasidone 32% PANSS total, positive and negative subscales, CGI-S - both treatment arms improved (MMRM,p=NS)	TG(median): Ziprasidone +6.0, aripiprazole -3.0 HDL-C: ziprasidone 0, aripiprazole 0 TC(median): Ziprasidone -2.0, aripiprazole -6.0 LDL-C(median): ziprasidone -1.0, aripiprazole -4.0 Fbs(median): Ziprasidone +2.0, aripiprazole +3.0 weight : Ziprasidone +0.45,aripiprazole +0.45

3.3.9. Research Question

Is aripiprazole has similar efficacy and safety with ziprasidone in the treatment of schizophrenia patients with metabolic syndrome and metabolic syndrome components?

3.3.10. Study Objectives

3.3.10.1 Primary Objective

To determine the efficacy of aripiprazole is not less effective than ziprasidone in reversing metabolic syndrome among the schizophrenia patients.

3.3.10.2 Secondary objective

i). To determine the efficacy of aripiprazole is not less effective than ziprasidone in reversing metabolic syndrome components among the schizophrenia patients.

ii). To determine the efficacy of aripiprazole is not less effective than ziprasidone in reducing metabolic syndrome parameters among the schizophrenia patients.

iii). To determine the efficacy of aripiprazole is not less effective than ziprasidone in improving psychotic symptoms among schizophrenia patients with metabolic syndrome components by using CGI-S, PANSS total and subscales.

iv). To determine the safety of aripiprazole and ziprasidone in the treatment of schizophrenia patients with metabolic syndrome components by using BARS, SAS and AIMS.

v). To describe the adverse events of aripiprazole and ziprasidone in the of treatment schizophrenia patients with metabolic syndrome components.

3.3.10.3 Tertiary objective

i). To determine the efficacy of aripiprazole is not less effective than ziprasidone in improving weight, body mass index (BMI), and total cholesterol and LDL cholesterol among the schizophrenia patients.

ii). To determine the efficacy of aripiprazole is not less effective than ziprasidone in improving the prevalence of cardiovascular risk factors (CVRFs) and coronary heart disease (CHD) risk among the schizophrenia patients.

iii). To determine the efficacy of aripiprazole and ziprasidone by using the discontinuation rate as the outcome measure.

3.3.11.   Hypotheses

3.3.11.1   Hypothesis for primary objective:

i). The proportion of reversed metabolic syndrome for aripiprazole-treated patients will be non-inferior to the proportion of reversed metabolic syndrome for ziprasidone-treated patients between baseline, week 4, week 8, week 12, week 16, week 20 and week 24.

3.3.11.2   Hypothesis for secondary objective:

i). The proportion of reversed metabolic syndrome components for aripiprazole-treated patients will be non-inferior to the proportion of reversed metabolic syndrome components for ziprasidone-treated patients between baseline, week 4, week 8, week 12, week 16, week 20 and week 24.

ii). There will be no difference in the least squares(LS) mean change of metabolic syndrome parameters between aripiprazole and ziprasidone-treated patients at baseline, week 4, week 8, week 12, week 16, week 20 and week 24.

iii). There will be no difference in the least squares(LS) mean change of rating scales such as PANNS total, PANSS positive and negative subscales, CGI-S, BAS, SAS, AIMS between aripiprazole and ziprasidone-treated patients at baseline, week 4, week 8, week 12, week 16, week 20 and week 24.

3.3.11.3   <u>Hypothesis for tertiary objective:</u>

i). There will be no difference in the least squares(LS) mean change of weight, BMI, total cholesterol and LDL cholesterol between aripiprazole and ziprasidone-treated patients at baseline, week 4, week 8, week 12, week 16, week 20 and week 24.

ii). The proportion of cardiovascular risk factors (CVRFs) and coronary heart disease (CHD) risk for aripiprazole-treated patients will be non-inferior to the proportion in the ziprasidone-treated patients between baseline, week 4, week 8, week 12, week 16, week 20 and week 24.

iii). There will be no difference in the discontinuation rate between aripiprazole-treated and ziprasidone-treated patients.

3 RCT Aripiprazole vs. Ziprasidone

3.4 Methods

3.4.1. Study Population

The study population included male or female with current DSM-IV TR diagnoses of schizophrenia.

3.4.2. Inclusion Criteria

i). Having at least one component of metabolic syndrome.

ii). Male or female, aged 18 – 65 years.

iii). Having at least one year treatment of current antipsychotic treatment.

iv). Patients who were treated with antihypertensive, antidiabetic or antihyperlipidemia prior the study, and the treatment was initiated $\geq$ 3 months prior to screening with no dosage changes 30 days before study recruitment.

v). Able to provide written informed consent and to comply with all study procedures.

vi). Using a barrier (diaphragm or condom) with spermicide, intrauterine device (IUD), or complete abstinence as a method of birth control (if a woman of child-bearing capacity).

3.4.3. Exclusion Criteria

i). Serious medical illnesses that potentially progress to life-threatening medical illness which may compromise patient safety or study conduct.

ii). Patients who are currently treated with clozapine.

iii). Patients who are currently treated with atypical antipsychotic either ziprasidone or aripiprazole.

iv). Known hypersensitivity or allergy to aripiprazole or ziprasidone.

v). Patient with history of diabetes mellitus or hypertension prior to the treatment of schizophrenia.

vi). Patient who was suicidal or homicidal.

vii). Female who is positive on a urine pregnancy test or lactating.

3.4.4. Study Design

This study was a 6-month randomized double-blind parallel clinical trial.

Figure 3.4   The overall study design for randomized controlled trial between aripiprazole and ziprasidone in the treatment of metabolic syndrome components and metabolic syndrome
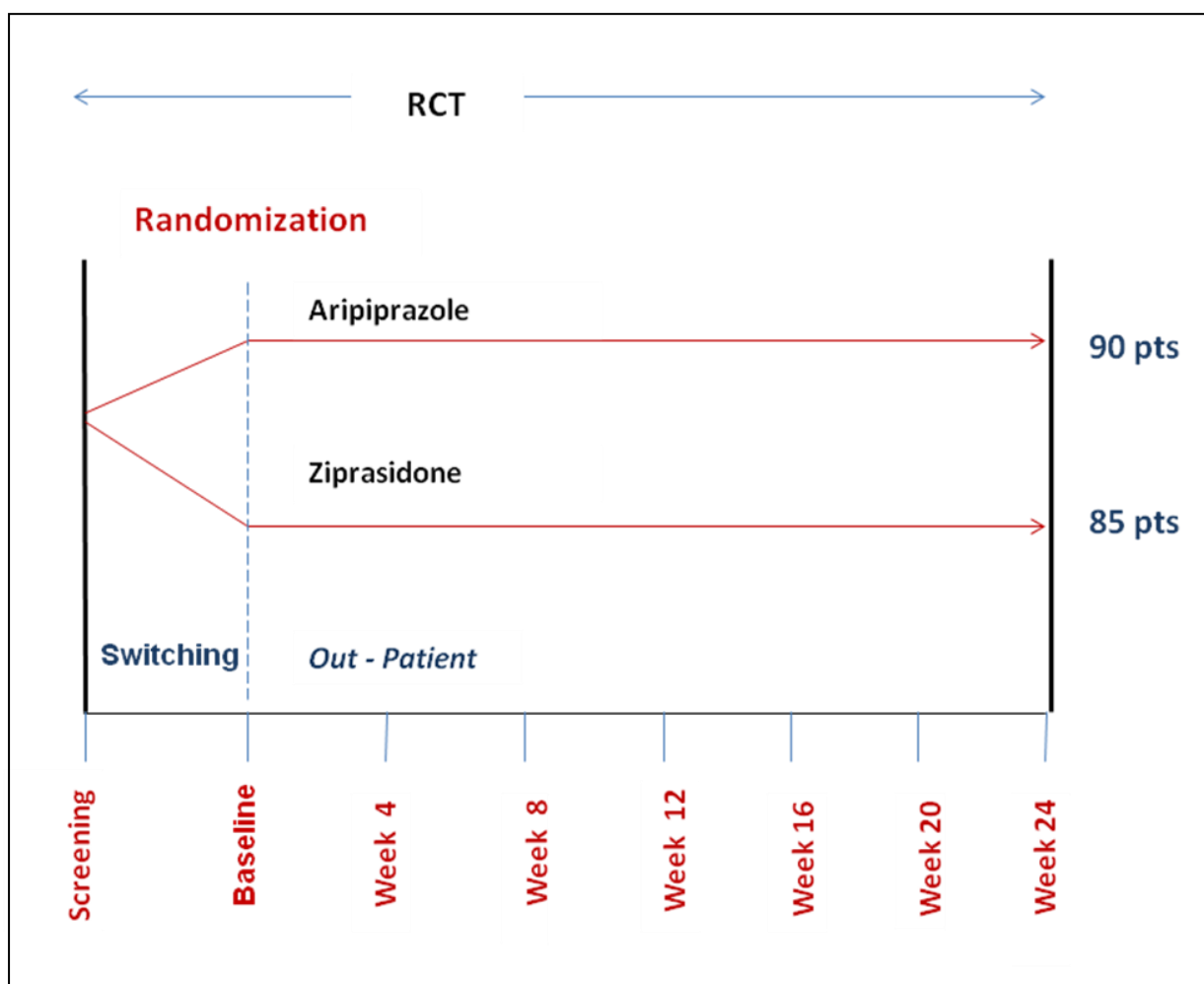
3.4.5. Study Period

The study period was from April 2008 until April 2012. Data was collected from May 2009 to September 2011.

3.4.6. Location of Study

This study was conducted at the outpatient psychiatric clinic in University Malaya Medical Centre (UMMC), Army Hospital namely Hospital Terendak Melaka and Hospital Tentera Laut Lumut, Perak, Hospital from Ministry of Health e.g Hospital Sungai Petani, Kedah, Hospital Bahagia, Ulu Kinta Perak, Hospital Permai, Johor, Hospital Mesra Kota Kinabalu, Sabah and Hospital Sentosa Kuching Sarawak.

3.4.7. Study Variables

The study variables that were considered for analysis in this study population were as follows:

(Operational definitions in ANNEX A)

3.4.8. Primary Study Endpoints

i). The proportion of reversed metabolic syndrome among schizophrenia patients after treated with either aripiprazole or ziprasidone.

Patients were scheduled for research evaluation visits on week 4, week 8, week 12, week 16, week 20 and week 24.

3.4.9. Secondary Study Endpoint

i). The proportion of reversed metabolic syndrome components among schizophrenia patients after treated with either aripiprazole or ziprasidone.

ii). The least squares (LS) mean change of metabolic syndrome parameters among schizophrenia patients after treated with either aripiprazole or ziprasidone.

iii). The least squares (LS) mean change of rating scales such as PANNS total, PANSS positive and negative subscales, CGI-S, BAS, SAS, AIMS among schizophrenia patients after treated with either aripiprazole or ziprasidone.

iv). To describe all side effects reported by patients during the study.

Patients were scheduled for research evaluation visits on week 4, week 8, week 12, week 16, week 20 and week 24.

3.4.10. Tertiary Study Endpoint

i).   The least squares (LS) mean change of weight, BMI, total cholesterol and LDL cholesterol among schizophrenia patients after treated with either aripiprazole or ziprasidone.

ii). The proportion of cardiovascular risk factors (CVRFs), coronary heart disease (CHD) risk among schizophrenia patients after treated with either aripiprazole or ziprasidone.

iii). The discontinuation rate between aripiprazole-treated and ziprasidone-treated patients.

Patients were scheduled for research evaluation visits on week 4, week 8, week 12, week 16, week 20 and week 24.

3.4.11.   Descriptive Variables

Sociodemographic Variables

i).   Age

ii).   Sex

iii). Race

iv).   Occupational

v).   Educational level

vi).   Marital status

Medical and Psychiatric History

i).   History of Smoking

ii).   Physical activities

iii).   History of hypertension and diabetes mellitus

iv).   History of gestational diabetes

v).   Age of onset for schizophrenia

vi).   Duration of schizophrenia

vii).   Current medication

viii).   Previous medication

ix).   History of weight after antipsychotics treatment

x).   History of hospitalization due to relapse

xi).   Number of relapse

Family History

i).   History of hypertension

ii).   History of Diabetes Mellitus

iii).   Parent obese

iv).   Sibling obese

3.4.12.   Study Instruments

3.4.12.1 Structured Questionnaires

A structured questionnaire was used which consisted of three sections. The first section was to assess the demographic data of the study population. The second

section was to assess medical and psychiatric history. The third section was to obtain the family medical history.

3.4.12.2.   Major Axis I Psychiatric Disorder Assessment

MINI International Neuropsychiatric Interview (M.I.N.I.)

M.I.N.I. is a face-to-face structured interview for the Major Axis I psychiatric disorder in DSM-IV and ICD-10. M.I.N.I. is used as a short structured diagnostic interview for DSM-IV or ICD-10 psychiatric disorders for the Major Axis I psychiatric disorder (D.V. Sheehan et al.,1998). It has been widely used in international clinical trials and epidemiological studies (Joling et al.,2008; van't Veer-Tazelaar et al.,2009). The M.I.N.I was available in local language for Malaysian population (D.V. Sheehan et al.,1998).

3.4.12.3. Efficacy Assessment

i)   Positive and Negative Symptoms Scale(PANSS)

The Positive and Negative Syndrome Scale (PANSS) is a medical scale used for measuring symptom severity of patients with schizophrenia (Kay et al.,1987). It refers to the two types of symptoms in schizophrenia, as defined by the American Psychiatric Association: positive symptoms, which refer to an excess or distortion of normal functions (e.g. hallucinations and delusions), and negative symptoms, which represent a diminution or loss of normal functions. A face-to-face interviewed of the scale will capture three components: positive scale (7 items), negative scale (7 items) and general psychopathology scale (16 items).

ii) Clinical Global Impression Scale- Severity Scale (CGI-S)

The Clinical Global Impression rating scales are commonly used measures of symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders (Guy,1976). The Clinical Global Impression - Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1,normal/not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

3.4.12.4. Safety Assessment

i) Abnormal Involuntary Movement Scale (AIMS) (Rush,2000)

The Abnormal Involuntary Movement Scale (AIMS) is a rating scale that was originally designed in Italian language in the 1980s (Burti et al.,1981), to measure involuntary movements known as tardive dyskinesia (TD). TD is a disorder that sometimes develops as a side effect of long-term treatment with neuroleptic (antipsychotic) medications. The AIMS test is used not only to detect tardive dyskinesia but also to follow the severity of a patient's TD over time. It is a valuable tool for clinicians who are monitoring the effects of long-term treatment with neuroleptic medications.

ii) Barnes Akathasia Scale (BAS) (Barnes,1989)

The Barnes Akathisia Scale (commonly known as BAS or BARS) is a rating scale that is administered by physicians to assess the severity of drug-induced akathisia. Akathisia is a syndrome of motor restlessness, principally seen in association with

antipsychotic medication. It is characterized by a subjective experience of mental unease and the urge to move, and manifests physically as particular patterns of restless movement.

The Barnes Akathisia Scale is the most widely used rating scale for akathisia. This scale includes objective and subjective items such as the level of the patient's restlessness. It comprises items for rating the observable, restless movements which characterise the condition, the subjective awareness of restlessness, and any distress associated with the akathisia. In addition, there is an item for rating global severity. A standard examination procedure is recommended. The inter-rater reliability for the scale items (Cohen's kappa) ranged from 0.738 to 0.955.

iii)   Simpson Angus Scale (SAS) (Simpson and Angus,1970)

Simpson-Angus Scale (SAS) is a 10-item rating scale that has been used widely for assessment of Neuroleptic Induce Parkinson in both clinical practice and research settings. It consists of one item measuring gait (hypokinesia), six items measuring rigidity and three items measuring glabella tap, tremor and salivation, respectively. Items are rated for severity on a 0-4 scale, with definitions given for each anchor point. SAS is a reliable and a valid instrument. It performs well and similarly to DSM-IV in Neuroleptic Induce Parkinsonism case detection (Janno et al.,2005).

iv) Adverse events

All adverse events, either observed or spontaneously reported were recorded.

3.4.13.   Study Drug - Intervention

i) Ziprazidone

Ziprazidone is a psychotropic drug and supplied in 40mg, 60mg and 80mg capsules. Different doses of ziprasidone has different colour of capsule. Ziprasidone was given twice daily as active treatment and was put in an opaque gelatine capsule in order to be identical to aripiprazole and placebo.

ii) Aripiprazole

Aripiprazole is a psychotropic drug. It is a light yellow colour, round, flat, bevelled edged, uncoated tablets that contain 10mg of aripiprazole. Aripiprazole was put in an opaque gelatine capsule in order to be identical to ziprasidone and placebo. Patients treated with aripiprazole received active treatment daily in the morning and matching with placebo compose only of vitamin B complex daily at night to simulate twice daily dosage as ziprasidone. Patients were advised to take each daily dose at 8:00 a.m or after breakfast and 8:00 p.m.

iii) Placebo

The placebo formulation for this study is vitamin B complex in a tablet form. In order for the placebo to appear identical to aripiprazole, the placebo was put in an opaque gelatine capsule that has same colour, shape and size for aripiprazole.

3.4.14.   Packaging of Study Drug

Study drug (intervention) was supplied in bulk shipments by a pharmaceutical company whereas placebo (vitamin B complex) was obtained from a pharmacy. A study coordinator repackaged the bulk drug into packs containing of 28 gelatin capsules per pack (4 weekly study follow up).

3.4.15.   Concomitant Therapy

The concomitant medications such as antidepressant, benzodiazepine and benzhexol were allowed for this study. Commitment therapy that not permitted during the study was:

i).   Carbamazepine

ii).   Ketoconazole

iii).   Quinidine

iv).   Fluoxetine

v).   Paroxetine

3.4.16.   Receiving, Storage, Dispensing and Return
i).   Receipt of Drug Supplies

An inventory was performed after accepting the drug shipment. The study coordinator counted and verified the shipment contained all the items mentioned in the supply. The principle investigator (PI) would notify to the pharmaceutical company of any damaged of the study drug.

ii).   Storage

Stock study drug and drug packaged in patient kits was stored in a locked cabinet in the research centre with climate control maintaining the temperatures within a range of 20°C to 25°C. Only the study coordinator and principle investigator have accessed to the study drug.

iii).   Dispensing of Study Drug

The principle investigator or study coordinator would dispense the appropriate amount of study drug, according to the number of day of follow up to the research subject base

on the randomization list. Subject compliance monitoring was conducted by doing pill counts at every study visit for all patients.

iv). Return of Study Drug

At the completion of the study, the final reconciliation of drug shipped, drug consumed and drug remaining was done. After appropriate accounting the pharmaceutical company was informed, the unused study drug was returned to the pharmaceutical company.

3.4.17. Study procedures

3.4.17.1 Patients screening and recruitment

i). All schizophrenia patients were approached during the screening of this study. Prior to the written consent, patients were briefed on detail this study. Patient was explained information regarding aripiprazole and ziprasidone, the rationale for why they were being studied, frequency of dosing, and length of treatment, potential benefits, side effects and risks, safeguards and emergency procedures. The collections of all laboratory specimens were described in detail, as the number and frequency of the research follow up. They were asked to fast for at least 8 hour for baseline laboratory blood evaluations. Only patients with at least one metabolic syndrome component were approached for clinical trial study.

ii). Patients were assured that their participation was voluntary and that withdrawal from the study would not jeopardize current or future treatment. Randomization was explained to the patients, as they would know their treatment assignment at the end of the study, after the blind has broken.

iii). A Mini International Neuropsychiatric Inventory (M.I.N.I.) was administered to obtain DSM-IV diagnoses of schizophrenia. All current medications taken by the

patient prior to screening was documented. A face-to-face interview was conducted to collect primary data by using a structured questionnaire. Some secondary data pertaining medication, dosage and history of relapse and hospitalisation were obtained from patient's case note. The principal investigator (PI) confirmed and signed off on the inclusion and exclusion criteria on a case report form (CRF) prior to the patient formally recruited in the study.

3.4.17.2   Randomization

The treatment started after the screening visit and once the laboratory results have been reviewed by the investigator. Patient was assigned to study drug either aripiprazole or ziprasidone according to a randomization list in a ratio of 1:1. The randomization list in the block of 4, 6 and 8 was computer generated using Randomization.com programme by a statistician. The blinded randomisation list with randomization code for aripiprazole and ziprasidone, A and B was given to principle investigator. The statistician put the randomization code in an envelope for individual patient according to randomization list and kept in the Psychiatric Unit Research Center, PPUM. Envelop with the randomization code of the particular patient can only be assessed by principle investigator in the case of severe adverse event happen during the study.

3.4.17.3   Treatment Regimen

Patients were tapered from prior antipsychotic treatment and discontinued within 4 weeks and at the same time, study drug such as aripiprazole and ziprasidone were titrated simultaneously to reach target doses within 4 weeks according to clinical effect, at the discretion of the study psychiatrists. Patients on aripiprazole were started with fixed dose 10mg/day which could be increased up to 30mg/day depending on the

clinical response for subsequent visits. Patients on ziprasidone were started fixed dose 40mg twice daily which could be increased to 80mg twice daily later depending on the clinical response. Flexible dosing of study medications was then permitted, which means that the dose of aripiprazole and ziprasidone can be adjusted either increased or reduced based on clinical assessment. The total daily dosage of ziprasidone ranges at 80mg, 100mg, 120mg, 140mg and 160mg and the total daily dosage of aripiprazole at 10mg, 15mg, 20mg, 25mg and 30 mg. All patients were recommended to take medication with a meal. This was because the optimum absorption of ziprasidone required to be taken with meal.

Patient could receive antidepressants, trihexyphenidyl to control of extrapyramidal symptoms (EPS) and lorazepam was permitted for control of agitation or insomnia. Trihexyphenidyl was permitted for EPS but only after assessment with the BARS, SAS and AIMS Rating Scales were performed. Lorazepam was permitted after administration, for a minimum of 4 hours had to elapse before completing efficacy evaluations. Treatment of antihypertensive, antidiabetic or antihyperlipidemia prior the study were allowed, provided the treatment was initiated $\geq$ 3 months prior to screening with no dosage changes 30 days before study recruitment. Schizophrenia patients were treated as per clinical practice, when diabetes mellitus, hypertension or hyperlipidemia was detected during study visit. The initiation of antidiabetic, antihyperlipidemia and antihypertensive was allowed after randomization when clinically indicated. Patients were also excluded if they had been treated with depot neuroleptics, unless the last injection had been at least one treatment cycle before entry.

3.4.17.4   Blinding of Study Drug

For the conduct of this double blind study, both patients and the independent rater who was the non treating psychiatrist, were blinded to the study drug. After assignment to treatment groups, patients received a fixed dose of their assigned study drug for the first week of treatment. For the subsequent visits, the dosage of the medication was flexible as the psychiatrists' clinical decision. The study medications were repackaged in opaque capsule and labeled as "1", "2a", "2b", "3a" and "3b" strength (Appendix M) to maintain blinding from the rater.

3.4.17.5   Baseline visit

Patients would be assessed for baseline visit only when prior antipsychotic treatment completely discontinued. The patients were evaluated with Positive and Negative Symptoms Scale (PANSS), Clinical Global Impression - Severity Scale (CGI-S), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathasia Scale (BAS) and Simpson Angus Scale (SAS). A complete physical examination was done including vital signs, weight, height, waist circumference, blood pressure (BP) and baseline ECG (12-lead). BP was performed as a single, seated determination. Baseline blood tests were taken for fasting blood sugar(1 ml),fasting lipid profile (2.5ml) and Hba1c (1.5ml). A urine pregnancy test was conducted for female patients with history of amenorrhea or delayed in their menses.

3.4.17.6   Follow-Up Evaluation

A follow-up evaluation was scheduled on day week 4, week 8, week 12, week 16, week 20 and week 24 after the beginning of the study. If patients could not attend the scheduled visit, patients were given appointment on the subsequent day.

The patients were evaluated with Positive and Negative Symptoms Scale (PANSS), Clinical Global Impression - Severity Scale (CGI-S), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathasia Scale (BAS), Simpson Angus Scale (SAS) and assessment of the side effects. Weight, waist circumference, blood pressure were also taken. Fasting blood tests were taken for blood sugar (1 ml) and lipid profile (2.5ml). HbA1c (1.5ml) was only taken during last study visit. A urine pregnancy test was conducted for female patients with history of amenorrhea or delayed in their menses.

If patients experienced significant side effects from the study drug, the principal investigator (PI) would inform the study psychiatrist. The psychiatrist would decide to reduce the dose for study drug during the study, depending on the clinical interview. Upward titration following a dose reduction was allowed in order to maintain efficacy of treatment during the study. Dose titration was documented in the study chart along with the clinical rationale. The concomitant medications were reviewed. During the study visit, the study termination form was completed in case of discontinuation of patient from this study.

3.4.17.7 Subject Compliance Monitoring

The research coordinator conducted pill counts at the follow-up visit for all study patients. The unused study drug was collected from the previous follow up and documented. Proper drug dosing was reviewed with patients at each visit with clear instructions to take all study drugs. The new study drug would be dispensed for every study visit.

3.4.17.8 Safety and Tolerability - Early Withdrawal of Patients

Any patients experiencing a serious adverse event felt to be related to study drug were withdrawn from the study. Patients were also withdrawn if they required hospitalization for psychiatric treatment, received other psychotropic medications, or if discontinuation from the study was deemed by the psychiatrist base on their best interest. Patients discontinued from the clinical trial were given appropriate treatment referrals to the outpatient psychiatric clinic. Patients were instructed to return all unused medications. For the early withdrawal, patients had all final assessments that originally were scheduled for the end of study visit.

All patients randomized into the study were included in the final study analyses. Although patients were withdrawn from the study, they were still contactable unless they requested not to be contacted or could not be located for the 2-weeks follow-up assessment. Patients were informed at the consent session that treatment might be discontinued due to:

i)   Intolerable side effects

ii)   Development or exacerbation of psychiatric symptoms necessitating inpatient admission or a more aggressive therapeutic intervention needed than was provided by the protocol

iii) Clinical deterioration for any reason or any clinical status that necessitates inpatient admission

iv)   Incarceration for more than 2 weeks

v)   Failure to attend 3 consecutive outpatient evaluation visits

vi)   Failure to provide 2 consecutives laboratory specimens

Reasons why patients discontinued from the clinical trial were documented on the Study Termination Form, along with any referrals that were made. A final safety

evaluation was conducted as soon as possible on all randomized patients who have been discontinued from the study.

3.4.18.   Adverse Events

i).   Recording of Adverse Events

During the research evaluation visit, the patient was asked on adverse events through specific questioning and by examination. Information on all adverse events was recorded immediately in the case report form (CRF). Each adverse event was followed up until resolution or stabilization has been achieved.

In the case of the occurrence of serious adverse event (SAE), it was followed up to determine the final outcome. Any serious adverse event that occurred after the study period was recorded and reported immediately, if PI considered possibly related to the study drug.

ii).   Reporting of Serious Adverse Events To Ethic Committee (EC) by Principle Investigator

A serious adverse event must be reported to the EC within 24 hours (one working day) of the event. The principle investigator would keep a copy of the SAE form in the file. Within the following 48 hours, the principle investigator would provide further information and progress on the serious adverse event to the EC.

In the SAE form, the following information should be provided:

(a)   Study identifier

(b)   Subject number

(c)   A description of the event

(d)   Date of onset

(e)   Current status

(f)   Whether study treatment was discontinued

(g)   The reason why the event was classified as serious

(h)   Principle investigator assessment of the association between the event and study drug

iii).   Unblinding Procedures

In the event that patients were prematurely discontinued from the trial, it was necessary to avoid breaking the blind whenever possible, in order to protect the integrity of the study. If an emergency necessitates that the blind be broken, only the principle investigator (PI) has the authority to inform the actual study drug to the study psychiatrist.

iv).   Medical Monitoring

The PI was responsible to oversee the safety of the study. This safety monitoring would include careful assessment and appropriate reporting of adverse events. Medical monitoring would include a regular assessment of the number and type of serious adverse events.

v).   Protection of Subjects

Additional procedures would be conducted to protect the safety of the study patients. Potential patients would be screened for medical illnesses that would preclude the use of aripiprazole and ziprasidone. Patients selected for the study would be evaluated for AE while receiving study drug. Venipuncture was carried out with good aseptic technique by an experienced nurse or physician. Before randomized to study drug, a physical examination, ECG and a urine pregnancy test (if female of childbearing

capability) were performed. Patients were given a 24-hour emergency number to call if necessary. The PI would follow all patients who were discontinued due to any serious AEs until the AE resolved and become completely stable, unless a referral to another physician or specialist was clinically indicated or requested by the patient.

3.4.19. Data Handling and Record Keeping

i). Data Management

The data were checked before ending each interview session and before compilation to ensure completeness. If missing data was found, the patient will be contacted through telephone. Raw data obtained were coded and entered into Statistical Package for Social Sciences (SPSS) Version 16.0. Statistical analysis was done on an intention-to-treat basis.

The data were summarized by running frequency distributions and simple descriptive statistics (means and standard deviations). Cleaning for double entry and outliers before analysis was done.

ii). Confidentiality

Information about study patients was kept confidential and managed according to the requirements of the EC.

iii). Source Data and Case Report Form

Source data was all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the evaluation of the trial. Source data were contained in source documents such as hospital records, clinic charts, laboratory results, pharmacy dispensing records, recorded data such as ECG from automated

instruments, x-rays, subject files, records kept at the pharmacy, at the laboratories, at medical record department and other related documents.

The study case report form (CRF) was the primary data collection instrument for the study. All data requested on the CRF were recorded and all missing data were explained. "N/D" was written if a space on the CRF was left blank because the procedure was not done or the question was not asked. "N/A" was written if the item was not applicable to the individual case. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line was drawn through the incorrect entry and the correct data was entered above it. All such changes were initialed and dated.

3.4.20.   Ethical consideration

Ethical clearance had been obtained earlier from UMMC's and Ministry of Health (MOH) ethical committees (Appendix I). Before any interview, patients had been informed regarding the nature and purpose of study and ensuring the respondent on confidentiality of the information.

3.4.21.   Sample Size Estimation

Based on non-inferior of efficacy and safety between aripiprazole and ziprasidone, the minimum sample size required for this study was calculated by using the PS software.

i).   The power of the study was taken at 80% level.

ii).   The significance level of the statistic tests done was at 95% Confidence Interval level and α was set at 0.05. The Null hypothesis was rejected when $p < 0.05$.

iii). p_0 - The probability of the outcome for aripiprazole (reduction of prevalence of metabolic syndrome) was 0.45.

iv). p_1 - The probability of the outcome for ziprasidone (reduction of prevalence of metabolic syndrome) was 0.3.

v).   The ratio of intervention drug to comparison drug was 1: 1.

Therefore the sample size obtained for this study as follow:

Number of treatment arm   =   162 patients

Number of control arm   =   162 patients

Total number of subjects   =   324 patients

3.4.22.   Statistical Analysis

The analyses were done on an intent-to-treat (ITT) basis. Patients with both a baseline assessment and had at least one follow-up visit and assessment were included in efficacy analyses. Patients receiving at least one dose of study drug were included in safety analyses.

The independent *t*-test was used to examine changes in means of continuous variables and rating scales such as PANSS ,CGI-S, BARS, SAS and AIMS. Skewed data was analysed using non parametric test. Categorical values were compared between groups using chi-square analysis. The discontinuation rate in treatment was analyzed using the log-rank test, and the respective survival distributions were estimated using the Kaplan-Meier Survival analysis.

Bivariate analysis was also used to observe the reversing of metabolic syndrome and its components from baseline to 6-month visit, by using the last observation carried forward (LOCF) and on the ITT population. The outcome for metabolic syndrome and its components either resolved or not, were determined by the change form baseline to endpoint with at least one study visit (LOCF).

In addition, the mean of Framingham risk score was also compared according to patients' age group with the treatment groups (aripiprazole and ziprasidone) at baseline and 6-month visit. The multiple comparisons were analyzed using Two-Way Interaction in Three-Way Anova with Bonferroni correction and adjusting for sex.

The measures of comparative efficacy and safety were determined by using two analytic approaches: mixed-effects model with repeated measures (MMRM) to analyze continuous data repeated measures such PANSS, CGI-S, BARS, SAS, AIMS,

the metabolic effects such as fasting glucose level, waist circumference, lipid levels and other paremeters (e.g weight, BMI, CHD risk score-Framingham). The MMRM provided estimates of missing data by using available data from all subjects. Generalised estimating equations (GEE) was used of analysing categorical data repeated measures such as prevalence of metabolic syndrome and its components, CVRF and CHD risk –Framingham and discontinuation rate. GEE assumed that missing data were missing 'completely at random'

For MMRM, least squares (LS) means were used to estimate the treatment effects from an analysis of covariance model, with fixed effect terms for treatment (aripiprazole and ziprasidone), study visit (baseline, month 1, 2, 3, 4, 5, 6) and interaction of treatment and visit on the ITT population. The correlation of the repeated measures within each subject was modeled with an unstructured covariance matrix. The LS mean change of each study visit was the difference of LS means each study visit with baseline, after adjusting with pairwise comparisons and Bonferroni correction. The overall difference in LS means over a 24-week period was evaluated by having the p value associated with the overall drug effect in MMRM obtained using type III analysis.

The adverse events between aripiprazole and ziprasidone were described as proportion on the ITT population. Sensitivity analyses were conducted by excluding from the analysis individuals who began antihyperlipidemic, antihypertensive and antidiabetic drug therapy after randomization as concomitant medication. The SPSS version 16.0 statistical package was used throughout. An alpha level of significance $p < 0.05$ was set for all analyses.

3.5 Results

3.5.1. RESULTS AT THE BASELINE OF RANDOMIZATION

Demographics

Out of 175 patients recruited for the study, 51.4% (90/175) was randomized to aripiprazole and 48.6% (85/175) to ziprasidone.

At baseline, 30% of the patients randomized to aripiprazole have age 30-39 years old whereas 25.9% of the patients randomized to ziprasidone have age 40-49 years old. The mean age of the patient randomized to ziprasidone was younger than aripiprazole group although not statistically significant. (38.8 ± 11.8 vs. 40.5 ± 11.8 years old). The means BMI of the patients randomized to aripiprazole and ziprasidone were in the overweight group (BMI 25 to < 30). Majority of the patients randomized in both groups were male, single, has education level of secondary school and unemployed.

There was no statistically significant for demographic characteristic among schizophrenic patients either randomized to aripiprazole or ziprasidone at baseline (Table 3.4).

Lifestyle

At baseline, the percentage of smokers and former smokers were high in the aripiprazole and ziprasidone group (47.1% vs. 49.4%). Among the current and former smokers, majority smoked less than 20 sticks cigarettes/day for both groups. Majority of the patients have sedentary lifestyle with hardly any physical activity for both aripiprazole and ziprasidone group (Table 3.5).

3 RCT Aripiprazole vs. Ziprasidone

Table 3.4 Demographics characteristics at baseline of schizophrenia patient between aripiprazole and ziprasidone

Characteristics	Aripiprazole (n=90)	Ziprasidone(n=85)	P value
Age(year)mean ± SD	40.5 ± 11.8	38.8.± 11.8	p>0.05*
Age group (n =175),n (%)			
< 20[‡]	0(0)	3(3.5)	p>0.05
20 – 29	19(21.1)	20(23.5)	
30 – 39	27(30.0)	21(24.7)	
40 – 49	17(18.9)	22(25.9)	
50 – 59	20(22.2)	15(17.6)	
> 60	7(7.8)	4(4.8)	
BMI(kg/m^2) mean ± SD	27.7 ± 5.2	28.1± 5.6	p>0.05*
BMI[¶](n =175),n(%)			
Underweight(<18.5)	2(2.2)	0(0)	p>0.05
Normal(18.5 – 24.9) [‡]	28(31.1)	28(32.9)	
Overweight(25 – < 30)	35(38.9)	32(37.6)	
Obese(≥ 30)	25(27.8)	25(29.5)	
Sex (n =175),n (%)			
Male[‡]	52(57.8)	55(64.7)	
Female	38(42.2)	30(35.3)	p>0.05
Race (n = 175),n (%)			
Malay[‡]	34(37.8)	31(36.5)	p>0.05
Chinese	35(38.9)	29(34.1)	
Indian	9(10.0)	12(14.1)	
others	12(13.3)	13(15.3)	
Marital status (n=173) ,n (%)			
Married[‡]	30(33.3)	17(20.5)	p>0.05
Single	51(56.7)	58(69.9)	
Divorced	5(5.6)	6(7.2)	
widowed	4(4.4)	2(2.4)	
Education level(n=164) ,n (%)			
No formal education[‡]	4(4.7)	2(2.6)	p>0.05
Primary	15(17.4)	17(21.8)	
Secondary	56(65.1)	55(70.5)	
Tertiary	11(12.8)	4(5.1)	
Occupation (n=172),n (%)			
Employed[‡]	29(32.6)	23(27.7)	p>0.05
Unemployed	55(61.8)	56(67.5)	
Housewife	5(5.6)	4(4.8)	
Care setting (n=175), n (%)			
General hospital[‡]	42(46.7)	42(49.4)	p>0.05
Institution	48(43.3)	43 (50.6)	

Chi square test, *t-test, ‡ Reference group

BMI[¶] - Chi square test based on category normal (reference group), overweight and obese.

Medical and Psychiatric History

At baseline, only four out of ten patients in the aripiprazole randomized group and one out of five patients in ziprasidone randomized group knew they developed hypertension after initiation of antipsychotics treatment.

Only two out of 15 patients in the aripiprazole randomized group and three out of six patients in ziprasidone randomized group knew they developed diabetes mellitus after initiation of antipsychotics treatment.

At baseline, patients randomized to aripiprazole have 31.3% family history of hypertension and patients randomized to ziprasidone have 42.3% family history of hypertension. Patients in ziprasidone randomized group have 32.9% family history of diabetes mellitus and 24.4% of aripiprazole randomized group has family history of diabetes mellitus. Patients in ariprazole randomized group have 17.8% family history of obese and 25.9% of ziprasidone randomized patients have family history of obese.

The mean age of onset for schizophrenia in aripiprazole randomized group was slightly younger (25.7 ± 8.7 vs. 27.2 ± 8.6 years old) and the mean duration of illness in year was longer (12.5 ± 10.0 vs. 10.5 ± 8.9 year) compared to ziprasidone randomized group. About one third of both treatment groups had history of relapse of schizophrenia.

However, there was no statistically significant for lifestyle, medical and psychiatric history among schizophrenia patients randomized to aripiprazole and ziprasidone at baseline (Table 3.5).

3 RCT Aripiprazole vs. Ziprasidone

Table 3.5 Lifestyle, medical and psychiatric history between aripiprazole and ziprasidone

Characteristics	Aripiprazole (n=90)	Ziprasidone(n=85)	P value
	n (%)	n (%)	
Smoking	n=85	n=79	
Never[‡]	45(52.9)	40(50.6)	p>0.05
Former smoker < 20 sticks/day	17(20.0)	11(13.9)	
Former smoker > 20 sticks/day	2(2.4)	1(1.3)	
Current smoker < 20 sticks/day	13(15.3)	18(22.8)	
Current smoker > 20 sticks/day	8(9.4)	9(11.4)	
Duration of quitting smoking	n=4	n=6	
≥ 10 years[‡]	3(75.0)	5(83.3)	p>0.05
5 - 9 years	0(0)	1(16.7)	
1 – 4 years	1(25.0)	0(0)	
< 1 year	0(0)	0(0)	
Physical activity	n=86	n=79	
Never[‡]	35(40.7)	38(48.1)	p>0.05
Rarely	24(27.9)	22(27.8)	
1 -3 times/month	3(3.5)	1(1.4)	
1-2 times /week	5(5.8)	8(10.1)	
3 -4 times /week	9(10.5)	5(6.3)	
≥ 5 times /week	10(11.6)	5(6.3)	
Medical history			
Hypertension after initiation of antipsychotics(n=161)	10(11.9)	5(6.5)	p>0.05
Diabetes mellitus after initiation of antipsychotics(n=158)	15(18.1)	6(8.0)	p>0.05
Gestational diabetes (female)(n=30)	1(5.9)	1(7.7)	p>0.05
Family history			
Hypertension(n=154)	26(31.3)	30(42.3)	p>0.05
Diabetes mellitus(n=155)	20(24.4)	24(32.9)	p>0.05
Parent obese(n=156)	7(8.5)	13(17.6)	p>0.05
Siblings obese(n=156)	9(11.0)	9(12.2)	p>0.05
Psychiatric history			
Age of onset(year) **mean ± SD**	26.3 (8.9)	27.2 (8.5)	p>0.05*
Duration of illness (year) **mean ± SD**	12.6 (9.3)	10.5 (9.2)	p>0.05*
History of relapse(n=175)	27(30.0)	27(31.8)	p>0.05
No of psychiatric hospitalization, **mean ± SD**	1.2(2.6)	0.8(1.6)	p>0.05*

Chi square test, *t-test, ‡ Reference group

3 RCT Aripiprazole vs. Ziprasidone

Characteristics of treatment with antipsychotics and other medication

Comparing the antipsychotic used before the randomization of aripiprazole and ziprasidone, the usage of atypical antipsychotics monotherapy (60.0% vs. 56.5%) was more than typical antipsychotics monotherapy (17.8% vs. 17.6%) for both groups. As for the combination of antipsychotics, the combination of typical and atypical antipsychotics was commonly used before the randomization of aripiprazole and ziprasidone (Table 3.6).

Perphenazine and chlorpromazine were the commonest typical antipsychotics used as monotherapy before randomization to aripiprazole and ziprasidone. Olanzapine has the highest proportion of monotherapy usage of atypical antipsychotics (42.6% vs. 43.7%) followed by risperidone (31.5% vs. 37.5%) and paliperidone (24.1% vs. 12.5%) prior to randomization to aripiprazole and ziprasidone.

Prior to randomization, anticholinergic e.g trihexyphenydyl (benzhexol) was commonly used for both patients randomized to aripiprazole and ziprasidone. The usage of benzodiazepine prior randomized to ziprassidone and aripiprazole was 15.3% vs. 13.3%. ($p < 0.05$). Very few patients were on hyperglycaemic agent, antihypertensive and lipid-lowering medications prior randomized to aripiprazole and ziprasidone (Table 3.6).

Table 3.6 Characteristics of treatment with antipsychotic and other medication between aripiprazole and ziprasidone at baseline

Characteristics	Aripiprazole (n=90)	Ziprasidone (n=85)	P value
Use antipsychotic before study	n(%)	n(%)	
Atypical antipsychotics (monotherapy)[‡]	54(60.0)	48(56.5)	p>0.05
Typical antipsychotics (monotherapy)	16(17.8)	15(17.6)	
Combination of Typical and Atypical Antipsychotics	12(13.3)	11(12.9)	
Combination of Atypical Antipsychotics	4(4.4)	3(3.6)	
Combination of Typical Antipsychotics	4(4.4)	8(9.4)	
Typical antipsychotics(monotherapy)			
Haloperidol[‡]	1(6.2)	2(13.3)	p>0.05
Perphenazine	5(31.3)	3(20.0)	
Sulpiride	3(18.8)	4(26.7)	
Chlorpromazine	4(25.0)	3(20.0)	
Trifluoperazine	2(12.5)	1(6.7)	
Flupenthixol decanoate	0(0)	2(13.3)	
Fluphenazine decanoate	1(6.2)	0(0)	
Atypical antipsychotics(monotherapy)			
Olanzapine[‡]	23(42.6)	21(43.7)	p>0.05
Risperidone	17(31.5)	18(37.5)	
Quetiapine	1(1.8)	2(4.2)	
Amisulpride	0(0)	1(2.1)	
Paliperidone	13(24.1)	6(12.5)	
Concomitant medication			
Anticholinergic	32(35.6)	30(35.3)	p>0.05
Benzodiazepine	12(13.3)	13(15.3)	**p<0.05**
antidepressants	10(11.1)	6(7.1)	p>0.05
Other medication			
Antidiabetic medication	5(5.6)	7(8.2)	p>0.05
Blood pressure lowering	2(2.2)	7(8.2)	p>0.05
Lipid-lowering medication	9(10.0)	5(5.9)	p>0.05

Chi square test, ‡ Reference group, NA- not applicable

3 RCT Aripiprazole vs. Ziprasidone

Table 3.6 Characteristics of treatment with antipsychotic and other medication between aripiprazole and ziprasidone at baseline (con't)

Characteristics	Aripiprazole (n=90)	Ziprasidone (n=85)	P value
Antipsychotic Mean Daily Dose, mg(SD)			
Typical antipsychotics			
Haloperidol	15.6(9.3)	11(8.6)	p>0.05
Perphenazine	8(3.3)	15(10.0)	p>0.05
Sulpiride	470(282.0)	475(452.8)	p>0.05
Chlorpromazine	230(168.7)	210(157.0)	p>0.05
Trifluoperazine	10(0.0)	15(5.0)	p>0.05
Flupenthixol decanoate	-	35.7(19.7)	NA
Fluphenazine decanoate	50(14.1)	-	NA
Atypical antipsychotics			
Olanzapine	13(4.9)	14.6(7.7)	p>0.05
Oral risperidone	3(1.8)	3.3(1.6)	p>0.05
IM risperidone	25(0.0)	43.8(8.8)	p>0.05
Quetiapine	372(240.7)	550(353.6)	p>0.05
Amisulpride	-	800	NA
Paliperidone	6.9(2.2)	9(6.9)	p>0.05
Duration of antipsychotics treatment in year, mean(SD)			
Typical antipsychotics			
Haloperidol	15.3(6.3)	7.4(5.6)	p>0.05
Perphenazine	2.9(2.3)	4.8(1.4)	p>0.05
Sulpiride	6.6(6.1)	9.3(9.8)	p>0.05
Chlorpromazine	5.5(2.7)	9.7(8.6)	p>0.05
Trifluoperazine	10.7(5.4)	11.4(2.4)	p>0.05
Flupenthixol decanoate	-	7.8(8.9)	NA
Fluphenazine decanoate	3.5(1.8)	-	NA
Atypical antipsychotics			
Olanzapine	4.5(4.0)	3.1(0.9)	p>0.05
risperidone	5.6(3.9)	3.3(2.3)	p>0.05
Quetiapine	3.0(1.2)	2.7(1.0)	p>0.05
Amisulpride	-	2.2(1.1)	NA
Paliperidone	4.6(0.4)	5.7(0.3)	p>0.05

Chi square test, ‡ Reference group, NA- not applicable

Table 3.7 Mean and Median of Clinical Rating Scale Scores between aripiprazole or ziprasidone treatment at baseline

Rating Scale	Aripiprazole (n=90)	Ziprasidone(n=85)	P value
PANSS score			
Total			
Mean (±SD)	56.4 ± 17.0	59.4.± 21.8	
Median (Interquartile range)	53.5(46.0-65.3)	56.0(43.5-71.5)	p>0.05*
Positive			
Mean (±SD)	13.5 ± 4.7	14.7 ± 6.3	
Median (Interquartile range)	12.5(10.0-16.0)	13.0(10.0-17.0)	p>0.05*
Negative			
Mean (±SD)	14.9 ± 5.8	16.1 ± 7.2	
Median (Interquartile range)	14.0(10.0-18.3)	15(10.0-21.0)	p>0.05*
CGI-S score			
Mean (±SD)	3.1 ± 0.8	3.3 ± 1.0	p>0.05
Median (Interquartile range)	3.0(3.0-3.0)	3.0(3.0-4.0)	
BARS			
Mean (±SD)	0.7 ± 2.2	0.4 ± 1.4	
Median (Interquartile range)	0(0.0-0.0)	0(0.0-0.0)	p>0.05*
SAS			
Mean (±SD)	1.1 ± 2.4	1.2 ± 2.6	
Median (Interquartile range)	0(0-1.0)	0(0-1.0)	p>0.05*
AIMS			
Mean (±SD)	0.8 ± 2.8	0.8 ± 2.2	
Median (Interquartile range)	0(0.0-0.0)	0(0.0-0.0)	p>0.05*

t-test ,* Mann-Whitney U test
PANSS -Positive and Negative Syndrome Scale, CGI-S : Clinical Global Impression-Severity Scale, SAS- Simpson-Angus Rating Scale, BARS-Barnes Akathisia Rating Scale, AIMS- Abnormal Involuntary Movement Scale

Rating Scales

At baseline, there was no statistically significant difference in the mean and median of

all the rating scales (PANSS, CGI-S, BARS, SAS and AIMS) between patients

randomized to aripiprazole and ziprasidone (Table 3.7).

3 RCT Aripiprazole vs. Ziprasidone

Prevalence of metabolic syndrome and its criteria

The definition of metabolic syndrome was based on two different definitions, namely Modified National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) with Asians values for waist circumference and modified International Diabetes Federation (IDF) with South Asians values for waist circumference.

At baseline, the prevalence of metabolic syndrome was higher in aripiprazole randomized group compare to ziprasidone randomized group either using NCEP ATP III (60.0% vs. 51.8%) or IDF criteria (57.8% vs. 51.8%). The overall prevalence of metabolic syndrome was 56% (95% CI: 48.6 - 63.2) with NCEP ATP III and 54.9% (95% CI: 47.5 − 62.1) with IDF criteria. There was no statistically significant in the proportion of metabolic syndrome status among those randomized to aripiprazole and ziprasidone (Table 3.8).

For the prevalence of metabolic syndrome components at baseline in those randomized to aripiprazole and ziprasidone, the prevalence of abnormal waist circumference was the highest (83.3% vs. 88.2%) followed by abnormal HDL (54.4% vs. 48.2%).

The mean waist circumference for male was higher than female in those randomized to aripiprazole (97.6 ± 13.7cm vs. 93.8 ± 9.1cm) and ziprasidone (97.7± 11.2cm vs. 94.6 ± 12.6 cm). The median of HDL cholesterol for female in patients randomized to aripiprazole and ziprasidone at baseline fulfilled the metabolic syndrome criteria (45.4 mg/dl, Interquartile range: 36.6 - 56.0 mg/dl vs. 44.1 mg/dl, Interquartile range: 36.8 - 53.6 mg/dl).

There was statistically significant difference in the proportion and median of FBS between those randomized to aripiprazole and ziprasidone. The median of FBS for

aripiprazole baseline group was higher compared to ziprasidone group (95.4 mg/dL,interquartile range 86.4-113.4 mg/dl vs. 90.0 mg/dL, interquartile range 84.6-100.8 mg/dl). There was statistically significant difference also for median of Hba1c between both randomized to aripiprazole and ziprasidone (Table 3.8).

Table 3.8 Prevalence of Metabolic Syndrome(MetS) and its components according aripiprazole and ziprasidone at Baseline

	Aripiprazole(n=90)		Ziprasidone(n=85)		Overall (n=175)		*p*
	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	
MetS Prevalence							
NCEP ATP III*	53(58.9)	48.6-68.5	44(51.8)	41.8-62.7	97(55.4)	48.0-62.6	p>0.05
IDF**	52(57.8)	47.5-67.5	44(51.8)	41.8-62.7	96(54.9)	47.5-62.1	p>0.05
Metabolic syndrome components							
Waist circumference (Male ≥90 cm , female ≥80 cm)	76(84.4)	75.6-90.5	74(87.1)	78.3-92.6	150(85.7)	79.8-90.1	p>0.05
HDL (Male< 40 mg/dL ,female < 50mg/dL)	49(54.4)	44.2-64.3	45(52.9)	42.4-63.2	94(53.7)	46.3-60.9	p>0.05
Triglyceride (≥150mg/dL)	45(50.0)	39.9-60.1	32(37.6)	28.1-48.3	77(44.0)	36.9-51.4	p>0.05
BP(≥130/85 mmHg)	37(41.1)	31.5-51.4	42(49.4)	39.0-59.8	79(45.1)	38.0-52.5	p>0.05
Fasting glucose(≥100 mg/dL)	38(42.2)	32.5-52.5	22(25.9)	17.8-36.1	60(34.3)	27.7-41.6	**p<0.05**
Laboratory test parameters		95% CI		95% CI		95% CI	
Fasting blood glucose(mg/dL) Mean(SD)	109.9(40.9)	101.3-118.5	95.8(24.7)	90.5-101.2	103.1(34.7)	97.9-108.3	
Median (Interquartile range)		95.4 (86.4-113.4)		90.0 (84.6-100.8)		91.8 (86.4-106.2)	**p<0.05****
HbA1c (%)							
Mean(SD)	6.5(1.8)	6.1-6.8	5.9(0.9)	5.7-6.1	6.2(1.4)	5.9-6.4	
Median (Interquartile range)		5.8 (5.5-6.6)		5.7(5.4-6.0)		5.8 (5.5-6.2)	**p<0.05****
Total Cholesterol (mg/dL)							
mean(SD)	214.2(50.0)	203.7-224.7	206.4(36.8)	198.5-214.3	210.4(44.1)	203.8-217.0	p>0.05*
LDL Cholesterol (mg/dL)							
Mean(SD)	137.6(44.2)	128.3-147.0	131.5(33.4)	124.2-138.8	134.7(39.3)	128.7-140.6	
Median (Interquartile range)		129.2 (108.9-157.7)		129.9 (114.8-152.8)		129.7 (111.2-155.1)	p>0.05**
HDL Cholesterol(mg/dL)							
Male, Mean(SD)	41.3(8.7)	38.9-43.7	43.1(14.8)	39.2-47.1	42.3(12.2)	39.9-44.6	
Median (Interquartile range)		39.8 (34.9-48.2)		41.4 (35.6-46.0)		40.6 (35.2-46.8)	p>0.05**
Female, Mean(SD)	47.8(13.0)	43.5-52.1	46.2(11.8)	41.8-50.6	47.1(12.4)	44.1-50.1	
Median (Interquartile range)		45.4 (36.6-56.0)		44.1 (36.8-53.6)		45.1 (36.8-53.9)	p>0.05**
Triglycerides (mg/dL)							
Mean(SD)	176.6(140.0)	147.3-205.9	161.1(126.1)	133.9-188.3	169.1 (133.3)	149.2-189.0	
Median (Interquartile range)		150.1 (112.5-204.8		131.1 (101.9-191.3)		138.2 (108.9-194.0)	p>0.05**

Table 3.8   Prevalence of Metabolic Syndrome(MetS) and its components according aripiprazole and ziprasidone at Baseline(Cont')

	Aripiprazole(n=90)		Ziprasidone(n=85)		Overall (n=175)		*p*
	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	
Other parameters	Mean(SD)	95% CI	Mean(SD)	95% CI	Mean(SD)	95% CI	
Waist circumference (cm)							
Male	97.6(13.7)	93.8-101.4	97.7(11.2)	94.7-100.7	97.7(12.4)	95.3-100.1	p>0.05*
Female	93.8(9.1)	90.8-96.8	94.6(12.6)	89.9-99.3	94.2(10.7)	91.6-96.8	
Median (Interquartile range)	93.0	(87.4-100.3)	92.5	(84.6-104.5)	92.5	(85.3-101.0)	p>0.05**
Systolic BP(mm Hg)	125.0(16.7)	121.5-128.5	123.6(15.1)	120.3-126.9	124.3(16.0)	122.6-126.1	p>0.05*
Diastolic BP(mm Hg)	80.8(12.4)	78.2-83.4	80.9(11.4)	78.4-83.4	80.9(11.9)	79.6-82.8	p>0.05*

NCEP ATP-III* and IDF** have Asian values for waist circumference
Chi square test, *t-test ,** Mann-Whitney U test

Prevalence of CVRFs and CHD risk (Framingham)

Among the cardiovascular risk factors (CVRFs) according to Framingham criteria, there was statistically significant difference for the proportion of diabetes mellitus between patients randomized to aripiprazole and ziprasidone at baseline. The prevalence of diabetes mellitus in aripiprazole randomized group was much higher than ziprasidone randomized group at baseline (22.2%, 95% CI: 14.9%-31.9% vs. 9.4%, 95% CI: 4.9%-17.5%). For other risk factors, the prevalence of HDL cholesterol was the highest (66.7%, 95% CI: 56.4%-75.6% vs. 74.1%, 95% CI: 63.9%-82.2%) followed by total cholesterol (56.7%, 95% CI: 46.4%-66.4% vs. 61.2%, 95% CI: 50.6%-70.8%) for both randomized groups of aripiprazole and ziprasidone at baseline, however there was no statistically significant for the above findings (Table 3.9).

There was no statistically significant difference in the median of Framingham risk score between patients randomized to aripiprazole and ziprasidone at baseline. In the

ziprasidone group, the means of Framingham risk score was 4.5 ± 5.7, which means about 5 of 100 people with this level of risk would have a heart attack in the next 10 years. In the aripiprazole group, the means of Framingham risk score was 3.6 ± 4.3, which means that about 4 of 100 people with this level of risk would have a heart attack in the next 10 years.

The prevalence of patients with high and very high risk of CHD in 10 years (Framingham) was much higher at baseline in those randomized to ziprasidone compared to aripiprazole randomized group. (18.8%, 95% CI: 11.9%-28.4% vs. 8.9%, 95% CI: 4.6%-16.6%) However there was no statistically significant difference between patients with high and very high risk of CHD in 10 years at baseline between patients randomized to aripiprazole and ziprasidone.

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Table 3.9 Prevalence of CVRFs and CHD risk (Framingham) according to aripiprazole and ziprasidone at Baseline

	Aripiprazole (n=90)		Ziprasidone(n=85)		Overall (n=175)		*p*
	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	
Age≥40(male) or≥45(female) years	42(46.7)	36.7-56.9	36(42.4)	32.4-53.0	78(44.6)	37.4-52.0	p>0.05
Smoker	21(23.3)	15.8-33.1	27(31.8)	22.8-42.3	48(27.4)	21.4-34.5	p>0.05
Diabetes (known diagnosis or glucose ≥126 mg/dL)	20(22.2)	14.9-31.9	8(9.4)	4.9-17.5	28(16.0)	11.3-22.2	**p<0.05**
Total cholesterol ≥ 200 mg/dL	51(56.7)	46.4-66.4	52(61.2)	50.6-70.8	103(58.9)	51.5-65.9	p>0.05
HDL cholesterol (male< 45mg/ dL or female< 50mg/dL)	60(66.7)	56.4-75.6	63(74.1)	63.9-82.2	123(70.3)	63.1-76.6	p>0.05
SBP ≥140 or ≥ 130 mmHg (Diabetes, prior cardiovascular or kidney disease)	20(22.2)	14.9-31.9	15(17.6)	11.0-27.1	35(20.0)	14.8-26.5	p>0.05
DBP ≥90 or ≥ 80 mmHg (Diabetes, prior cardiovascular or kidney disease)	21(23.3)	15.8-33.1	22(25.9)	17.8-36.1	43(24.6)	18.8-31.5	p>0.05
Risk of CHD in 10 years(Framingham) Mean(SD)	3.6(4.3)	2.7-4.5	4.5(5.7)	3.3-5.8	4.1(5.0)	3.3-4.8	
Median (Interquartile range)	2.0 (0.5-5.0)		2.0 (0.5-7.0)		2.0 (0.5-6.0)		p>0.05*
Patients (%)with very high/high(≥10%) risk of CHD in 10 years(Framingham)	n(%)	95% CI	n(%)	95% CI	n(%)	95% CI	
	8(8.9)	4.6-16.6	16(18.8)	11.9-28.4	24(13.7)	9.4-19.6	p>0.05

Chi square test, * Mann-Whitney U test
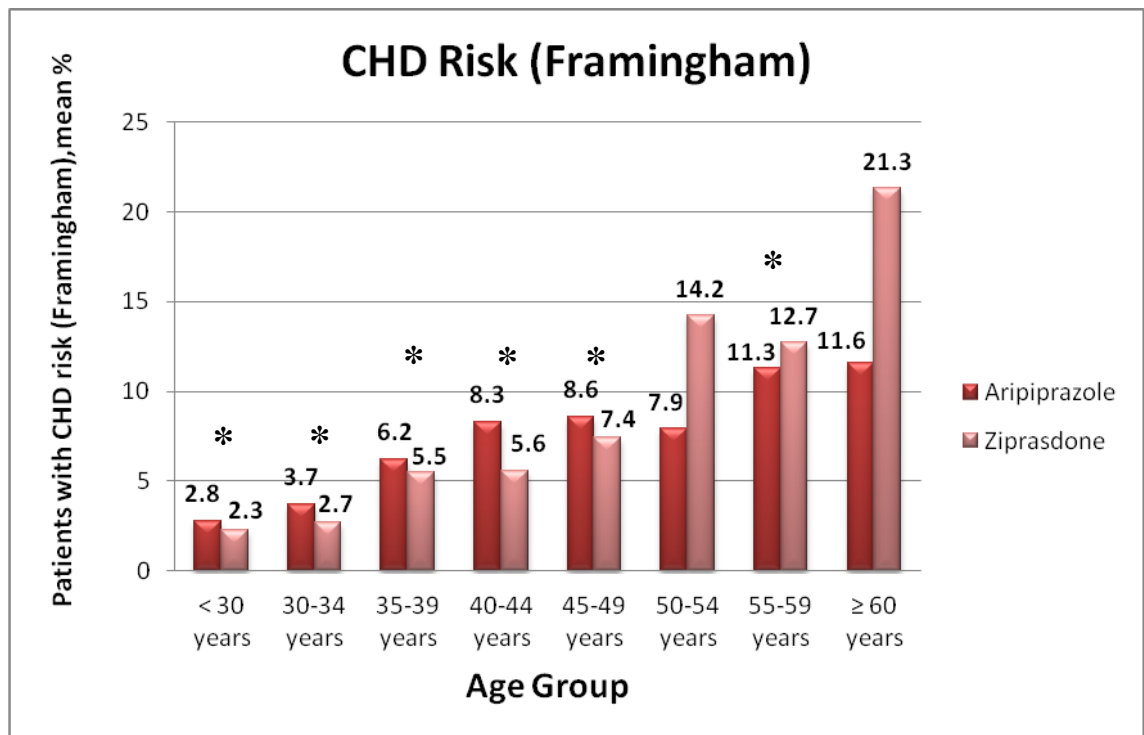
Figure 3.5 Risk of CHD (Framingham) at baseline according to aripiprazole and ziprasidone

MANCOVA adjusted for sex , corrected by Bonferroni formula for multiple comparisons *p<0.007
Model:Intercept , sex, age group, randomization, age group*randomization
CHD - coronary heart disease

The means of CHD risk score (Framingham) was increased in trend from age group < 30 years old to ≥ 60 years old for aripiprazole and ziprasidone group at baseline. Later, a Multivariate General Linear Model (MANCOVA) was performed adjusted for sex and using Bonferroni correction p<0.007 for multiple comparisons of means age group. There was significant differences in comparing the effect of all age groups and randomization at baseline (aripiprazole vs. ziprasidone) with the means CHD risk score (Framingham) except for age groups 50-54 years old and ≥ 60 years old (Figure 3.5).

Figure 3.6 Flow Chart of Screening, Randomization, Follow-up and Assessments of Study Participants


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                    ┌─────────────────────────┐
                    │ Assessed for eligibility │
                    │       (n= 527)           │
                    └─────────────────────────┘
```

Excluded (n= 352)
Not meeting inclusion criteria=57
- Bipolar disorder=42, clozapine=6, aripiprazole =7, no medication=2
No fasting blood investigation=87
Absence of metabolic abnormalities=57
Antipsychotics treatment < 1 year=52
Refused to participate= 99

Enrollment

Allocation

Aripiprazole
Allocated to intervention
(n=90)

Ziprasidone
Allocated to intervention
(n= 85)

Lost to follow-up (n=9)
Discontinued intervention(n= 26)
-Withdraw consent =16
-Lack of efficacy = 6
-Adverse event=2
- Non compliance=2

Follow-up

Lost to follow-up (n=4)
Discontinued intervention(n=36)
-Withdraw consent =20
-Lack of efficacy = 3
-Adverse event=9
- Non compliance=2
- Relapse =2

Per protocol Analysis (n=55)
ITT Analysis (n=90)

Analysis

Per protocol Analysis (n=45)
ITT Analysis (n=85)

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RESULTS AT THE STUDY VISITS

Prevalence of Metabolic Syndrome

The prevalence of metabolic syndrome was significantly reduced from baseline to 6 months study visit for both aripiprazole and ziprasidone group either using NCEP ATP III and IDF definitions. The prevalence of metabolic syndrome was slightly lower with IDF definition compared to NCEP ATP III definition. At 6 months, the prevalence of metabolic syndrome dropped by 30.0% for aripiprazole and 36.5% for ziprasidone by using to NCEP ATP III definition. Whereas by using IDF definition, the prevalence of metabolic syndrome dropped by 27.8% for aripiprazole and 36.5% for ziprasidone (Table 3.10).

Both aripiprazole and ziprasidone significantly cause reduction in prevalence of metabolic syndrome at 6 month, and there was statistically significant difference in the prevalence of metabolic syndrome at 6 months between aripiprazole and ziprasidone. When GEE was performed, there was statistically significant for the time effect for prevalence of metabolic syndrome, indicating reduction in prevalence of metabolic syndrome over time. However there was no statistically significant difference for intervention x time interaction effect comparing the reduction of prevalence of metabolic syndrome between aripiprazole and ziprasidone (Table 3.11).

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Table 3.10 Prevalence of metabolic syndrome with NCEP ATP III and IDF definition by study visit

	Baseline %	(n)	1 month %	(n)	2 months %	(n)	3 months %	(n)	4 months %	(n)	5 months %	(n)	6 months %	(n)
NCEP ATP III*														
Aripiprazole (N=90)	58.9	(53)	40.0	(36)	32.2	(29)	33.3	(30)	33.3	(30)	25.6	(23)	30.0	(27)
Ziprasidone (N=85)	51.8	(44)	41.2	(35)	31.8	(27)	27.1	(23)	24.7	(21)	23.5	(20)	¶ 15.3	(13)
IDF**														
Aripiprazole (N=90)	57.8	(52)	37.8	(34)	31.1	(28)	33.3	(30)	33.3	(30)	25.6	(23)	30.0	(27)
Ziprasidone (N=85)	51.8	(44)	35.3	(30)	30.6	(26)	25.9	(22)	24.7	(21)	22.4	(19)	¶ 15.3	(13)

Chi square test, ¶ p<0.05 , NCEP ATP-III* and IDF** have Asians values for waist circumference

Table 3.11 Generalized estimating equation (GEE) for NCEP ATP III and IDF among schizophrenia patients

Source	NCEP ATP III* Wald Chi-Square	Sig.	IDF** Wald Chi-Square	Sig.
Intercept	0.799	0.371	1.731	0.188
Time	15.407	0.017	13.387	0.037
Intervention	0.535	0.464	0.890	0.345
Intervention * Time	13.599	0.034	8.923	0.178

Dependent Variable: NCEP ATP III and IDF, Model: Intercept, Time (Baseline, month 1, 2, 3, 4, 5 and 6),
Intervention (aripiprazole and ziprasidone), Intervention * Time

Metabolic syndrome and its components resolved or developed after 6 months of treatment

The overall prevalence of metabolic syndrome and its components reduced at 6 months visit as compared to baseline for both NCEP ATP III and IDF definitions. At 6 months, the prevalence of waist circumference dropped by 45.1%, 26.3% dropped for the prevalence of triglycerides and 23.4% dropped for the prevalence of HDL cholesterol. For both definitions, the overall cases of metabolic syndrome resolved were 16% vs. 15.4%, whereas only 5.1% vs. 4.6% new cases of metabolic syndrome developed. For metabolic syndrome components, the highest overall prevalence of cases resolved was triglycerides followed by waist circumference (16.0% vs. 15.4%). However, the highest overall prevalence of cases developed was blood pressure followed by HDL cholesterol (13.1% vs. 8.6%) after 6 months of treatment. Nevertheless, the overall cases resolved for metabolic syndrome components were more than new cases developed except for blood pressure (Table 3.12).

Metabolic syndrome resolved or developed after 6 months of treatment between aripiprazole and ziprasidone

The cases of metabolic syndrome resolved for both aripiprazole and ziprasidone were 14.4% vs. 17.6% using NCEP ATP III definition and 13.3% vs.17.6% when using IDF definition. The cases resolved for metabolic syndrome in aripiprazole and ziprasidone group were much higher as compared to new cases of metabolic syndrome developed in both groups (NCEP ATP III: 6.7% vs. 3.5%, IDF: 5.6% vs.3.5%) (Table 3.13).

3 RCT Aripiprazole vs. Ziprasidone

Table 3.12 Prevalence of metabolic syndrome at baseline and 6 months after randomization, metabolic syndrome and its components resolved or developed after 6 months of randomization

Criterion	Baseline prevalence n (%)(N=175)	6-months prevalence n (%)(N=175)	Cases resolved (N=175) n(%)	Cases developed (N=175) n (%)
NCEP ATP III*	97(55.4)	40(22.9)	29(16.6)	9(5.1)
IDF**	96(54.9)	40(22.9)	29(16.6))	9(5.1)
Waist circumference	150(85.7)	70(40.0)	25(14.3)	2(1.1)
Blood pressure	79(45.1)	40(22.9)	18(10.3)	23(13.1)
HDL	94(53.7)	50(28.6)	23(13.1)	16(9.1)
Triglycerides	77(44.0)	30(17.1)	27(15.4)	9(5.1)
Blood glucose	60(34.3)	25(14.3)	16(9.1)	5(2.9)

NCEP ATP-III* and IDF** have Asian values for waist circumference

Table 3.13 Prevalence of metabolic syndrome (MetS) at baseline and 6 months after randomization, metabolic syndrome (MetS) resolved or developed 6 months after randomization

	Aripiprazole(N= 90) % (n)	Ziprasidone(N=85) % (n)	p value
Baseline prevalence MetS	58.9(53)	51.8(44)	p> 0.05
6-month prevalence MetS	30.0(27)	15.3(13)	**p< 0.05**
Cases resolved MetS	14.4(13)	18.8(16)	p> 0.05
Cases developed MetS	5.6(5)	4.7(4)	p> 0.05
Baseline prevalence IDF	57.8(52)	51.8(44)	p> 0.05
6-month prevalence IDF	30.0(27)	15.3(13)	**p< 0.05**
Cases resolved IDF	14.4(13)	18.8(16)	p> 0.05
Cases developed IDF	5.6(5)	4.7(4)	p> 0.05

Chi square test

Mets based on definition NCEP ATP-III , IDF - International Diabetes Federation

Prevalence of metabolic syndrome components by study visit between aripiprazole and ziprasidone

From baseline to 6 months study visit, there was reduction in the prevalence of all metabolic syndrome components for both aripiprazole and ziprasidone group. The highest reduction in prevalence was waist circumference, dropped by 40.0% in aripiprazole and 51.8% in ziprasidone group. The lowest reduction in prevalence was blood pressure in both groups (15.5% vs. 15.9%) (Table 3.14).

There was statistically significant difference in the prevalence of triglycerides at baseline between aripiprazole and ziprasidone (50.0% vs. 37.6%). There was also statistically significant difference in the prevalence of fasting blood glucose at baseline (42.2% vs. 25.9%) and 6 months (20.0% vs. 8.2%) between aripiprazole and ziprasidone (Table 3.14). When GEE was performed for metabolic syndrome components, there was statistically significant for intervention x time interaction effect comparing the reduction of prevalence of fasting blood glucose between aripiprazole and ziprasidone. There was also statistically significant in the time effect for waist circumference, indicating reduction in prevalence of waist circumference over time. However there was no statistically significant difference for intervention x time interaction effect for waist circumference (Table 3.15).

3 RCT Aripiprazole vs. Ziprasidone

Table 3.14 Prevalence of metabolic syndrome components by study visit between aripiprazole and ziprasidone

Variable	Aripiprazole(N=90) % (n)	Ziprasidone(N=85) % (n)	p value
Waist circumference			
Baseline prevalence	84.4(76)	87.1(74)	NS
1-month prevalence	58.9(53)	60.0(51)	NS
2-month prevalence	53.3(48)	54.1(46)	NS
3-month prevalence	48.9(44)	48.2(41)	NS
4-month prevalence	46.7(42)	42.4(36)	NS
5-month prevalence	45.6(41)	38.8(33)	NS
6-month prevalence	44.4(40)	35.3(30)	NS
HDL cholesterol			
Baseline prevalence	54.4(49)	52.9(45)	NS
1-month prevalence	43.3(39)	48.2(41)	NS
2-month prevalence	36.7(33)	37.6(32)	NS
3-month prevalence	34.4(31)	34.1(29)	NS
4-month prevalence	31.1(28)	25.9(22)	NS
5-month prevalence	31.1(28)	25.9(22)	NS
6-month prevalence	33.3(30)	23.5(20)	NS
Blood pressure			
Baseline prevalence	41.1(37)	32.9(28)	NS
1-month prevalence	35.6(32)	35.3(30)	NS
2-month prevalence	18.9(17)	27.1(23)	NS
3-month prevalence	22.2(20)	30.6(26)	NS
4-month prevalence	26.7(24)	23.5(20)	NS
5-month prevalence	26.7(24)	18.8(16)	NS
6-month prevalence	25.6(23)	20.0(17)	NS

3 RCT Aripiprazole vs. Ziprasidone

Table 3.14 Prevalence of metabolic syndrome components by study visit between aripiprazole and ziprasidone (cont')

Variable	Aripiprazole(N=90) % (n)	Ziprasidone(N=85) % (n)	p value
Triglycerides			
Baseline prevalence	50.0(45)	37.6(32)	**p< 0.05**
1-month prevalence	28.9(26)	27.1(23)	NS
2-month prevalence	26.7(24)	25.9(22)	NS
3-month prevalence	25.6(23)	17.6(15)	NS
4-month prevalence	27.8(25)	16.5(14)	NS
5-month prevalence	22.2(20)	10.6(9)	NS
6-month prevalence	21.1(19)	12.9(11)	NS
Fasting Blood Glucose			
Baseline prevalence	42.2(38)	25.9(22)	**p< 0.05**
1-month prevalence	26.7(24)	23.5(20)	NS
2-month prevalence	23.3(21)	23.5(20)	NS
3-month prevalence	22.2(20)	16.5(14)	NS
4-month prevalence	23.3(21)	18.8(16)	NS
5-month prevalence	17.8(16)	18.8(16)	NS
6-month prevalence	20.0(18)	8.2(7)	**p< 0.05**

Chi square test, NS – not significant

Metabolic syndrome components based on NCEP ATP-III definition

Table 3.15 Generalized estimating equation (GEE) for metabolic syndrome components among the schizophrenia patients

Source	Fasting glucose		Triglycerides		HDL	
	Wald Chi-Square	Sig.	Wald Chi-Square	Sig.	Wald Chi-Square	Sig.
Intercept	23.618	0.001	19.482	0.001	0.264	0.607
Time	9.504	0.147	12.210	0.057	8.478	0.205
Intervention	0.824	0.364	2.223	0.136	0.016	0.899
Intervention * Time	19.588	0.003	8.389	0.211	6.452	0.374

Source	Systolic		Diastolic		Waist	
	Wald Chi-Square	Sig.	Wald Chi-Square	Sig.	Wald Chi-Square	Sig.
Intercept	182.744	0.001	162.061	0.001	41.751	0.001
Time	9.892	0.129	4.527	0.606	19.530	0.003
Intervention	0.029	0.865	1.902	0.168	0.019	0.889
Intervention * Time	12.068	0.060	6.529	0.367	3.336	0.766

Dependent Variable: Fasting glucose, Triglycerides, HDL, Blood pressure, Waist circumference
Model: Intercept, Time (Baseline, month 1, 2, 3, 4, 5 and 6), Intervention (aripiprazole and ziprasidone), Intervention * Time

Metabolic syndrome components resolved or developed after 6 months treatment of aripiprazole and ziprasidone

The highest prevalence of metabolic syndrome component resolved 6 months after treatment of aripiprazole was triglycerides followed by waist circumference (17.8% vs. 15.6%). In ziprasidone group, the highest prevalence of metabolic syndrome components resolved 6 months after treatment were waist circumference and triglycerides (12.9% respectively). The lowest prevalence of metabolic syndrome component resolved 6 months after treatment of aripiprazole and ziprasidone was fasting blood glucose (1.1% vs. 4.7%, respectively).

The highest prevalence of metabolic syndrome component developed 6 months after treatment of aripiprazole and ziprasidone was blood pressure (14.4% vs. 11.8%, respectively). The lowest prevalence of metabolic syndrome component developed 6 months after treatment of aripiprazole and ziprasidone was waist circumference (1.1% vs. 1.2%, respectively) (Table 3.16).

Table 3.16 Prevalence of metabolic syndrome components at baseline and 6 months after randomization, metabolic syndrome components resolved or developed 6 months after randomization

Variable	Aripiprazole(N=90) % (n)	Ziprasidone(N=85) % (n)	p value
Waist circumference			
Baseline prevalence	84.4(76)	87.1(74)	NS
6-month prevalence	44.4(40)	35.3(30)	NS
Cases resolved	15.6(14)	12.9(11)	NS
Cases developed	1.1(1)	1.2(1)	NS
HDL cholesterol			
Baseline prevalence	54.4(49)	52.9(45)	NS
6-month prevalence	33.3(30)	23.5(20)	NS
Cases resolved	14.4(13)	11.8(10)	NS
Cases developed	10.0(9)	8.2(7)	NS
Blood pressure			
Baseline prevalence	41.1(37)	32.9(28)	NS
6-month prevalence	25.6(23)	20.0(17)	NS
Cases resolved	13.3(12)	7.1(6)	NS
Cases developed	14.4(13)	11.8(10)	NS
Triglycerides			
Baseline prevalence	50.0(45)	37.6(32)	NS
6-month prevalence	21.1(19)	12.9(11)	NS
Cases resolved	17.8(16)	12.9(11)	NS
Cases developed	4.4(4)	5.9(5)	NS
Glucose			
Baseline prevalence	42.2(38)	25.9(22)	**p< 0.05**
6-month prevalence	20.0(18)	8.2(7)	**p< 0.05**
Cases resolved	8.9(8)	9.4(8)	NS
Cases developed	1.1(1)	4.7(4)	NS

Chi square test

3 RCT Aripiprazole vs. Ziprasidone

MMRM least squares mean change over 6 months in rating scales between aripiprazole and ziprasidone

Table 3.17 showed the mixed model estimated mean change in rating scale scores over time by treatment group. There was marked reduction of LS mean change of all rating scales for every monthly study visits after treatment of aripiprazole and ziprasidone. The ziprasidone group improved more than the aripiprazole group for PANSS total and positive score but not statiscally significant. Significant pairwise differences were found in aripiprazole and ziprasidone groups for PANSS total, positive and negative score. There were also significant pairwise differences for both aripiprazole and ziprasidone groups for SAS.

When MMRM was performed for the rating scales, there was statistically significant in the time effect for PANSS total and Positive subscales, CGI-S, BARS and SAS indicating reduction in LS mean change over time. However there was no statistically significant difference for intervention x time interaction effect for all rating scales (Table 3.18).

3 RCT Aripiprazole vs. Ziprasidone

Table 3.17 MMRM least squares mean change of rating scale by study visit between aripiprazole and ziprasidone

	Baseline		1 month		2 months		3 months		4 months		5 months		6 months	
	Mean	(±SD)	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE
PANSS , Total score														
Aripiprazole	56.4	±17.0	-4.4	1.1¶	-5.6	1.2¶	-5.1	1.3¶	-7.5	1.3¶	-8.7	1.3¶	-10.5	1.3¶
Ziprasidone	59.4	±21.8	-4.0	1.1¶	-4.9	1.2¶	-7.4	1.2¶	-8.5	1.3¶	-9.4	1.3¶	-11.3	1.3¶
PANSS, Positive score														
Aripiprazole	13.5	±4.7	-1.1	0.3¶	-1.5	0.3¶	-1.1	0.3¶	-1.8	0.4¶	-2.3	0.4¶	-2.5	0.4¶
Ziprasidone	14.7	±6.3	-1.8	0.4¶	-1.9	0.4¶	-2.7	0.4¶	-2.7	0.4¶	-2.9	0.4¶	-3.7	0.4¶
PANSS, Negative score														
Aripiprazole	14.9	±5.8	-1.1	0.3¶	-1.4	0.4¶	-1.4	0.4¶	-2.0	0.4¶	-2.8	0.4¶	-2.9	0.4¶
Ziprasidone	16.1	±7.2	-0.9	0.4	-1.2	0.4¶	-2.0	0.4¶	-2.4	0.4¶	-2.7	0.4¶	-3.0	0.4¶
CGI-S score														
Aripiprazole	3.1	±0.8	-0.2	0.1	-0.2	0.1	-0.2	0.1	-0.3	0.1¶	-0.4	0.1¶	-0.4	0.1¶
Ziprasidone	3.3	±1.0	-0.1	0.1	-0.2	0.1¶	-0.3	0.1¶	-0.4	0.1¶	-0.4	0.1¶	-0.5	0.1¶
BARS														
Aripiprazole	0.7	±2.2	-0.3	0.1	-0.4	0.1	-0.3	0.1	-0.5	0.1	-0.5	0.1	-0.5	0.1
Ziprasidone	0.4	±1.4	-0.1	0.1	-0.2	0.1	-0.3	0.1	-0.2	0.1	-0.3	0.1	-0.3	0.1
SAS														
Aripiprazole	1.1	±2.4	-0.7	0.1¶	-0.7	0.1¶	-0.7	0.1¶	-0.8	0.1¶	-0.8	0.1¶	-0.9	0.1¶
Ziprasidone	1.2	±2.6	-0.5	0.2	-0.8	0.2¶	-0.98	0.2¶	-1.1	0.2¶	-1.1	0.2¶	-1.1	0.3¶
AIMS														
Aripiprazole	0.8	±2.8	-0.1	0.2	-0.4	0.2	-0.6	0.2	-0.6	0.2	-0.7	0.2	-0.7	0.2¶
Ziprasidone	0.8	±2.2	-0.5	0.2	-0.5	0.2¶	-0.6	0.2¶	-0.6	0.2¶	-0.5	0.2	-0.4	0.2

PANSS -Positive and Negative Syndrome Scale, CGI-S : Clinical Global Impression-Severity Scale, SAS- Simpson-Angus Rating Scale, BARS-Barnes Akathisia Rating Scale, AIMS-Abnormal Involuntary Movement Scale, ¶LS – Least square mean change for multiple comparison with Bonferonni correction p< 0.008, MMRM- mixed models for repeated measures, SE-standard error

Table 3.18 Mixed Model Repeated Measures (MMRM) for rating scale between aripiprazole and ziprasidone

Source	PANSS		PANSS -positive score		PANSS -negative score		CGI-S	
	F	Sig.	F	Sig.	F	Sig.	F	Sig.
Intercept	1739	0.001	1298	0.001	5170	0.001	8118	0.001
Time	29.948	0.001	27.094	0.001	1.750	0.111	2.420	0.028
Intervention	1.042	0.309	0.481	0.489	31.994	0.001	45.192	0.001
Intervention * Time	0.605	0.727	1.746	0.108	0.413	0.870	0.764	0.599

Source	BARS		SAS		AIMS	
	F	Sig.	F	Sig.	F	Sig.
Intercept	8.818	0.003	90.484	0.001	59.634	0.001
Time	3.793	0.001	3.978	0.001	1.813	0.098
Intervention	0.488	0.486	4.948	0.026	0.534	0.465
Intervention * Time	0.690	0.658	0.266	0.952	0.831	0.547

Dependent Variable: PANSS, PANSS positive score, PANSS negative score, CGI-S, BARS, SAS and AIMS
Model: Intercept, Time (Baseline, month 1, 2, 3, 4, 5 and 6), Intervention (aripiprazole and ziprasidone), Intervention * Time

MMRM least squares mean change of metabolic syndrome components over 6 months between aripiprazole and ziprasidone

Table 3.19 showed the LS mean change and statistical significant of individual treatment, with no comparison between aripiprazole and ziprasidone. There was marked reduction of least square mean change of total cholesterol, LDL, weight, BMI and waist circumference from study visit 1 to 6 months after treatment of aripiprazole. The reduction of least square mean change of TG was only noted after 6 months treatment of aripiprazole. There was marked reduction of least square mean change of total cholesterol, weight, BMI and waist circumference from study visit 1 to 6 months after treatment of ziprasidone. The reduction of least square mean change of TG was only noted after 5 months treatment of ziprasidone. The reduction of the LS mean change of total cholesterol for aripiprazole and ziprasidone has significant clinical implication for reduction of cardiovascular risk, as both groups had mean baseline total cholesterol $\geq$ 200 mg/dL (Table 3.19).

For MMRM analysis of metabolic syndrome components, there were statistically significant in the time effect for LS mean change of total cholesterol, LDL, triglycerides, weight, and waist circumference. However there was no statistically significant difference for intervention x time interaction effect for these parameters (Table 3.20).

3 RCT Aripiprazole vs. Ziprasidone

Table 3.19 MMRM least squares mean change of metabolic syndrome components and other parameters by study visit in schizophrenia patients

	Baseline		1 month		2 months		3 months		4 months		5 months		6 months	
	Mean	(±SD)	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE
Total Cholesterol (mg/dL)														
Aripiprazole	214.2	±50.0	-17.4	3.9¶	-15.8	4.1¶	-22.9	4.2¶	-23.6	4.2¶	-29.4	4.3¶	-27.3	4.3¶
Ziprasidone	206.4	±36.8	-9.7	3.1¶	-9.7	3.2¶	-12.6	3.3¶	-10.3	3.4¶	-19.0	3.4¶	-13.2	3.5¶
LDL(mg/dL)														
Aripiprazole	137.6	±44.2	-15.8	3.7¶	-14.2	3.9¶	-20.5	4.1¶	-23.9	4.2¶	-25.5	4.2¶	-22.9	4.2¶
Ziprasidone	131.5	±33.4	-5.5	3.1	-6.5	3.2¶	-9.1	3.3	-7.3	3.4	-11.1	3.4¶	-10.4	3.5¶
HDL(mg/dL)														
Aripiprazole	44.0	±11.2	0.1	1.2	0.6	1.3	-0.2	1.3	1.4	1.3	0.4	1.3	1.0	1.3
Ziprasidone	44.2	±13.8	-1.0	1.2	-0.9	1.2	-0.2	1.3	0.3	1.3	-0.1	1.3	1.1	1.4
Triglyceride(mg/dL)														
Aripiprazole	176.6	±140.0	-20.4	8.9	-20.2	9.4	-16.9	9.7	-16.7	9.8	-22.6	9.9	-35.7	9.9¶
Ziprasidone	161.1	±126.1	-18.7	6.7	-12.2	6.9¶	-15.4	7.2	-16.5	7.3	-28.2	7.5¶	-21.4	7.6¶
FBS (mg/dL)														
Aripiprazole	109.9	±40.9	-2.7	2.9	-1.5	3.2	-3.8	3.3	-0.8	3.3	-6.1	3.3	-8.3	3.3
Ziprasidone	95.8	±24.7	2.7	2.3	2.2	2.3	1.3	2.4	0.8	2.5	1.3	2.5	2.5	2.6
Systolic(mm/Hg)														
Aripiprazole	125.0	±16.7	0.8	1.8	-1.9	1.9	-0.7	1.9	0.1	1.9	1.3	2.0	-0.2	2.7
Ziprasidone	123.6	±15.1	4.5	1.9	4.1	2.0	2.9	2.1	1.3	2.1	0.97	2.2	0.8	2.2
Diastolic (mm/Hg)														
Aripiprazole	80.8	±12.4	1.2	1.2	-0.7	1.3	-0.9	1.4	-1.2	1.4	-1.5	1.4	-3.1	1.4
Ziprasidone	80.9	±11.4	1.3	1.3	0.6	1.3	0.7	1.4	2.5	1.4	0.7	1.4	0.3	1.4
Waist(cm)														
Aripiprazole	96.0	±12.1	-1.7	0.6¶	-1.9	0.6¶	-2.3	0.7¶	-2.4	0.7¶	-2.9	0.7¶	-3.4	0.7¶
Ziprasidone	96.6	±11.7	-1.4	0.5¶	-2.2	0.5¶	-2.9	0.5¶	-3.4	0.5¶	-4.2	0.5¶	-3.7	0.5¶

Table 3.19 MMRM least squares mean change of metabolic syndrome components and other parameters by study visit in schizophrenia patients(con't)

	Baseline		1 month		2 months		3 months		4 months		5 months		6 months	
	Mean	(±SD)	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE
Weight(kg)														
Aripiprazole	73.5	±16.8	-1.2	0.3¶	-1.5	0.3¶	-1.6	0.4¶	-1.6	0.4¶	-1.5	0.4¶	-1.8	0.4¶
Ziprasidone	75.0	±15.1	-1.9	0.9	-3.0	0.9¶	-2.3	0.96	-2.9	0.98¶	-3.4	0.99¶	-3.4	1.0¶
BMI														
Aripiprazole	27.7	±5.2	-0.5	0.1¶	-0.6	0.1¶	-0.6	0.1¶	-0.6	0.1¶	-0.6	0.1¶	-0.7	0.1¶
Ziprasidone	28.1	±5.6	-0.6	0.3	-1.1	0.3¶	-0.8	0.3	-1.1	0.3¶	-1.2	0.3¶	-1.2	0.3¶
Framingham														
Aripiprazole	6.7	±5.2	-0.9	0.8	-0.3	0.8	-0.5	0.8	-0.4	0.8	-0.3	0.9	-0.9	0.8
Ziprasidone	6.6	±6.7	-1.1	1.2	-1.2	1.2	-0.9	1.3	-1.5	1.4	-0.1	1.2	-0.2	1.2

FBS- Fasting blood sugar, BMI - body mass index; HDL- high-density lipoprotein cholesterol; LDL- low density lipoprotein cholesterol

¶LS – Least square mean change for multiple comparison with Bonferonni correction p< 0.008, MMRM- mixed models for repeated measures, SE- standard error

Table 3.20 Mixed Model Repeated Measures (MMRM) for metabolic syndrome components and other parameters among schizophrenia patients

Source	Total Cholesterol		LDL		HDL		TG	
	F	Sig.	F	Sig.	F	Sig.	F	Sig.
Intercept	5527	0.001	2915	0.001	3810	0.001	298.2	0.001
Time	15.931	0.001	10.831	0.001	0.643	0.696	4.410	0.001
Intervention	0.039	0.845	0.845	0.359	0.078	0.781	0.531	0.467
Intervention * Time	1.512	0.171	2.074	0.054	0.231	0.966	0.462	0.836

Source	FBS		Systolic		Diastolic		Weight	
	F	Sig.	F	Sig.	F	Sig.	F	Sig.
Intercept	1753	0.001	42650	0.001	12710	0.001	3043	0.001
Time	0.676	0.669	0.341	0.915	1.323	0.244	6.467	0.001
Intervention	3.687	0.056	0.630	0.428	0.322	0.571	1.120	0.291
Intervention * Time	1.348	0.234	0.644	0.695	1.037	0.400	0.853	0.529

Source	BMI		Waist		Framingham	
	F	Sig.	F	Sig.	F	Sig.
Intercept	3862	0.001	1160	0.001	979.39	0.001
Time	7.671	0.001	17.091	0.001	3.875	0.049
Intervention	1.063	0.304	0.387	0.535	0.512	0.799
Intervention * Time	1.009	0.418	0.806	0.565	0.365	0.900

Dependent Variable: Total Cholesterol, LDL, HDL, TG, FBS, Systolic, Diastolic, weight, BMI, Waist and Framingham
Model: Intercept, Time (Baseline, month 1, 2, 3, 4, 5 and 6), Intervention (aripiprazole and ziprasidone), Intervention * Time

MMRM least squares mean change of total cholesterol and LDL over 6 months between aripiprazole and ziprasidone

There was marked reduction of least square mean change of total cholesterol and LDL for study visit 1 to 6 months after treatment of aripiprazole and ziprasidone. There were statistically significant differences of LS mean change for multiple comparisons with Bonferonni correction p< 0.008 for study visit 1 to 6 months in total cholesterol in both groups. For aripiprazole group, there was statistically significant difference of LS mean change for every study visit in LDL cholesterol. For ziprasidone group, there was statistically significant different of LS mean change at study visit month 2, 5 and 6 in LDL cholesterol (Table 3.19).

For MMRM analysis of total cholesterol and LDL, there was statistically significant in the time effect for both lipid profile parameters, indicating reduction in LS mean change over time. However there was no statistically significant difference for intervention x time interaction effect for cholesterol and LDL cholesterol (Table 3.20).

MMRM least squares mean change of CHD risk score (Framingham) and other parameters over 6 months between aripiprazole and ziprasidone

There was marked reduction in least square mean change of weight, BMI and CHD risk score (Framingham) after treatment of aripiprazole and ziprasidone. There were significant differences in LS mean change of weight and BMI from study visit 1 to 6 months for aripiprazole. Whereas in ziprasidone group, the significant differences in LS mean change of weight and BMI were for study visit month 2, 4, 5 and 6 (Table 3.19).

For the overall modelling analysis (MMRM), there were statistically significant in the time effect for weight, BMI and CHD risk score (Framingham) but not for intervention x time interaction effect for these variables (Table 3.20).

TABLE 3.21 Prevalence of CVRFs and CHD risk (Framingham) between aripiprazole(N=90) and ziprasidone(N=85) by study visit

CVRFs	Baseline		1 month		2 months		3 months		4 months		5 months		6 months	
	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)
Diabetes Mellitus														
Aripiprazole	22.2	(20)	16.7	(15)	15.6	(14)	14.4	(13)	12.2	(11)	11.1	(10)	8.9	(8)
Ziprasidone ¶	9.4	(8)	10.6	(9)	17.8	(10)	10.6	(9)	9.4	(8)	8.2	(7)	8.2	(7)
Total Cholesterol														
Aripiprazole	56.7	(51)	37.8	(34)	33.3	(30)	26.7	(24)	23.3	(21)	20.0	(18)	20.0	(18)
Ziprasidone	61.2	(52)	28.2	(24)	31.8	(27)	28.2	(24)	21.2	(18)	17.6	(15)	20.0	(17)
HDL														
Aripiprazole	66.7	(60)	55.6	(50)	53.3	(48)	44.4	(40)	38.9	(35)	37.8	(34)	40.0	(36)
Ziprasidone	74.1	(63)	54.1	(46)	42.4	(36)	40.0	(34)	38.8	(33)	37.6	(32)	35.3	(30)
Systolic														
Aripiprazole	22.2	(20)	22.2	(20)	13.3	(12)	12.2	(11)	10.0	(9)	14.4	(13)	16.7	(15)
Ziprasidone	17.6	(15)	23.5	(20)	23.5	(20)	15.3	(13)	11.8	(10)	12.9	(11)	9.4	(8)
Diastolic														
Aripiprazole	23.3	(21)	21.1	(19)	17.8	(16)	12.2	(11)	8.9	(8)	11.1	(10)	11.1	(10)
Ziprasidone	25.9	(22)	18.8	(16)	17.6	(15)	20.0	(17)	18.8	(16)	11.8	(10)	11.8	(10)
Patients (%)with very high/high risk (≥10%) of CHD in 10 years (Framingham)														
Aripiprazole	25.5	(23)	21.1	(19)	13.3	(12)	13.3	(12)	13.3	(12)	16.5	(14)	10.0	(9)
Ziprasidone	21.2	(18)	21.2	(18)	20.0	(17)	14.1	(12)	16.5	(14)	10.6	(9)	11.8	(10)

Chi square test,¶ p < 0.05. CVRFs- Cardiovascular risk factors, CHD- coronary heart disease

Table 3.22 Generalized estimating equation (GEE) for CVRFs and CHD risk (Framingham) between aripiprazole and ziprasidone

Source	Diabetes Mellitus		Total Cholesterol		HDL	
	Wald Chi-Square	Sig.	Wald Chi-Square	Sig.	Wald Chi-Square	Sig.
Intercept	1739	0.001	1298	0.001	5170	0.001
Time	29.948	0.001	27.094	0.001	1.750	0.111
Intervention	1.042	0.309	0.481	0.489	31.994	0.001
Intervention * Time	0.605	0.727	1.746	0.108	0.413	0.870

Source	Systolic		Diastolic		Framingham	
	Wald Chi-Square	Sig.	Wald Chi-Square	Sig.	Wald Chi-Square	Sig.
Intercept	8118	0.001	8.818	0.003	44.881	0.001
Time	2.420	0.028	3.793	0.001	9.484	0.148
Intervention	45.192	0.001	0.488	0.486	0.142	0.707
Intervention * Time	0.764	0.599	0.690	0.658	9.746	0.136

Dependent Variable: Diabetes Mellitus, Total Cholesterol, HDL, Systolic, Diastolic, CHD
Model: Intercept, Time (Baseline, month 1, 2, 3, 4, 5 and 6), Intervention (aripiprazole and ziprasidone), Intervention * Time

3 RCT Aripiprazole vs. Ziprasidone

Prevalence of CVRFs and CHD risk (Framingham) by study visit between aripiprazole and ziprasidone

For prevalence of all CVRFs showed reduction by study visit after treatment of aripiprazole and ziprasidone. For CVRFs of diabetes mellitus, the reduction of prevalence was 13.3% and the dropped was greater after treatment of aripiprazole. There was statistically significant difference in the prevalence of CVRFs diabetes mellitus between aripiprazole and ziprasidone at baseline (22.2% vs. 9.4%). For other CVRFs, the dropped of prevalence was observed greater in ziprasidone group. The highest dropped of prevalence were total cholesterol followed by HDL cholesterol in ziprasidone group (41.2% vs. 38.8%).

For patients with high risk and very high risk in CHD (Framingham), the dropped in prevalence were more in aripiprazole than ziprasidone group. The reduction in prevalence of patients with high risk and very high risk in CHD (Framingham) were 15.5% in aripiprazole and 9.4% in ziprasidone group (Table 3.21).

When GEE was performed for CVRFs, there were statistically significant in the time effect for diabetes mellitus, total cholesterol and diastolic blood pressure, indicating reduction in the above prevalence of over time. There were statistically significant in the intervention effect for HDL cholesterol, indicate significant reduction in the prevalence of HDL cholesterol between aripiprazole and ziprasidone. Although systolic blood pressure has statistically significant in time and intervention effect, the overall intervention x time interaction effect did not show statistically significant in the reduction of all prevalence between aripiprazole and ziprasidone (Table 3.22).

The discontinuation rate by study visit between aripiprazole and ziprasidone

The discontinuation rate of ziprasidone was higher than aripiprazole for all study visits, however there was no statiscally significant of log rank test in survival analysis (Figure 3.7). The discontinuation rates of ziprasidone compared to aripiprazole at study visit 6 months were 47.1% (40/85) vs. 38.9% (35/90) (Table 3.23).

Figure 3.7 Survival Analysis of Months to Discontinuation According to Aripiprazole and Ziprasidone
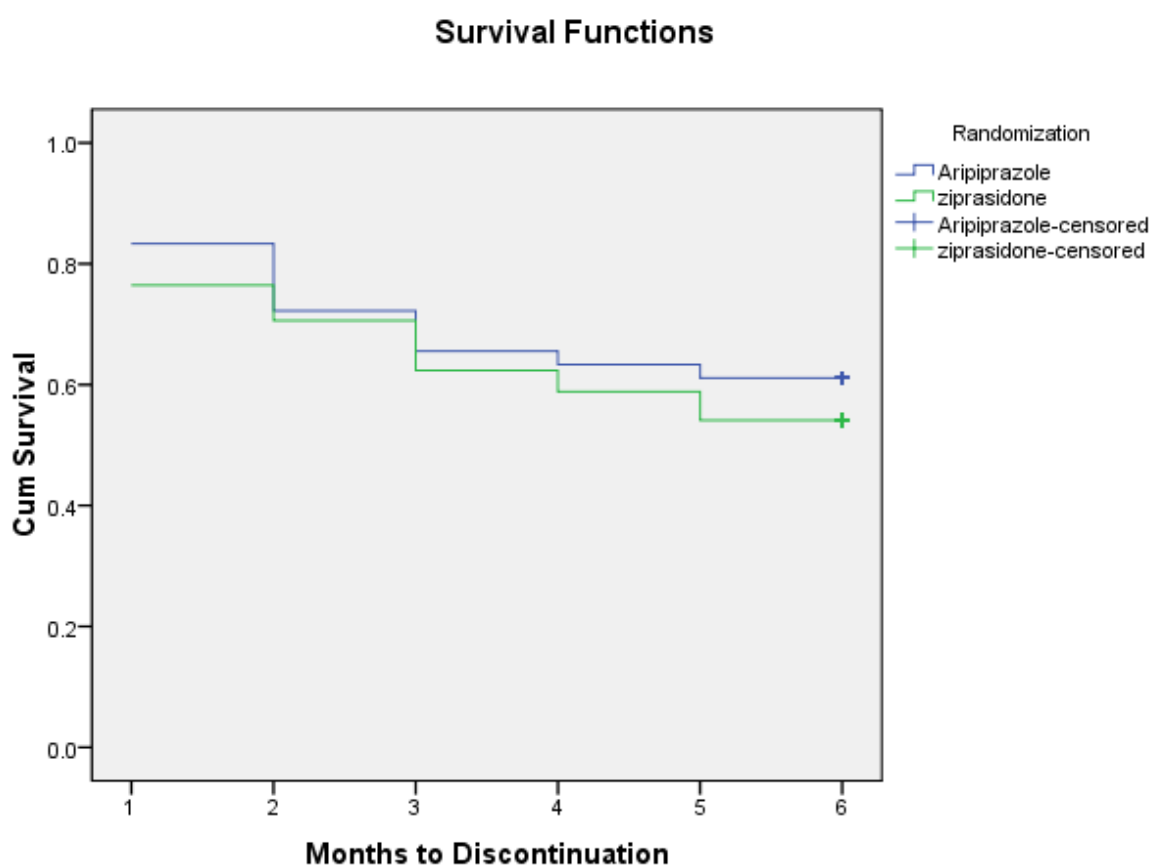
3 RCT Aripiprazole vs. Ziprasidone

Table 3.23 The discontinuation rate between aripiprazole(N=90) and ziprasidone(N=85) by study visit

	Baseline		1 month		2 months		3 months		4 months		5 months		6 months	
	%	(n)	**%**	(n)	**%**	(n)	**%**	(n)	**%**	(n)	**%**	(n)	**%**	(n)
NCEP ATP III*														
Aripiprazole	100.0	(90)	16.7	(15)	27.8	(25)	34.4	(31)	36.7	(33)	38.9	(35)	38.9	(35)
Ziprasidone	100.0	(85)	23.5	(20)	29.4	(25)	37.6	(32)	41.2	(35)	44.7	(38)	47.1	(40)

Chi square test , p>0.05

Table 3.24 Generalized estimating equation (GEE) of discontinuation rate between aripiprazole and ziprasidone

	Discontinuation rate	
Source	Wald Chi-Square	Sig.
Intercept	115.534	0.001
Time	132.592	0.001
Intervention	0.606	0.436
Intervention * Time	5.797	0.446

Dependent Variable: Discontinuation rate
Model: Intercept, Time (Baseline, month 1, 2, 3, 4, 5 and 6),
Intervention (aripiprazole and ziprasidone), Intervention * Time

3 RCT Aripiprazole vs. Ziprasidone

The mean score of CHD risk (Framingham) between age groups and treatment

When Multivariate General Linear Model (MANCOVA) was performed adjusted for sex for multiple comparisons of means CHD risk score (Framingham) by age group, there was no statistically significant (Bonferroni correction $p<0.008$) for intervention x age group interaction effect with the means of CHD risk score (Framingham) (Figure 3.7).
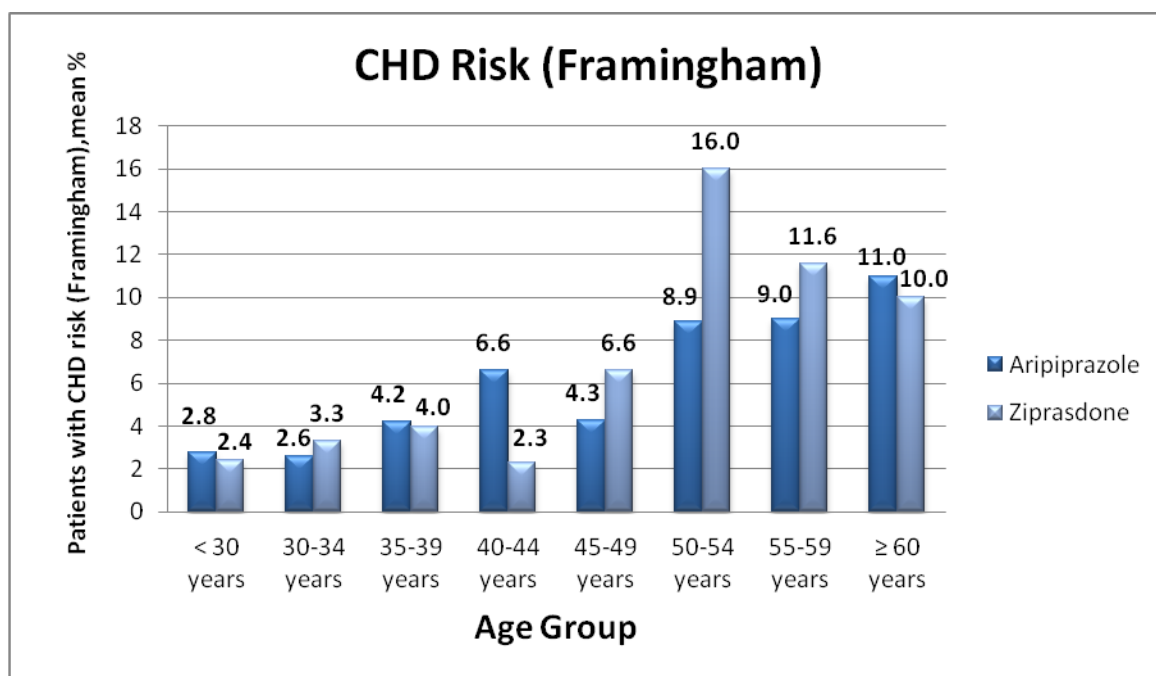
Figure 3.8 Risk of CHD (Framingham) at 6 months according to aripiprazole and ziprasidone

MANCOVA adjusted for sex , corrected by Bonferroni formula for multiple comparisons $p < 0.008$
Model:Intercept , sex, age group, intervention, age group*intervention
CHD - Coronary Heart Disease

3 RCT Aripiprazole vs. Ziprasidone

The adverse events between aripiprazole and ziprasidone

The common adverse events reported for aripiprazole and ziprasidone group were extrapyramidal syndrome (EPS) (20.0% vs. 18.8%) and insomnia (25.6% vs. 24.7%). Patients in the ziprasidone group reported to have higher incidence of somnolence as compared to aripiprazole group (18.8% vs. 2.2%). For serious adverse event, there were two cases of relapse in the ziprasidone group (Table 3.25).

3 RCT Aripiprazole vs. Ziprasidone

Table 3.25 Incidence of treatment-emergent adverse events between aripiprazole and ziprasidone

Body system	Aripiprazole (N=90)	Ziprasidone (N=85)
	% (n)	% (n)
Body as a whole		
Asthenia	3.3(3)	7.1(6)
Pain	4.4(4)	5.9(5)
Digestive		
Constipation	1.1(1)	-
Diarrhoea	1.1(1)	-
Dyspepsia	-	3.5(3)
Nausea	2.2(2)	1.2(1)
Vomiting	-	1.2(1)
Skin & musculoskeletal		
Arthralgia	2.2(2)	1.2(1)
Itchiness	1.1(1)	1.2(1)
Cellulites	-	1.2(1)
Nervous system		
Agitation	2.2(2)	7.1(6)
Akathisia	2.2(2)	4.7(4)
Dizziness	5.6(5)	5.9(5)
Headache	2.2(2)	7.1(6)
Extrapyramidal Syndrome	20.0(18)	18.8(16)
Insomnia	25.6(23)	24.7(21)
Somnolence	2.2(2)	18.8(16)
Cardiovascular		
Palpitation	-	2.4(2)
Respiratory		
Upper respiratory tract infection	-	1.2(1)
Urogenital		
Incontinence	-	1.2(1)
Others		
Fall	-	1.2(1)
Tinnitus	-	1.2(1)
Conjunctivitis	-	1.2(1)
Relapse		2.4(2)

RESULTS FOR SENSITIVITY ANALYSIS

Table 3.26   Sentitivity Analysis: Prevalence of metabolic syndrome (MetS) at baseline and 6 months after randomization, metabolic syndrome (MetS) resolved or developed 6 months after randomization

	Aripiprazole(N= 63) % (n)	Ziprasidone(N=73) % (n)	p value
Baseline prevalence MetS	49.2(31)	49.3(36)	p> 0.05
6-month prevalence MetS	19.0(12)	15.1(11)	p> 0.05
Cases resolved MetS	15.9(10)	15.1(11)	p> 0.05
Cases developed MetS	6.3(4)	5.5(4)	p> 0.05
Baseline prevalence IDF	47.6(30)	49.3(36)	p> 0.05
6-month prevalence IDF	19.0(12)	15.1(11)	p> 0.05
Cases resolved IDF	15.9(10)	15.1(11)	p> 0.05
Cases developed IDF	6.3(4)	5.5(4)	p> 0.05

Chi square test

Mets based on definition NCEP ATP-III , IDF - International Diabetes Federation

Metabolic syndrome resolved or developed after 6 months of treatment between aripiprazole and ziprasidone

For sentivitivy analysis, thirty-nine schizophrenia patients were excluded when treated with antihyperlipidemic, antihypertensive and antidiabetic after randomization as concomitant medication. The cases of metabolic syndrome resolved for both aripiprazole and ziprasidone were 15.9% vs. 15.1% respectively using NCEP ATP III definition and IDF definition. The cases resolved for metabolic syndrome in aripiprazole and ziprasidone group were much higher as compared to new cases of metabolic syndrome developed in both groups (NCEP ATP III & IDF: 6.3% vs. 5.5%) (Table 3.26).

Table 3.27 Sensitivity Analysis: Prevalence of metabolic syndrome components by study visit between aripiprazole and ziprasidone

Variable	Aripiprazole(N=63) % (n)	Ziprasidone(N=73) % (n)	p value
Waist circumference			
Baseline prevalence	81.0(51)	86.3(63)	NS
1-month prevalence	52.4(33)	57.5(42)	NS
2-month prevalence	47.6(30)	50.7(46)	NS
3-month prevalence	41.3(26)	43.8(32)	NS
4-month prevalence	36.5(23)	38.4(28)	NS
5-month prevalence	36.5(23)	35.6(26)	NS
6-month prevalence	34.9(22)	32.9(24)	NS
HDL cholesterol			
Baseline prevalence	50.8(32)	54.8(40)	NS
1-month prevalence	38.1(24)	43.8(32)	NS
2-month prevalence	30.2(19)	38.4(28)	NS
3-month prevalence	25.4(16)	32.9(24)	NS
4-month prevalence	22.2(14)	26.0(19)	NS
5-month prevalence	20.6(13)	24.7(18)	NS
6-month prevalence	23.8(15)	20.5(15)	NS
Blood pressure			
Baseline prevalence	38.1(24)	30.1(22)	NS
1-month prevalence	30.0(17)	32.9(24)	NS
2-month prevalence	12.7(8)	24.7(18)	NS
3-month prevalence	12.7(8)	26.0(19)	$p<0.05$
4-month prevalence	17.5(11)	19.2(14)	NS
5-month prevalence	20.6(13)	15.1(11)	NS
6-month prevalence	17.5(11)	19.2(14)	NS

3 RCT Aripiprazole vs. Ziprasidone

Table 3.27 Sensitivity Analysis: Prevalence of metabolic syndrome components by study visit between aripiprazole and ziprasidone (cont')

Variable	Aripiprazole(N=63) % (n)	Ziprasidone(N=73) % (n)	p value
Triglycerides			
Baseline prevalence	47.6(30)	38.4(28)	NS
1-month prevalence	17.5(11)	23.3(17)	NS
2-month prevalence	22.2(14)	24.7(18)	NS
3-month prevalence	17.5(11)	16.4(12)	NS
4-month prevalence	15.9(10)	16.4(12)	NS
5-month prevalence	14.3(9)	8.2(6)	NS
6-month prevalence	17.5(11)	9.6(7)	NS
Fasting Blood Glucose			
Baseline prevalence	33.3(21)	24.7(18)	NS
1-month prevalence	15.9(10)	20.5(15)	NS
2-month prevalence	12.7(8)	20.5(15)	NS
3-month prevalence	12.7(8)	13.7(10)	NS
4-month prevalence	15.9(10)	16.4(12)	NS
5-month prevalence	11.1(7)	16.4(12)	NS
6-month prevalence	12.7(8)	8.2(6)	NS

Chi square test, NS – not significant
Metabolic syndrome components based on NCEP ATP-III definition

Table 3.28   Sensitivity Analysis : Generalized estimating equation (GEE) for metabolic syndrome components among the schizophrenia patients

Source	Fasting glucose Wald Chi-Square	Sig.	Triglycerides Wald Chi-Square	Sig.	HDL Wald Chi-Square	Sig.
Intercept	27.158	0.001	23.920	0.001	0.170	0.680
Time	8.861	0.182	19.908	0.003	7.138	0.308
Intervention	0.116	0.733	0.171	0.679	0.924	0.336
Intervention * Time	17.298	0.008	9.999	0.125	3.750	0.711

Source	Systolic Wald Chi-Square	Sig.	Diastolic Wald Chi-Square	Sig.	Waist Wald Chi-Square	Sig.
Intercept	22.205	0.001	34.870	0.001	24.476	0.001
Time	5.043	0.538	2.562	0.862	18.802	0.005
Intervention	1.160	0.281	5.071	0.024	0.556	0.456
Intervention * Time	13.728	0.033	6.958	0.325	1.982	0.921

Dependent Variable: Fasting glucose, Triglycerides, HDL, Blood pressure, Waist circumference
Model: Intercept, Time (Baseline, month 1, 2, 3, 4, 5 and 6), Intervention (aripiprazole and ziprasidone), Intervention * Time

Prevalence of metabolic syndrome components by study visit between aripiprazole and ziprasidone

From baseline to 6 months study visit, there was reduction in the prevalence of all metabolic syndrome components for both aripiprazole and ziprasidone group. The highest reduction in prevalence was waist circumference, dropped by 46.1% in aripiprazole and 53.4% in ziprasidone group. The lowest reduction in prevalence was blood pressure in both groups (20.6% for aripiprazole vs. 10.9% for ziprasidone) (Table 3.27).

When GEE was performed for metabolic syndrome components, there was statistically significant for intervention x time interaction effect comparing the reduction of

prevalence of fasting blood glucose and systolic blood pressure between aripiprazole and ziprasidone. There was statistically significant in the time effect for waist circumference and triglyceride, indicating reduction in prevalence of waist circumference and triglyceride over time. There was also statistically significant in the treatment effect for diastolic blood pressure. However there was no statistically significant difference for intervention x time interaction effect for waist circumference, triglyceride, systolic and diastolic blood pressure (Table 3.28).

Metabolic syndrome components resolved or developed after 6 months treatment of aripiprazole and ziprasidone

The highest prevalence of metabolic syndrome component resolved 6 months after treatment of in aripiprazole group was waist circumference (18.9%). In ziprasidone group, the highest prevalence of metabolic syndrome component resolved 6 months after treatment was triglycerides (15.1%). As the lowest prevalence of metabolic syndrome component resolved 6 months after treatment of was fasting blood glucose for aripiprazole and blood pressure for ziprasidone (6.3% vs. 4.1% respectively).

The highest prevalence of metabolic syndrome component developed 6 months after treatment of aripiprazole and ziprasidone was blood pressure (11.1% vs. 12.3%). As the lowest prevalence of metabolic syndrome component developed 6 months after treatment ziprasidone was waist circumference (1.4%). No patient has impaired fasting blood glucose after 6 months treatment of aripiprazole (Table 3.29).

Table 3.29 Sensitivity Analysis: Prevalence of metabolic syndrome components at baseline and 6 months after randomization, metabolic syndrome components resolved or developed 6 months after randomization

Variable	Aripiprazole(N=63) % (n)	Ziprasidone(N=73) % (n)	p value
Waist circumference			
Baseline prevalence	81.0(51)	86.3(63)	NS
6-month prevalence	34.9(22)	32.9(24)	NS
Cases resolved	19.0(12)	12.3(9)	NS
Cases developed	1.6(1)	1.4(1)	NS
HDL cholesterol			
Baseline prevalence	50.8(32)	54.8(40)	NS
6-month prevalence	23.8(15)	20.5(15)	NS
Cases resolved	15.9(10)	12.3(9)	NS
Cases developed	9.5(6)	8.2(6)	NS
Blood pressure			
Baseline prevalence	38.1(24)	30.1(22)	NS
6-month prevalence	17.5(11)	19.2(14)	NS
Cases resolved	14.3(9)	4.1(3)	**p< 0.05**
Cases developed	11.1(7)	12.3(9)	NS
Triglycerides			
Baseline prevalence	47.6(30)	38.4(28)	NS
6-month prevalence	17.5(11)	9.6(7)	NS
Cases resolved	15.9(10)	15.1(11)	NS
Cases developed	4.8(3)	5.5(4)	NS
Glucose			
Baseline prevalence	33.3(21)	24.7(18)	NS
6-month prevalence	12.7(8)	8.2(6)	NS
Cases resolved	6.3(4)	6.8(5)	NS
Cases developed	0.0(0)	4.1(3)	NS

Chi square test

MMRM least squares mean change of metabolic syndrome components over 6 months between aripiprazole and ziprasidone

Table 3.30 showed the LS mean change and statistical significant of individual treatment, with no comparison between aripiprazole and ziprasidone. There was marked reduction of least square mean change of total cholesterol, LDL, FBS, weight, BMI and waist circumference from study visit 1 to 6 months after treatment of aripiprazole. The reduction of least square mean change of TG and diastolic blood pressure were only noted after 6 months treatment of aripiprazole. There was marked reduction of least square mean change of total cholesterol, weight, BMI and waist circumference from study visit 1 to 6 months after treatment of ziprasidone. The reduction of least square mean change of TG and LDL were only noted after 5 months treatment of ziprasidone.

The reduction of the LS mean change of total cholesterol for aripiprazole and ziprasidone has significant clinical implication for reduction of cardiovascular risk, as both groups had mean baseline total cholesterol $\geq$ 200 mg/dL. The reduction of the LS mean change of FBS for aripiprazole has significant clinical implication for prevalence reduction of impaired FBS and normalised the fasting blood sugar level, as aripiprazole group had mean baseline FBS $\geq$ 100 mg/dL (Table 3.30).

The MMRM analysis was used to compare the treatment differences and the interaction between time and treatment. For MMRM analysis of metabolic syndrome components, there were statistically significant differences for intervention x time interaction effect for FBS and systolic blood pressure. These indicating differences in LS mean change of FBS and systolic blood pressure observed in both groups were the interaction effect of time and treatment (Table 3.31). This can be explained as there was increased of LS mean change of FBS and systolic blood pressure from study visit

1 to 6 months after treatment of ziprasidone and there was reduction of LS mean change of FBS and systolic blood pressure from study visit 1 to 6 months after treatment of aripiprazole (Table 3.30). Although there were raised of FBS and systolic blood pressure from study visit 1 to 6 months after treatment of ziprasidone,   there was no significant clinical implication as the FBS and systolic blood pressure in range of the normal value.

Table 3.30 Sensitivity Analysis: MMRM least squares mean change of metabolic syndrome components and other parameters by study visit in schizophrenia patients

	Baseline		1 month		2 months		3 months		4 months		5 months		6 months	
	Mean	(±SD)	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE
Total Cholesterol (mg/dL)														
Aripiprazole	211.2	±42.9	-16.1	3.8¶	-16.4	4.1¶	-23.8	4.3¶	-24.2	4.4¶	-23.1	4.4¶	-20.1	4.4¶
Ziprasidone	205.5	±33.0	-7.3	3.3¶	-7.2	3.4¶	-9.0	3.6¶	-16.1	3.7¶	-8.3	3.6¶	-10.0	3.8¶
LDL(mg/dL)														
Aripiprazole	136.0	±36.2	-14.3	3.7¶	-14.9	3.9¶	-21.3	4.1¶	-18.9	4.3¶	-19.6	4.3¶	-15.4	4.3¶
Ziprasidone	132.5	±32.8	-3.8	3.4	-5.0	3.6	-7.4	3.7	-6.3	3.8	-8.4	4.0¶	-8.7	4.0¶
HDL(mg/dL)														
Aripiprazole	45.6	±12.0	-0.8	1.2	-0.1	1.3	-0.6	1.4	-0.7	1.4	0.4	1.4	1.6	1.4
Ziprasidone	44.0	±13.9	-0.4	1.4	-1.3	1.4	-0.2	1.5	0.2	1.5	0.04	1.6	1.2	1.6
Triglyceride(mg/dL)														
Aripiprazole	153.9	±71.3	-13.2	9.2	-10.4	9.8	-17.6	10.4	-21.0	10.6¶	-12.7	10.7	-31.9	10.7¶
Ziprasidone	156.2	±117.9	-19.7	6.2¶	-7.4	6.4	-10.1	6.8	-13.2	6.9	-24.0	7.1¶	-14.5	7.1¶
FBS (mg/dL)														
Aripiprazole	101.7	±33.1	-6.6	2.7¶	-7.4	2.8¶	-10.2	3.0¶	-7.3	3.0¶	-8.3	3.1¶	-8.4	3.1¶
Ziprasidone	94.4	±19.4	4.0	2.3	4.0	2.3	2.6	2.5	1.9	2.5	3.7	2.6	5.7	2.6¶
Systolic(mm/Hg)														
Aripiprazole	126.1	±16.6	-2.1	2.0	-5.7	2.1¶	-3.3	2.2	-2.7	2.2	-0.7	2.3	-1.6	2.3
Ziprasidone	122.7	±16.4	5.0	2.1¶	4.4	2.2¶	2.6	2.3	0.4	2.4	-0.2	2.4	1.7	2.4
Diastolic (mm/Hg)														
Aripiprazole	80.7	±12.7	-0.8	1.4	-2.6	1.5	-2.7	1.5	-1.8	1.6	-2.8	1.6	-4.2	1.6¶
Ziprasidone	79.4	±10.9	1.8	1.6	1.3	1.4	1.2	1.5	2.7	1.5	1.7	1.5	2.0	1.6
Waist(cm)														
Aripiprazole	92.8	±9.3	-2.2	0.6¶	-3.0	0.6¶	-3.8	0.6¶	-4.2	0.6¶	-4.2	0.6¶	-4.9	0.6¶
Ziprasidone	96.8	±11.1	-1.0	0.5¶	-1.7	0.5¶	-2.5	0.6¶	-3.0	0.6¶	-4.0	0.6¶	-3.5	0.6¶

Table 3.30 Sensitivity Analysis: MMRM least squares mean change of metabolic syndrome components and other parameters by study visit in schizophrenia patients(con't)

	Baseline		1 month		2 months		3 months		4 months		5 months		6 months	
	Mean	(±SD)	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE	LS Mean Change	SE
Weight(kg)														
Aripiprazole	69.6	±13.5	-1.6	0.3¶	-1.9	0.4¶	-1.9	0.4¶	-2.2	0.4¶	-2.1	0.4¶	-2.2	0.4¶
Ziprasidone	77.4	±21.4	-2.4	1.1¶	-3.3	1.1¶	-2.4	1.2¶	-3.0	1.2¶	-3.4	1.2¶	-3.3	1.2¶
BMI														
Aripiprazole	26.6	±4.5	-0.6	0.1¶	-0.7	0.1¶	-0.7	0.1¶	-0.8	0.2¶	-0.8	0.2¶	-0.8	0.2¶
Ziprasidone	29.1	±7.4	-0.8	0.4¶	-1.1	0.4¶	-0.8	0.4¶	-1.1	0.4¶	-1.2	0.4¶	-1.2	0.4¶

FBS- Fasting blood sugar, BMI - body mass index; HDL- high-density lipoprotein cholesterol; LDL- low density lipoprotein cholesterol

¶LS – Least square mean change for multiple comparison with Bonferonni correction $p < 0.008$, MMRM- mixed models for repeated measures, SE- standard error

Table 3.31 Sensitivity Analysis: Mixed Model Repeated Measures (MMRM) for metabolic syndrome components and other parameters among schizophrenia patients

Source	Total Cholesterol		LDL		HDL		TG	
	F	Sig.	F	Sig.	F	Sig.	F	Sig.
Intercept	5021	0.001	2615	0.001	3056	0.001	313.1	0.001
Time	10.78	0.001	6.437	0.001	0.770	0.594	3.100	0.005
Intervention	0.438	0.509	1.437	0.233	1.120	0.292	0.045	0.832
Intervention * Time	1.669	0.127	1.512	0.172	0.208	0.974	1.056	0.388

Source	FBS		Systolic		Diastolic		Weight	
	F	Sig.	F	Sig.	F	Sig.	F	Sig.
Intercept	2510	0.001	9104	0.001	9363	0.001	2608	0.001
Time	0.791	0.577	0.512	0.800	0.619	0.715	4.725	0.001
Intervention	0.534	0.466	0.098	0.755	2.059	0.154	6.372	0.013
Intervention * Time	3.273	0.004	2.622	0.016	1.623	0.139	0.278	0.947

Source	BMI		Waist	
	F	Sig.	F	Sig.
Intercept	2936	0.001	9974	0.001
Time	5.665	0.001	24.650	0.001
Intervention	5.234	0.024	7.158	0.008
Intervention * Time	0.280	0.946	0.967	0.447

Dependent Variable: Total Cholesterol, LDL, HDL, TG, FBS, Systolic, Diastolic, weight, BMI, Waist and Framingham

Model: Intercept, Time (Baseline, month 1, 2, 3, 4, 5 and 6), Intervention (aripiprazole and ziprasidone), Intervention * Time

3.6 Discussion

This was among the first double-blind, randomized study to evaluate the comparative efficacy and safety, between aripiprazole and ziprasidone in outpatients setting with schizophrenia disorder. Zimbroff at al.(2007) has conducted similar study however the study population include schizoaffective disorder in hospitalized patients.

Efficacy of Aripiprazole and Ziprasidone in Reversing Metabolic Syndrome

Following the initiation of treatment, our data showed that the prevalence of metabolic syndrome was significantly reduced from baseline to end of the study at 6 months in both aripiprazole and ziprasidone groups, regardless of the metabolic syndrome definition used. There was improvement in the prevalence of metabolic syndrome from baseline to 6-month after switching to aripiprazole or ziprasidone; NCEP ATP III definition (aripiprazole 58.9% vs. 30.0%, ziprasidone 51.8% vs. 15.3%), IDF definition (aripiprazole 57.8% vs. 30.0%, ziprasidone 51.8% vs. 15.3%). There was no statistically significant difference in the prevalence of metabolic syndrome between aripiprazole and ziprasidone from baseline to 6-month study visit. Overall, there were more cases of metabolic syndrome resolved than developed in both groups using NCEP ATP III; resolved cases (aripiprazole 14.4% vs. ziprasidone 18.8%, p>0.05), incidence cases (aripiprazole 5.6% vs. ziprasidone 4.7%, p>0.05). Both drugs demonstrate similar efficacy in reversing the metabolic syndrome as an effect from previous antipsychotics treatment.

This was the first nationwide survey, where we compare the prevalence of metabolic syndrome in a prospective 6-month study among Malaysian adults with schizophrenia based on NCEP ATP III criteria-modified for Asian waist circumference and modified

IDF definition. NCEP ATP III for Western populations and IDF had higher waist circumference cut-off values that might lead to an underestimation of Asian patients with metabolic syndrome. In our study, the prevalence of metabolic syndrome with modified IDF criteria was lower as compared to NCEP ATP III criteria-modified for Asian waist circumference. This was because modified IDF criteria include central obesity as a requisite feature causing underestimates the number of people with metabolic syndrome. NCEP ATP III criteria-modified for Asian waist circumference has the advantage of identifying more people with metabolic syndrome who might subsequently benefit from intervention targeted to reduce their risk of developing diabetes and cardiovascular disease.

Efficacy of Aripiprazole and Ziprasidone in Reversing Metabolic Syndrome Components and Parameters

From baseline to 6 months study visit, there was reduction in the prevalence of all metabolic syndrome components for both aripiprazole and ziprasidone group. The highest reduction in prevalence was waist circumference and the lowest reduction in prevalence was blood pressure for both groups. There was statistically significant difference in modelling analysis of prevalence rate for FBS between aripiprazole and ziprasidone from baseline to the endpoint 6-month. This could be due to patients who were randomized to aripiprazole showed much more reduction in FBS level as compared to ziprasidone.

The highest prevalence of metabolic syndrome component resolved after 6 months treatment of aripiprazole was triglycerides followed by waist circumference and in ziprasidone group, the highest prevalence of metabolic syndrome components resolved were waist circumference and triglycerides. For both groups, the highest incidence of metabolic syndrome component after 6 months treatment was blood pressure.

3 RCT Aripiprazole vs. Ziprasidone

There were not many publications for randomised controlled trial in comparison of aripiprazole and ziprasidone for the metabolic effects among schizophrenia patients (Zimbroff et al.,2007). Our study showed statistically significant improvement in total cholesterol, waist circumference, body weight and BMI, occurred over 6 months following a switch to aripiprazole or ziprasidone from previous treatment with other antipsychotic drugs. However there was no significant difference between those who were randomised to aripiprazole or ziprasidone. These findings suggested that both drugs were equally effective in improving metabolic parameters in schizophrenia patients.

Many non randomized studies have shown switching to aripiprazole or ziprasidone in schizophrenia patients who required long-term antipsychotic treatment, managed to alleviate antipsychotic-induced obesity, hyperglycemia or dyslipidemia (Alptekin et al.,2009; Kim et al.,2009; Schorr et al.,2008; Takeuchi et al.,2010).

The results reported in this study provided further support to other randomized efficacy trials in the improvement of metabolic effects following a switch to aripiprazole or ziprasidone. In primary analyses, our study reported the mean weight loss of -1.2 to -1.8 kg, mean reduction of -0.5 to -0.7 for BMI and mean reduction of -1.7 to -3.4 cm for waist circumference over 6-month duration following initiation of aripiprazole. For the ziprasidone group our study reported significant mean weight loss of -1.9 to -3.4 kg, mean reduction of -0.6 to -1.2 for BMI and mean reduction of -1.4 to -4.2 cm for waist circumference over 6-month duration following initiation of ziprasidone.

A recent meta-analysis of nine published efficacy studies with various follow-up intervals following aripiprazole initiation reported a pooled mean weight loss of -2.55

± 1.5 kg (Barak and Aizenberg,2011). Other randomized studies found mean weight loss of 1.26kg ± 1.37kg in aripiprazole group (Pigott et al.,2003; McQuade et al.,2004; Kerwin et al.,2007). Weight loss was also noted in other randomized studies, with mean weight loss -0.29 to -3.6 kg in the ziprasidone group (Arato et al.,2002; Simpson et al.,2005; Stroup et al.,2006; Sacchetti et al.,2009; Potkin et al.,2011).

We found that switching to aripiprazole was associated with significant improvement in total cholesterol and LDL in patients who previously on antipsychotics. In primary analyses, our study reported the mean reduction of -15.8 to -29.4 mg/dL for total cholesterol, mean reduction of -14.2 to -25.5 mg/dL for LDL, over 6-month duration following initiation of aripiprazole. The mean HDL of 0.4 to 1.4 mg/dL only improved after 4 months and the significant reduction of TG -35.7 mg/dL was noted after 6 months following switching to aripiprazole. Six other randomized studies found improvement of lipid measures with mean reduction of -0.3 to -17.0 mg/dL for total cholesterol, mean reduction of -3.86 to -17.0 mg/dL for LDL, mean improvement of 1.43 to 5.4 mg/dL for HDL and mean reduction of -0.1 to -37.2 mg/dL for TG in aripiprazole group (Pigott et al.,2003; McQuade et al.,2004; Chan et al.,2007; Kane et al.,2009; Fleischhacker et al.,2009; Macfadden et al.,2010).

Switching to ziprasidone was associated with significant improvement in total cholesterol in patients who previously on antipsychotics. In primary analyses, our study reported the mean reduction of -9.7 to -19.0 mg/dL for total cholesterol over 6-month duration following initiation of ziprasidone. The mean HDL of 0.3 to 1.1 mg/dL only improved after 4 months and the significant reduction of TG -21.4 to -28.2 mg/dL, mean reduction of -10.4 to -11.1 mg/dL for LDL, were noted after 5 months following switching to ziprasidone.

Several other randomized studies found improvement of lipid measures with mean reduction of -7.8 to -12.8 mg/dL for total cholesterol, mean reduction of -6.0 to -10.4 mg/dL for LDL, mean improvement of 0.8 to 8.0 mg/dL for HDL and mean reduction of -3.5 to -32.1 mg/dL for TG in ziprasidone group (Breier et al.,2005; Lieberman et al.,2005; Meyer et al.,2008; Sacchetti et al.,2009).

In primary analyses of our study, switching to aripiprazole was associated with improvement in FBS -0.8 to -8.3 mg/dL. Mean FBS reduction of -1.3 mg/dL over 52 weeks was reported in a randomized trial by Chrzanowski et al (2006). Switching to ziprasidone was associated with slight increased of FBS 0.8 to 2.7 mg/dL. Increased of mean FBS range from 2.9 to 4.8 mg/dL was also reported by other randomized trial (Grootens et al.,2011; Potkin et al.,2011; Cutler et al.,2008; Lieberman et al.,2005).

Sensitivity Analyses for Aripiprazole and Ziprasidone

Aripiprazole and ziprasidone demonstrated similar efficacy in reversing the metabolic syndrome as an effect from previous antipsychotics treatment, and the proportion resolved cases was higher than incidence cases. The findings of sensitivity analyses were consistent with the results of the primary analyses.

There was statistically significant difference in modelling analysis of mean change FBS and systolic blood pressure between aripiprazole and ziprasidone from baseline to the endpoint 6-month. Therefore, there were independent effects of treatments on FBS and systolic blood pressure response over time. This could be due to increased of mean change of FBS and systolic blood pressure from study visit 1 to 6 months after treatment of ziprasidone and there was reduction of mean change of FBS and systolic blood pressure from study visit 1 to 6 months after treatment of aripiprazole. For metabolic syndrome components, aripiprazole has better effect in improving FBS and systolic blood pressure than ziprasidone.

Efficacy of Aripiprazole and Ziprasidone in Improving Coronary Heart Disease Risk

From baseline to 6 months study visit, there was reduction in the prevalence of all CVRFs for both aripiprazole and ziprasidone group. However, there was no statistically significant difference observed for all CVRFs for both groups.

There was significant reduction on CHD risk score (Framingham) for both aripiprazole and ziprasidone. Both drugs demonstrated similar efficacy in reducing CHD risk among schizophrenia patients.

Efficacy of Aripiprazole and Ziprasidone in Improving Psychotic Symptoms among Schizophrenia Patients with Metabolic Syndrome

Aripiprazole and ziprasidone demonstrated similar efficacy in the positive and negative symptoms of schizophrenia indicating that patients who were switched to aripiprazole or ziprasidone did not experience worsening of their psychotic symptoms. In fact both drugs produced statistically significant improvements which were sustained throughout the whole duration of 6-month study (PANSS total, PANSS positive, PANSS negative and CGI-S scores). The efficacy data of this study were similar to that of previous studies (Grootens et al.,2011; Potkin et al.,2011; Macfadden et al.,2010; Kane et al.,2009).

Safety of Aripiprazole and Ziprasidone in the Treatment of Schizophrenia Patients with Metabolic Syndrome

For the safety assessment of aripiprazole and ziprasidone, both drugs were not associated with worsening of EPS symptoms. There was statistically significant reduction of SAS, BARS and AIMS score throughout 6-month study. In this study, discontinuation rate was used as a proxy measure for clinical effectiveness. Although ziprasidone group showed a higher discontinuation rate than aripiprazole group from

baseline to 6-month study visit, the difference in the discontinuation rates was not statistically significant.

The adverse events reported in our study patients were the common side effects associated with antipsychotic therapy, including extrapyramidal syndrome and insomnia, with similar prevalence across aripiprazole and ziprasidone groups. However, the incidence of somnolence was higher in the ziprasidone group than in the aripiprazole group (18.8% vs 2.2%). This was not unexpected, as a small 12-week study reported that when switching patients to ziprasidone, sedation was the most common adverse event associated with the switch (Kim et al.,2010). Somnolence caused by ziprasidone might be a result of histamine H_1 receptor antagonism. All the adverse events reported were mild to moderate in severity. The adverse events were resolved before the trial end. There were only two serious adverse events (SAE) during the study. Both events were hospitalization due to relapse of psychotic symptoms.

Strengths

Our study has several methodological strengths:

i). This was the first randomized efficacious study with head to head comparisons between aripiprazole and ziprasidone in the treatment of schizophrenia patients with metabolic syndrome for 6-month duration. Among atypical antipsychotics, aripiprazole and ziprasidone were associated with a lower metabolic risk (ADA-APA-AACE,2004; Newcomer,2005). Both medications were used in this study to reverse the metabolic effects from previous antipsychotics treatment without compromising the efficacy of controlling the psychotic symptoms.

ii). The study population was schizophrenia patients with at least one year duration of antpsychotic treatment. The minimal one year duration of antipsychotic exposure would be sufficient for the development of metabolic abnormalities. During screening, patients who were on mood stabilizer were excluded from this study. This is because mood stabilizer can be associated with weight gain, therefore could confound the results.

iii). Beside primary analysis, we conducted a series of sensitivity analyses in order to assess the robustness of our findings in the face of concomitant medication use. Schizophrenia patients were treated as per clinical practice, when diabetes mellitus, hypertension or hyperlipidemia was detected during study visit. The initiation of antidiabetic, antihyperlipidemia and antihypertensive was allowed after randomization when clinically indicated. It was unethical for not treating such conditions during the trial. Any of these concomitant treatments could have obscured the effects of aripiprazole or ziprasidone on metabolic and anthropometric measures. For sensitivity analyses, patients with these medications were excluded from the analysis.

Limitations

The primary limitations of this study include a relatively small sample size and the omission of behavioural measures of reinforcing effects of aripiprazole and ziprasidone.

i). Adequacy of Sample Size

Although the required sample size was 162 per arm and maintained 80% power of the study, we only managed to get aripiprazole n=90 and ziprasidone n=85. A fundamental issue in non-inferiority analysis was defining the non-inferiority margin.

A larger sample size may have been necessary to maintain 80% power for the demonstration of non-inferiority for the endpoints in this study.

Although with the relatively small sample size, there were statistical significance differences in the reduction of psychotics symptoms and some metabolic syndrome components in both groups, either in primary analyses (cohen's *d,* effect size *r* : PANSS total = 0.81,0.38 and PANSS positive = 0.72,0.34) and sensitivity analyses (cohen's *d,* effect size *r* : FBS = 0.02,0.01 and systolic blood pressure = - 0.06, -0.03).

We were not able to enroll a larger number of samples due to financial limitations. We were only given a small amount of study grants (RM136,000) by University of Malaya. In order to get more samples, we need to open up more study sites, hire more investigators and study coordinators, and have enough funds to buy the study medications.

Another factor that limits bigger sample recruitment was time factor. We have to complete the whole project within two years as required by the research grant provider.

ii). Instruments of the study

All the scales have been used widely in this country however until now, there was no paper being published regarding the validation of the scales in the local population.

iii).Conduct of Study

We did not examine the effects of psychosocial treatments aimed at improving lifestyle factors known to impact body weight and metabolic profile, nor were we able to account for such factors in our data analyses.

3.7 Conclusions

Switching to aripiprazole or ziprazidone was effective in reversing the metabolic syndrome and its components among schizophrenia patients who had metabolic syndrome. Aripiprazole and ziprasidone were efficacious and safe in the treatment of schizophrenia patients with metabolic syndrome.

Chapter FOUR: Overall Conclusions and Recommendations

4.1   Overall Conclusions

Atypical antipsychotics were reported to be associated with increased risk of impaired glucose level and hyperglycaemia, and subsequently increase the risk of the metabolic syndrome (Newcomer et al.,2002). Nevertheless, it has been shown that psychiatric disorders, including schizophrenia, were associated with an elevated risk of developing diabetes regardless of antipsychotic use (Henderson,2002). Patients with schizophrenia were at greater risk for metabolic dysfunctions than other individuals due to a number of reasons, including inactive lifestyle, poor dietary choices, and side effects of antipsychotic medications (Cohn,2009).

While the metabolic syndrome itself poses serious health complications, it also places individuals at an increased risk for other serious medical conditions, such as cardiovascular mortality. Individuals with the metabolic syndrome were three times as likely to have a myocardial infarction or stroke compared with people without the syndrome. While the pathophysiology of the metabolic syndrome was extremely complex and remained to be fully elucidated, currently both insulin resistance and central obesity were considered to be the significant underlying causes of this syndrome (Anderson et al.,2001; Nesto,2003).

We conducted a study to determine the prevalence of metabolic syndrome and prevalence of coronary heart disease risk among schizophrenia patients receiving antipsychotics in Malaysia. The study was conducted at four mental institutions, two army hospitals and two general hospitals namely Hospital Bahagia Ulu Kinta, Perak, Hospital Permai Johor Bahru, Johor, Hospital Sentosa Kuching, Sarawak, Hospital Mesra Kota Kinabalu, Sabah, Hospital Terendak Melaka, Navy Hospital Lumut,

Overall Conclusions and Recommendations

Perak, University Malaya Medical Centre (UMMC), Kuala Lumpur and Hospital Sg. Petani, Kedah. Study population were schizophrenia patients aged between 18 and 65 years old, who met the DSM-IV TR criteria for schizophrenia. Patients should receive antipsychotic treatment for at least 1 year and were not on mood stabilizer or depot neuroleptics. Metabolic syndrome was defined by using the NCEP ATP III criteria-modified for Asian waist circumference. The cardiovascular heart disease risk was assessed by using Framingham function (10-year all coronary heart disease event). A structured questionnaire to assess: (i) sociodemographic and lifestyle background (ii) medical, psychiatry and family history (iii) physical examination and blood investigation for metabolic syndrome profile.

A total of 270 patients were screened for metabolic syndrome. The prevalence of metabolic syndrome was 46.7%. The mean BMI value was 29.4 ± 5.1 kg/m^2 for patients with metabolic syndrome and 25.0 ± 5.6 kg/m^2 for patient, without metabolic syndrome ($p<0.05$). The usage of commonest monotherapy atypical antipsychotics was olanzapine (42.2%) and chlorpromazine for typical antipsychotics (33.3%) in the metabolic syndrome group. The prevalence of diabetes mellitus after initiation of antipsychotics was 15.2%. There was statistically significant for all metabolic syndrome components between metabolic syndrome and non-metabolic syndrome groups i.e. Waist circumference (OR=34.8, 95% CI: 12.2, 99.4), HDL Cholesterol (OR=5.4, 95% CI: 3.2, 9.2), Triglycerides (OR= 8.6, 95% CI: 4.9, 15.2), BP (OR=5.5, 95% CI: 3.2, 9.3), FBS (OR= 11.4, 95% CI: 5.5, 23.6). Coronary heart disease 10-year risk was significantly higher in the metabolic syndrome patients. The prevalence of patients with high/very high cardiovascular event risk (Framingham $\geq$ 10%) was 31.5% in the metabolic syndrome patients vs. 11.0% in the non-metabolic syndrome patients (OR = 3.7, 95% CI: 1.9, 7.1, $p<0.0001$).

Overall Conclusions and Recommendations

The prevalence of metabolic syndrome in schizophrenia patients receiving antipsychotic in Malaysia was very high. It was associated with increased cardiovascular risk. Our data adds to the mounting evidence that schizophrenia patients are at increased risk for developing metabolic syndrome. The high prevalence of the syndrome underscores an urgent need to formulate a comprehensive intervention measures to combat these problems.

4.1.1. Safety and Efficacy of Aripiprazole Vs Ziprazidone in Schizophrenic Patients with Metabolic Syndrome

Not all antipsychotic agents carry the same adverse metabolic risk. Of the atypical antipsychotics, aripiprazole and ziprasidone were associated with a lower metabolic risk (ADA-APA-AACE,2004; Newcomer,2005). Both ziprasidone and aripiprazole were known to be the second generation atypical antipsychotics that were least likely to cause dyslipidaemia, and in fact might improve the lipid profile of patients switched from another antipsychotic drug to one of these agents (Spurling et al.,2007; Greenberg and Citrome,2007).

Therefore, switching patients with schizophrenia who require long-term treatment with antipsychotic drugs to either aripiprazole or ziprasidone appeared as a rational choice to lessen the metabolic effects (e.g. obesity, hyperglycaemia, dyslipidaemia) induced by the antipsychotics.

We conducted a study to determine the improvement and reversibility of metabolic syndrome, its components and lipid profiles after switching to aripiprazole or ziprasidone. We also determine the safety and efficacy of aripiprazole and ziprasidone in the treatment of schizophrenia patients with metabolic syndrome.

Overall Conclusions and Recommendations

We conducted a double blind randomized controlled trial at four mental institutions and four general hospitals. Study population were patients aged between 18 and 65 years old, with a current Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision (DSM-IV TR) diagnosis of schizophrenia. Eligible patients were randomised either to aripiprazole or ziprasidone. The dose of aripiprazole and ziprasidone, can be either increased or reduced based on clinical assessment. The total daily dosage of ziprasidone ranges from 80mg - 160mg.The total daily dosage of aripiprazole ranges from 10mg - 30 mg. Metabolic syndrome was defined by using the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria-modified for Asian waist circumference. For baseline and follow-up evaluation, the outcome measures included body mass index (BMI), waist circumference, blood pressure (BP), fasting blood sugar (FBS), lipid profile, adverse effects monitoring and clinical rating scale such as Positive and Negative Symptoms Scale (PANSS), Clinical Global Impression Scale (CGI), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathasia Scale (BAS) and Simpson Angus Scale (SAS). Intention-to-treat was used for the data analysis. Generalized Estimating Equation (GEE) and Mixed-Effects Model Repeated-Measures (MMRM) analysis was utilized to examine changes in outcome measures over time with the treatment of aripiprazole and ziprasidone.

175 patients were recruited for the study. 51.4% (90/175) of patients was randomized to aripiprazole and 48.6% (85/175) to ziprasidone. There was improvement in the prevalence of metabolic syndrome from baseline to 6-month after switching to aripiprazole or ziprasidone; (aripiprazole 58.9% vs. 30.0%, ziprasizone 51.8% vs. 15.3%, p<0.05), 14.4% of patients had resolved metabolic syndrome after switching to aripiprazole and 18.8% of patients had resolved metabolic syndrome after switching to

ziprasidone. There was improvement in the prevalence of all metabolic syndrome component from baseline to 6-month after switching to aripiprazole or ziprasizone; waist circumference (aripiprazole 84.4% vs. 44.4%, ziprasizone 87.1% vs. 35.3%), HDL cholesterol (aripiprazole 54.4% vs. 33.3%, ziprasizone 52.9% vs. 23.5%), triglycerides (aripiprazole 50.0% vs. 21.1%, ziprasizone 37.6% vs. 12.9%), BP (aripiprazole 41.1% vs. 25.6%, ziprasizone 32.9% vs. 20.0%) ,FBS (aripiprazole 42.2% vs. 20.0%, ziprasizone 25.9% vs. 8.2%, p<0.05). There was statistically significant improvement in PANSS, CGI, BARS and SAS after switching to aripiprazole or ziprasidone. The commonest side effects reported were EPS and insomnia for both treatment groups.

Switching to aripiprazole or ziprazidone was effective in reversing the metabolic syndrome and its components among schizophrenia patients who had metabolic syndrome. Our study showed that aripiprazole was not inferior to ziprasidone in improving metabolic syndrome and metabolic syndrome components. The results reported here provide further support for the improvement in metabolic effects following a switch to aripiprazole or ziprasidone. An appropriately powered study with larger sample size is warranted to further confirm our results and address several issues that the current study design is not able to account for.

4.2 Recommendations

4.2.1. We feel that identification and treatment of metabolic syndrome in this population is of utmost importance. It is unethical not to screen and treat metabolic syndrome in this population, and cause unnecessary suffering, knowing very well the rate of morbidity and mortality in them is high. Failure

to identify metabolic syndrome here means an opportunity for treatment is lost in a population that is otherwise difficult to reach in the community.

4.2.2. Identification and treatment of metabolic syndrome must be address as a central role and should be part of overall management of schizophrenia. Treatment should not only focus on the efficacy of antipsychotic treatment but also must address the potential side effect profile such as metabolic syndrome.

4.2.3. Since the prevalence of metabolic syndrome was very high among schizophrenia patients receiving antipsychotics in Malaysia, the screening should be mandatory for all patients. The screening should not be limited to atypical antipsychotics or certain antipsychotics but should be employed to all types of antipsychotics.

4.2.4. We would like to recommend developing a practice guideline in Malaysia where all schizophrenia patients should have their waist circumference, blood pressure and BMI being routinely measured every time they come for follow up. Blood screening for fasting blood and lipids must be scheduled regularly for all patients. Currently this is not done regularly in many hospitals and clinics in Malaysia.

4.2.5. Among schizophrenia patients who developed metabolic syndrome, they can be safety switched to aripiprazole or ziprazidone as an alternative treatment.

4.2.6. Aripiprazole and ziprazidone were both efficacious treatment for schizophrenia patients who developed metabolic syndrome.

4.2.7. Aripiprazole and ziprazidone could be used to reverse the metabolic syndrome among schizophrenia patients who developed metabolic syndrome while they were on other antipsychotics.

Overall Conclusions and Recommendations

4.2.8. We would like to recommend incorporating aripiprazole or ziprazidone as one of the antipsychotics of choice for the treatment of schizophrenia who had metabolic syndrome or who have high risk to develop metabolic syndrome. At the moment the Malaysian Clinical Practice guideline does not have such recommendations.

4.2.9. We would like to suggest conducting further study with a larger sample size and a longer duration of follow up to confirm the efficacy and safety of aripiprazole or ziprazidone in the treatment on schizophrenia patients with metabolic syndrome.

4.2.10. We would like to recommend conducting a study which combined aripiprazole or ziprazidone with one of the behavioural treatment method (wellness program, psychoeducation, diet and exercise) to confirm if it will yield a better outcome).
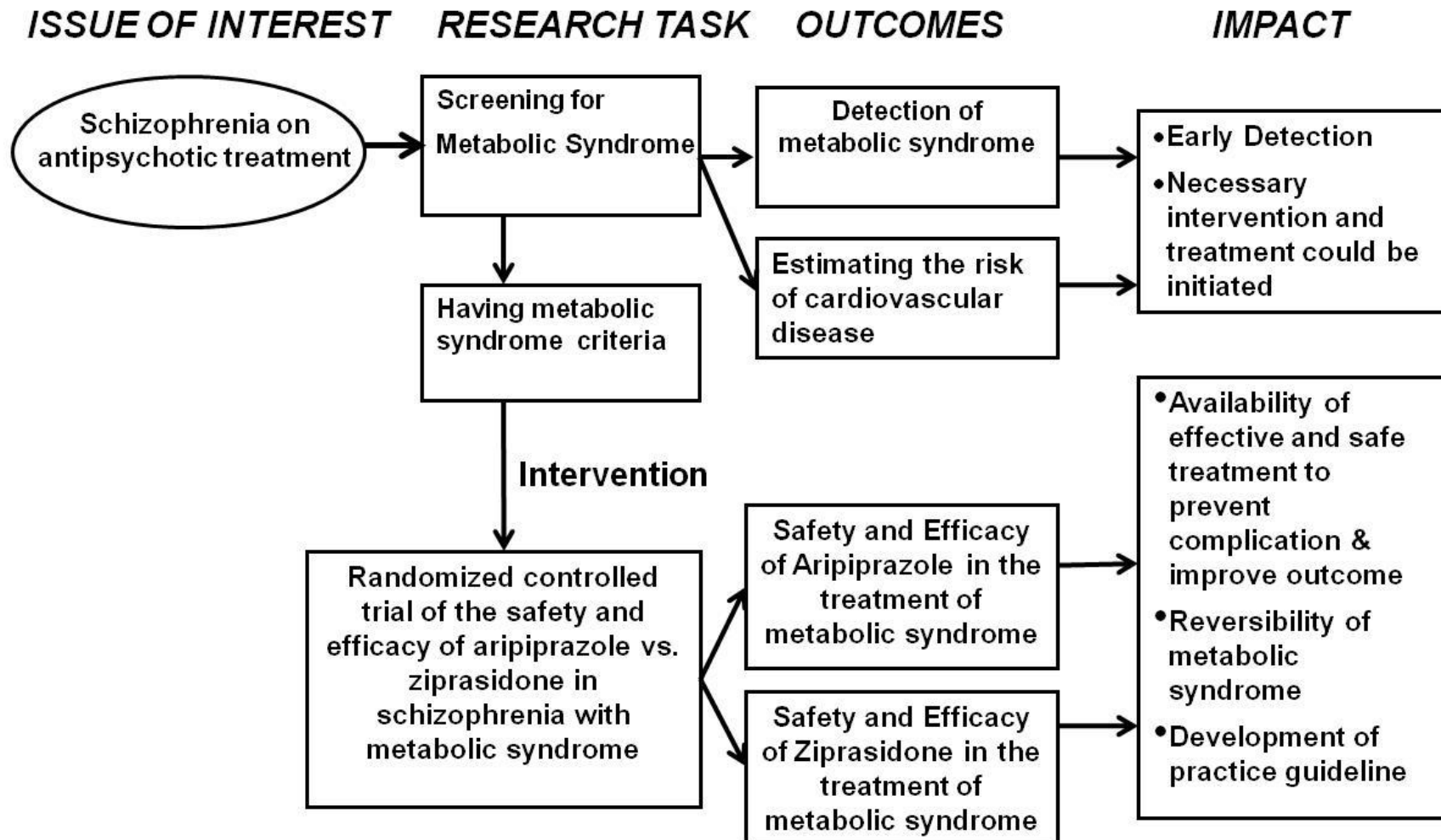
Appendix A - Operational Definitions

Age:

Age of the schizophrenia patient in years at last birthday.

Race:

Ethnicity recorded in the medical case record.

Marital status:

Legal marital status either single or married, widowed or divorce as mentioned

by patient during interview.

Education level:

Type of education institution last attended by the patient.

Occupation:

Patient's current occupation

Appendix B

Appendix B - Mini International Neuropsychiatric Interview (M.I.N.I.)

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 5.0.0

DSM-IV

USA: **D. Sheehan, J. Janavs, R. Baker, K. Harnett-Sheehan, E. Knapp, M. Sheehan**
University of South Florida - Tampa

FRANCE: **Y. Lecrubier, E. Weiller, T. Hergueta, P. Amorim, L. I. Bonora, J. P. Lépine**
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DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel.

M.I.N.I. 5.0.0 (July 1, 2006)

Appendix B

<table>
<tr><td colspan="2">Patient Name:</td><td colspan="2">Patient Number:</td></tr>
<tr><td colspan="2">Date of Birth:</td><td colspan="2">Time Interview Began:</td></tr>
<tr><td colspan="2">Interviewer's Name:</td><td colspan="2">Time Interview Ended:</td></tr>
<tr><td colspan="2">Date of Interview:</td><td colspan="2">Total Time:</td></tr>
</table>

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV	ICD-10	
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	☐	296.20-296.26 Single	F32.x	☐
		Recurrent	☐	296.30-296.36 Recurrent	F33.x	☐
	MDE WITH MELANCHOLIC FEATURES	Current (2 weeks)	☐	296.20-296.26 Single	F32.x	☐
	Optional			296.30-296.36 Recurrent	F33.x	☐
B	DYSTHYMIA	Current (Past 2 years)	☐	300.4	F34.1	☐
C	SUICIDALITY	Current (Past Month)	☐			☐
		Risk: ☐ Low ☐ Medium ☐ High				
D	MANIC EPISODE	Current	☐	296.00-296.06	F30.x-F31.9	☐
		Past	☐			
	HYPOMANIC EPISODE	Current	☐	296.80-296.89	F31.8-F31.9/F34.0	☐
		Past	☐			
E	PANIC DISORDER	Current (Past Month)	☐	300.01/300.21	F40.01-F41.0	☐
		Lifetime	☐			
F	AGORAPHOBIA	Current	☐	300.22	F40.00	☐
G	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)	☐	300.23	F40.1	☐
H	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	300.3	F42.8	☐
I	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	309.81	F43.1	☐
J	ALCOHOL DEPENDENCE	Past 12 Months	☐	303.9	F10.2x	☐
	ALCOHOL ABUSE	Past 12 Months	☐	305.00	F10.1	☐
K	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	☐
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	☐
L	PSYCHOTIC DISORDERS	Lifetime	☐	295.10-295.90/297.1/	F20.xx-F29	☐
		Current	☐	297.3/293.81/293.82/		
				293.89/298.8/298.9		
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime	☐	296.24/296.34/296.44	F32.3/F33.3/ ☐	
		Current	☐	296.24/296.34/296.44	F30.2/F31.2/F31.5	
					F31.8/F31.9/F39 ☐	
M	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	307.1	F50.0	☐
N	BULIMIA NERVOSA	Current (Past 3 Months)	☐	307.51	F50.2	☐
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	☐	307.1	F50.0	☐

Appendix B

O	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	300.02	F41.1	☐
P	ANTISOCIAL PERSONALITY DISORDER Optional	Lifetime	☐	301.7	F60.2	☐

Which problem troubles you the most? Indicate your response by checking the appropriate check box(es).

Appendix B

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for ICD-10). The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.
•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.
•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question H6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that <u>each dimension</u> of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).
<u>Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I.</u> The M.I.N.I. Plus has questions that investigate these issues.

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Appendix B

A. MAJOR DEPRESSIVE EPISODE

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?	NO	YES
A2	In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	NO	YES
		➡	
	IS A1 OR A2 CODED YES?	NO	YES

A3   Over the past two weeks, when you felt depressed or uninterested:

a   Was your appetite decreased or increased nearly every day? Did your weight
    decrease or increase without trying intentionally (i.e., by ±5% of body weight
    or ±8 lbs. or ±3.5 kgs., for a 160 lb./70 kg. person in a month)?   NO   YES *
    IF YES TO EITHER, CODE YES.

b   Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up   NO   YES
    in the middle of the night, early morning wakening or sleeping excessively)?

c   Did you talk or move more slowly than normal or were you fidgety, restless   NO   YES *
    or having trouble sitting still almost every day?

d   Did you feel tired or without energy almost every day?   NO   YES

e   Did you feel worthless or guilty almost every day?   NO   YES

f   Did you have difficulty concentrating or making decisions almost every day?   NO   YES

g   Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead?   NO   YES

ARE 5 OR MORE ANSWERS (A1-A3) CODED YES?

NO	YES *
MAJOR DEPRESSIVE EPISODE, CURRENT	

IF PATIENT HAS CURRENT MAJOR DEPRESSIVE EPISODE CONTINUE TO A4,
OTHERWISE MOVE TO MODULE B:

➡

A4   a   During your lifetime, did you have other episodes of two weeks or more when you felt   NO   YES
         depressed or uninterested in most things, and had most of the problems we just talked about?

     b   In between 2 episodes of depression, did you ever have an interval
         of at least 2 months, without any depression and any loss of interest?

NO	YES
MAJOR DEPRESSIVE EPISODE, RECURRENT	

* If patient has Major Depressive Episode, Current, use this information in coding the corresponding questions on page 5 (A6d, A6e).

MAJOR DEPRESSIVE EPISODE WITH MELANCHOLIC FEATURES (optional)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF THE PATIENT CODES POSITIVE FOR A CURRENT MAJOR DEPRESSIVE EPISODE (A3 = YES), EXPLORE THE FOLLOWING:

A5	a	During the most severe period of the current depressive episode, did you lose almost completely your ability to enjoy nearly everything?	NO	YES
	b	During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up? **IF NO:** When something good happens does it fail to make you feel better, even temporarily?	NO	YES
			➡	
		IS EITHER **A5a** OR **A5b** CODED **YES**?	NO	YES

A6		**Over the past two week period, when you felt depressed and uninterested:**		
	a	Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies?	NO	YES
	b	Did you feel regularly worse in the morning, almost every day?	NO	YES
	c	Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day?	NO	YES
	d	IS **A3c** CODED **YES** (PSYCHOMOTOR RETARDATION OR AGITATION)?	NO	YES
	e	IS **A3a** CODED **YES** FOR ANOREXIA OR WEIGHT LOSS?	NO	YES
	f	Did you feel excessive guilt or guilt out of proportion to the reality of the situation?	NO	YES

ARE **3** OR MORE **A6** ANSWERS CODED **YES**?

NO	YES
Major Depressive Episode	
with	
Melancholic Features	
Current	

Appendix B

B. DYSTHYMIA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

IF PATIENT'S SYMPTOMS CURRENTLY MEET CRITERIA FOR MAJOR DEPRESSIVE EPISODE, DO NOT EXPLORE THIS MODULE.

B1	Have you felt sad, low or depressed most of the time for the last two years?	➡ NO	YES
B2	Was this period interrupted by your feeling OK for two months or more?	➡ NO	YES
B3	**During this period of feeling depressed most of the time:**		
a	Did your appetite change significantly?	NO	YES
b	Did you have trouble sleeping or sleep excessively?	NO	YES
c	Did you feel tired or without energy?	NO	YES
d	Did you lose your self-confidence?	NO	YES
e	Did you have trouble concentrating or making decisions?	NO	YES
f	Did you feel hopeless?	NO	YES
	ARE **2** OR MORE **B3** ANSWERS CODED **YES**?	➡ NO	YES

B4   Did the symptoms of depression cause you significant distress or impair
your ability to function at work, socially, or in some other important way?

```
┌─────────────────────────────┐
│  NO                   YES    │
│                              │
│        DYSTHYMIA             │
│        CURRENT              │
└─────────────────────────────┘
```

Appendix B

C. SUICIDALITY

In the past month did you:

				Points
C1	Suffer any accident?	NO	YES	0
	IF NO TO C1, SKIP TO C2; IF YES, ASK C1a,:			
C1a	Plan or intend to hurt yourself in that accident either passively or actively?	NO	YES	0
	IF NO TO C1a, SKIP TO C2: IF YES, ASK C1b,:			
C1b	Did you intend to die as a result of this accident?	NO	YES	0
C2	Think that you would be better off dead or wish you were dead?	NO	YES	1
C3	Want to harm yourself or to hurt or to injure yourself?	NO	YES	2
C4	Think about suicide?	NO	YES	6

IF YES, ASK ABOUT THE INTENSITY AND FREQUENCY OF THE SUICIDAL IDEATION:

Frequency   Intensity

Occasionally ❑	Mild ❑	Can you control these impulses
Often ❑	Moderate ❑	and state that you will not act
Very often ❑	Severe ❑	on them while in this program?

Only score 8 points if response is NO. NO   YES   8

C5	Have a suicide plan?	NO	YES	8
C6	Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die?	NO	YES	9
C7	Deliberately injure yourself without intending to kill yourself?	NO	YES	4
C8	Attempt suicide?	NO	YES	10

Hoped to be rescued / survive   ❑
Expected / intended to die   ❑

In your lifetime:

C9	Did you ever make a suicide attempt?	NO	YES	4

IS AT LEAST **1** OF THE ABOVE (EXCEPT C1) CODED **YES**?

IF YES, ADD THE TOTAL NUMBER OF POINTS FOR THE ANSWERS (C1-C9) CHECKED 'YES' AND SPECIFY THE LEVEL OF SUICIDE RISK AS INDICATED IN THE DIAGNOSTIC BOX:

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDE RISK IN THE SPACE BELOW:

NO	YES
SUICIDE RISK	
CURRENT	
1-8 points Low	❑
9-16 points Moderate	❑
$\geq$ 17 points High	❑

Appendix B

D. (HYPO) MANIC EPISODE

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

D1	a	Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.)	NO	YES

IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior.

IF NO, CODE NO TO **D1b**: IF **YES** ASK:

	b	Are you currently feeling 'up' or 'high' or 'hyper' or full of energy?	NO	YES
D2	a	Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified?	NO	YES

IF NO, CODE NO TO **D2b**: IF **YES** ASK:

	b	Are you currently feeling persistently irritable?	NO ➡	YES
		IS **D1a** OR **D2a** CODED **YES**?	NO	YES

D3 IF **D1b** OR **D2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE IF **D1b** AND **D2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

During the times when you felt high, full of energy, or irritable did you:

		Current Episode		Past Episode	
a	Feel that you could do things others couldn't do, or that you were an especially important person? IF **YES**, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. ❏ No ❏ Yes	NO	YES	NO	YES
b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES
c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
d	Have racing thoughts?	NO	YES	NO	YES
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Become so active or physically restless that others were worried about you?	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES

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	Current Episode	Past Episode

D3 (SUMMARY): ARE **3** OR MORE **D3** ANSWERS CODED **YES**   NO   YES   NO   YES
(OR **4** OR MORE IF **D1a** IS **NO** (IN RATING PAST EPISODE) AND **D1b** IS **NO** (IN RATING CURRENT EPISODE)?
RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE D3 SYMPTOMS WHILE
IRRITABLE MOOD ALONE REQUIRES **4** OF THE **D3** SYMPTOMS.

VERIFY IF THE SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.

D4   Did these symptoms last at least a week **and** cause significant problems at home,   NO   YES   NO   YES
at work, socially, or at school, **or** were you hospitalized for these problems?

THE EPISODE EXPLORED WAS A:

❏ *HYPOMANIC EPISODE*   ❏ *MANIC EPISODE*   ❏ *HYPOMANIC EPISODE*   ❏ *MANIC EPISODE*

IS **D4** CODED **NO**?

	NO	YES
HYPOMANIC EPISODE		
CURRENT		❏
PAST		❏

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

IS **D4** CODED **YES**?

	NO	YES
MANIC EPISODE		
CURRENT		❏
PAST		❏

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

Appendix B

E. PANIC DISORDER

(➡ MEANS : CIRCLE NO IN E5, E6 AND E7 AND SKIP TO F1)

E1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➡ NO YES

E2	At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO YES
E3	Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack or did you make a significant change in your behavior because of the attacks (e.g., shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, or seeing your doctor more frequently because of the symptoms?	NO YES

E4   During the worst spell that you can remember:

	a	Did you have skipping, racing or pounding of your heart?	NO YES
	b	Did you have sweating or clammy hands?	NO YES
	c	Were you trembling or shaking?	NO YES
	d	Did you have shortness of breath or difficulty breathing?	NO YES
	e	Did you have a choking sensation or a lump in your throat?	NO YES
	f	Did you have chest pain, pressure or discomfort?	NO YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO YES
	j	Did you fear that you were losing control or going crazy?	NO YES
	k	Did you fear that you were dying?	NO YES
	l	Did you have tingling or numbness in parts of your body?	NO YES
	m	Did you have hot flushes or chills?	NO YES

E5	ARE BOTH **E3,** AND **4** OR MORE **E4** ANSWERS, CODED **YES**? IF YES TO E5, SKIP TO E7.	NO YES *PANIC DISORDER LIFETIME*
E6	IF **E5 = NO,** ARE ANY E4 ANSWERS CODED **YES**? THEN SKIP TO **F1.**	NO YES *LIMITED SYMPTOM ATTACKS LIFETIME*
E7	In the past month, did you have such attacks repeatedly (2 or more) followed by persistent concern about having another attack?	NO YES *PANIC DISORDER CURRENT*

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F. AGORAPHOBIA

F1	Do you feel anxious or uneasy in places or situations where you might have a panic attack or the panic-like symptoms we just spoke about, or where help might not be available or escape might be difficult: like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, traveling in a bus, train or car?	NO YES

IF **F1 = NO**, CIRCLE **NO** IN **F2**.

F2	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	NO YES *AGORAPHOBIA CURRENT*

IS **F2** (CURRENT AGORAPHOBIA) CODED **NO**

   and

IS **E7** (CURRENT PANIC DISORDER) CODED **YES**?

> NO   YES
>
> ***PANIC DISORDER*** *without Agoraphobia* **CURRENT**

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES**

   and

IS **E7** (CURRENT PANIC DISORDER) CODED **YES**?

> NO   YES
>
> ***PANIC DISORDER*** *with Agoraphobia* **CURRENT**

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES**

   and

IS **E5** (PANIC DISORDER LIFETIME) CODED **NO**?

> NO   YES
>
> ***AGORAPHOBIA, CURRENT*** *without history of* ***Panic Disorder***

Appendix B

G. SOCIAL PHOBIA (Social Anxiety Disorder)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1	In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	➡ NO	YES

G2	Is this social fear excessive or unreasonable?	➡ NO	YES

G3	Do you fear these social situations so much that you avoid them or suffer through them?	➡ NO	YES

G4   Do these social fears disrupt your normal work or social functioning or cause you significant distress?

SUBTYPES

Do you fear and avoid 4 or more social situations?

If YES   Generalized social phobia (social anxiety disorder)

If NO   Non-generalized social phobia (social anxiety disorder)

NOTE TO INTERVIEWER: PLEASE ASSESS WHETHER THE SUBJECT'S FEARS ARE RESTRICTED TO NON-GENERALIZED ("ONLY 1 OR SEVERAL") SOCIAL SITUATIONS OR EXTEND TO GENERALIZED ("MOST") SOCIAL SITUATIONS. "MOST" SOCIAL SITUATIONS IS USUALLY OPERATIONALIZED TO MEAN 4 OR MORE SOCIAL SITUATIONS, ALTHOUGH THE DSM-IV DOES NOT EXPLICITLY STATE THIS.

 EXAMPLES OF SUCH SOCIAL SITUATIONSTYPICALLY INCLUDE INITIATING OR MAINTAINING A CONVERSATION, PARTICIPATING IN SMALL GROUPS, DATING, SPEAKING TO AUTHORITY FIGURES, ATTENDING PARTIES, PUBLIC SPEAKING, EATING IN FRONT OF OTHERS, URINATING IN A PUBLIC WASHROOM, ETC.

NO	YES
SOCIAL PHOBIA (Social Anxiety Disorder) **CURRENT**	
GENERALIZED ❑	
NON-GENERALIZED ❑	

H. OBSESSIVE-COMPULSIVE DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO** AND MOVE TO THE NEXT MODULE)

H1	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though you didn't want to, **or** fearing you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** hoarding, collecting, **or** religious obsessions.) (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO ↓ SKIP TO **H4**	YES

H2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO ↓ SKIP TO **H4**	YES
H3	Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?	NO	YES obsessions

H4	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?	NO	YES compulsions

	IS **H3** OR **H4** CODED **YES**?	➡ NO	YES
H5	Did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?	➡ NO	YES

H6 Did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, your work or school, your usual social activities, or relationships, or did they take more than one hour a day?	**NO** **YES** *O.C.D.* *CURRENT*

Appendix B

I. POSTTRAUMATIC STRESS DISORDER (optional)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

I1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, SUDDEN DEATH OF SOMEONE CLOSE TO YOU, WAR, OR NATURAL DISASTER.	➡ NO	YES
I2	Did you respond with intense fear, helplessness or horror?	➡ NO	YES
I3	During the past month, have you re-experienced the event in a distressing way (such as, dreams, intense recollections, flashbacks or physical reactions)?	➡ NO	YES

I4 **In the past month:**

a	Have you avoided thinking about or talking about the event ?	NO	YES
b	Have you avoided activities, places or people that remind you of the event?	NO	YES
c	Have you had trouble recalling some important part of what happened?	NO	YES
d	Have you become much less interested in hobbies or social activities?	NO	YES
e	Have you felt detached or estranged from others?	NO	YES
f	Have you noticed that your feelings are numbed?	NO	YES
g	Have you felt that your life will be shortened or that you will die sooner than other people?	NO	YES
	ARE **3** OR MORE **I4** ANSWERS CODED **YES**?	➡ NO	YES

I5 **In the past month:**

a	Have you had difficulty sleeping?	NO	YES
b	Were you especially irritable or did you have outbursts of anger?	NO	YES
c	Have you had difficulty concentrating?	NO	YES
d	Were you nervous or constantly on your guard?	NO	YES
e	Were you easily startled?	NO	YES
	ARE **2** OR MORE **I5** ANSWERS CODED **YES**?	➡ NO	YES

I6 During the past month, have these problems significantly interfered with your work or social activities, or caused significant distress?	**NO** **YES** *POSTTRAUMATIC STRESS DISORDER CURRENT*

J. ALCOHOL ABUSE AND DEPENDENCE

(➡ MEANS: GO TO DIAGNOSTIC BOXES, CIRCLE NO IN BOTH AND MOVE TO THE NEXT MODULE)

J1	**In the past 12 months**, have you had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?	➡ NO	YES

J2   **In the past 12 months**:

a   Did you need to drink more in order to get the same effect that you got when you first started drinking?   NO   YES

b   When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, "the shakes", sweating or agitation?
IF YES TO EITHER, CODE YES.   NO   YES

c   During the times when you drank alcohol, did you end up drinking more than you planned when you started?   NO   YES

d   Have you tried to reduce or stop drinking alcohol but failed?   NO   YES

e   On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?   NO   YES

f   Did you spend less time working, enjoying hobbies, or being with others because of your drinking?   NO   YES

g   Have you continued to drink even though you knew that the drinking caused you health or mental problems?   NO   YES

ARE **3** OR MORE **J2** ANSWERS CODED **YES**?

* IF YES, SKIP J3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX
AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

NO   YES*
ALCOHOL DEPENDENCE **CURRENT**

J3   **In the past 12 months:**

a   Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems?
(CODE YES ONLY IF THIS CAUSED PROBLEMS.)   NO   YES

b   Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?   NO   YES

c   Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?   NO   YES

d   Did you continue to drink even though your drinking caused problems with your family or other people?   NO   YES

ARE **1** OR MORE **J3** ANSWERS CODED **YES**?

NO	N/A	YES
ALCOHOL ABUSE **CURRENT**		

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K. NON-ALCOHOL PSYCHOACTIVE SUBSTANCE USE DISORDERS

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

		Now I am going to show you / read to you a list of street drugs or medicines.		
K1	a	**In the past 12 months**, did you take any of these drugs more than once, to get high, to feel better, or to change your mood?	➡ NO	YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "crank", "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, codeine, Percodan, Darvon, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, PCP ("angel dust", "peace pill"), psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA, or ketamine ("special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Marijuana: hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

Miscellaneous: steroids, nonprescription sleep or diet pills. Any others?

SPECIFY MOST USED DRUG(S): _____

CHECK ONE BOX

ONLY ONE DRUG / DRUG CLASS HAS BEEN USED ☐

ONLY THE MOST USED DRUG CLASS IS INVESTIGATED. ☐

EACH DRUG CLASS USED IS EXAMINED SEPARATELY (PHOTOCOPY K2 AND K3 AS NEEDED) ☐

b SPECIFY WHICH DRUG/DRUG CLASS WILL BE EXPLORED IN THE INTERVIEW BELOW IF THERE IS CONCURRENT OR SEQUENTIAL POLYSUBSTANCE USE:_____

K2 **Considering your use of (**NAME THE DRUG / DRUG CLASS SELECTED**), in the past 12 months:**

	a	Have you found that you needed to use more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?	NO	YES
	b	When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better?	NO	YES

IF **YES** TO EITHER, CODE **YES**.

	c	Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would?	NO	YES
	d	Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed?	NO	YES
	e	On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or in recovering from the drug, or thinking about the drug?	NO	YES

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f Did you spend less time working, enjoying hobbies, or being with family NO YES
or friends because of your drug use?

g Have you continued to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused NO YES
you health or mental problems?

ARE **3** OR MORE **K2** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

* IF YES, SKIP K3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX FOR THIS
SUBSTANCE AND MOVE TO THE NEXT DISORDER.
DEPENDENCE PREEMPTS ABUSE.

NO	**YES ***
SUBSTANCE DEPENDENCE	
CURRENT	

Considering your use of (NAME THE DRUG CLASS SELECTED), **in the past 12 months:**

K3 a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) NO YES
more than once, when you had other responsibilities at school, at work, or at home?
Did this cause any problem?

(CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) NO YES
more than once in any situation where you were physically at risk (for example,
driving a car, riding a motorbike, using machinery, boating, etc.)?

c Did you have legal problems more than once because of your drug use, for example, NO YES
an arrest or disorderly conduct?

d Did you continue to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused NO YES
problems with your family or other people?

ARE **1** OR MORE **K3** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

NO	**N/A**	**YES**
SUBSTANCE ABUSE		
CURRENT		

Appendix B

L. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE **YES** ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

Now I am going to ask you about unusual experiences that some people have.

					BIZARRE
L1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? NOTE: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ➡L6
L2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ➡L6
L3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ➡L6
L4	a	Have you ever believed that you were being sent special messages through the TV, radio, or newspaper, or that a person you did not personally know was particularly interested in you?	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ➡L6
L5	a	Have your relatives or friends ever considered any of your beliefs strange or unusual? INTERVIEWER: ASK FOR EXAMPLES. ONLY CODE **YES** IF THE EXAMPLES ARE **CLEARLY** DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS L1 TO L4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITIUTION, ETC.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do they currently consider your beliefs strange?	NO	YES	YES
L6	a	Have you ever heard things other people couldn't hear, such as voices? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS **YES** TO THE FOLLOWING:	NO	YES	
		IF YES: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO		YES
	b	**IF YES OR YES BIZARRE TO L6a:** have you heard these things in the past month? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS **YES** TO THE FOLLOWING: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES	YES ➡L8b

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L7   a   Have you ever had visions when you were awake or have you ever seen things   NO   YES
other people couldn't see?
CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

    b   **IF YES:** have you seen these things in the past month?   NO   YES

        CLINICIAN'S JUDGMENT

L8   b   IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED   NO   YES
SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS?

L9   b   IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC   NO   YES
BEHAVIOR?

L10 b   ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE   NO   YES
FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE
OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING
THE INTERVIEW?

L11 a   ARE 1 OR MORE « a » QUESTIONS FROM L1a TO L7a CODED **YES OR YES BIZARRE**
AND IS EITHER:

            MAJOR DEPRESSIVE EPISODE, (CURRENT OR RECURRENT)
            OR
            MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED **YES**?   NO   YES
                                                                                              ➔L13

        IF NO TO L11 a, CIRCLE NO IN BOTH 'MOOD DISORDER WITH PSYCHOTIC
FEATURES' DIAGNOSTIC BOXES AND MOVE TO L13.

    b   You told me earlier that you had period(s) when you felt (depressed/high/persistently
irritable).

        Were the beliefs and experiences you just described (SYMPTOMS CODED YES FROM **L1a** TO **L7a**)
restricted exclusively to times when you were feeling depressed/high/irritable?

        IF THE PATIENT EVER HAD A PERIOD OF AT LEAST 2 WEEKS OF HAVING THESE
BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT
DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

        IF THE ANSWER IS NO TO THIS DISORDER, ALSO CIRCLE NO TO L12 AND MOVE TO L13

NO	YES
MOOD DISORDER WITH PSYCHOTIC FEATURES	
LIFETIME	

L12 a   ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L7b CODED **YES OR YES BIZARRE**
AND IS EITHER:

            MAJOR DEPRESSIVE EPISODE, (CURRENT)
            OR
            MANIC OR HYPOMANIC EPISODE, (CURRENT) CODED **YES**?

        IF THE ANSWER IS YES TO THIS DISORDER (LIFETIME OR CURRENT),
CIRCLE NO TO L13 AND L14 AND MOVE TO THE NEXT MODULE.

NO	YES
MOOD DISORDER WITH PSYCHOTIC FEATURES	
CURRENT	

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L13   ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L6b, CODED **YES BIZARRE**?

    OR

ARE 2 OR MORE « b » QUESTIONS FROM L1b TO L10b, CODED **YES** (RATHER THAN **YES BIZARRE**)?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO	YES
PSYCHOTIC DISORDER **CURRENT**	

L14   IS **L13** CODED **YES**

    OR

ARE 1 OR MORE « a » QUESTIONS FROM L1a TO L6a, CODED **YES BIZARRE**?

    OR

ARE 2 OR MORE « a » QUESTIONS FROM L1a TO L7a, CODED **YES** (RATHER THAN **YES BIZARRE**)

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO	YES
PSYCHOTIC DISORDER **LIFETIME**	

Appendix B

M. ANOREXIA NERVOSA

M1 a How tall are you? ☐ft ☐☐in.

☐ ☐☐cm.

b. What was your lowest weight in the past 3 months? ☐ ☐☐lbs.

☐ ☐☐kgs.

➡

c IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO   NO   YES
HIS / HER HEIGHT? (SEE TABLE BELOW)

In the past 3 months: ➡

M2   In spite of this low weight, have you tried not to gain weight?   NO   YES
➡

M3   Have you intensely feared gaining weight or becoming fat, even though you were underweight?   NO   YES

M4 a Have you considered yourself too big / fat or that part of your body was too big / fat?   NO   YES

b Has your body weight or shape greatly influenced how you felt about yourself?   NO   YES

c Have you thought that your current low body weight was normal or excessive?   NO   YES
➡

M5   ARE 1 OR MORE ITEMS FROM **M4** CODED **YES**?   NO   YES
➡

M6   FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual   NO   YES
periods when they were expected to occur (when you were not pregnant)?

FOR WOMEN: ARE **M5 AND M6** CODED **YES**?

FOR MEN: IS **M5** CODED **YES**?

NO	YES
ANOREXIA NERVOSA **CURRENT**	

HEIGHT / WEIGHT TABLE CORRESPONDING TO A BMI THRESHOLD OF 17.5 KG/M^2

Height/Weight													
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lbs.	81	84	87	89	92	96	99	102	105	108	112	115	118	122
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kgs	37	38	39	41	42	43	45	46	48	49	51	52	54	55

Height/Weight				
ft/in	5'11	6'0	6'1	6'2	6'3
lbs.	125	129	132	136	140
cm	180	183	185	188	191
kgs	57	59	60	62	64

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m^2 for the patient's height. This is the threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anorexia Nervosa.

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N. BULIMIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

N1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	➡ NO	YES
N2	In the last 3 months, did you have eating binges as often as twice a week?	➡ NO	YES
N3	During these binges, did you feel that your eating was out of control?	➡ NO	YES
N4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	➡ NO	YES
N5	Does your body weight or shape greatly influence how you feel about yourself?	➡ NO	YES
N6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO ↓ Skip to N8	YES
N7	Do these binges occur only when you are under (_____ lbs./kgs.)? INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO	YES

N8   IS **N5** CODED **YES** AND IS EITHER **N6** OR **N7** CODED **NO**?

```
┌─────────────────────────┐
│  NO            YES       │
│                          │
│  BULIMIA NERVOSA         │
│      CURRENT             │
└─────────────────────────┘
```

IS **N7** CODED **YES**?

```
┌─────────────────────────┐
│  NO            YES       │
│                          │
│  ANOREXIA NERVOSA        │
│  Binge Eating/Purging Type│
│      CURRENT             │
└─────────────────────────┘
```

Appendix B

O. GENERALIZED ANXIETY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

O1	a	Have you worried excessively or been anxious about several things over the past 6 months?	➡ NO	YES
	b	Are these worries present most days?	➡ NO	YES
		IS THE PATIENT'S ANXIETY RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	➡ NO	YES ➡
O2		Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing?	➡ NO	YES

O3   FOR THE FOLLOWING, CODE **NO** IF THE SYMPTOMS ARE CONFINED TO
FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT.

When you were anxious over the past 6 months, did you, most of the time:

a	Feel restless, keyed up or on edge?	NO	YES
b	Feel tense?	NO	YES
c	Feel tired, weak or exhausted easily?	NO	YES
d	Have difficulty concentrating or find your mind going blank?	NO	YES
e	Feel irritable?	NO	YES
f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES

ARE **3** OR MORE **O3** ANSWERS CODED **YES**?

NO	YES
GENERALIZED ANXIETY DISORDER **CURRENT**	

Appendix B

P. ANTISOCIAL PERSONALITY DISORDER (optional)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX AND CIRCLE NO.)

P1 **Before you were 15 years old, did you:**

a repeatedly skip school or run away from home overnight?   NO   YES

b repeatedly lie, cheat, "con" others, or steal?   NO   YES

c start fights or bully, threaten, or intimidate others?   NO   YES

d deliberately destroy things or start fires?   NO   YES

e deliberately hurt animals or people?   NO   YES

f force someone to have sex with you?   NO   YES
➡

ARE **2** OR MORE **P1** ANSWERS CODED **YES**?   NO   YES

DO NOT CODE **YES** TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY
POLITICALLY OR RELIGIOUSLY MOTIVATED.

P2 **Since you were 15 years old, have you:**

a repeatedly behaved in a way that others would consider irresponsible, like
failing to pay for things you owed, deliberately being impulsive or deliberately
not working to support yourself?   NO   YES

b done things that are illegal even if you didn't get caught (for example, destroying
property, shoplifting, stealing, selling drugs, or committing a felony)?   NO   YES

c been in physical fights repeatedly (including physical fights with your
spouse or children)?   NO   YES

d often lied or "conned" other people to get money or pleasure, or lied just
for fun?   NO   YES

e exposed others to danger without caring?   NO   YES

f felt no guilt after hurting, mistreating, lying to, or stealing from others, or
after damaging property?   NO   YES

ARE **3** OR MORE **P2** QUESTIONS CODED **YES**?

NO	YES
ANTISOCIAL PERSONALITY DISORDER LIFETIME	

THIS CONCLUDES THE INTERVIEW

Appendix B

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Translations	M.I.N.I. 4.4 or earlier versions	M.I.N.I. 4.6/5.0, M.I.N.I. Plus 4.6/5.0 and M.I.N.I. Screen 5.0:
Afrikaans	R. Emsley	W. Maartens
Arabic		O. Osman, E. Al-Radi
Bengali		H. Banerjee, A. Banerjee
Braille (English)		
Brazilian Portuguese	P. Amorim	P. Amorim
Bulgarian	L.G.. Hranov	
Chinese		L. Carroll, Y-J. Lee, Y-S. Chen, C-C. Chen, C-Y. Liu, C-K. Wu, H-S. Tang, K-D. Juang, Yan-Ping Zheng.
Czech		P. Zvlosky
Danish	P. Bech	P. Bech, T. Schütze
Dutch/Flemish	E. Griez, K. Shruers, T. Overbeek, K. Demyttenaere	I. Van Vliet, H. Leroy, H. van Megen
English	D. Sheehan, J. Janavs, R. Baker, K. Harnett-Sheehan, E. Knapp, M. Sheehan	D. Sheehan, R. Baker, J. Janavs, K. Harnett-Sheehan, M. Sheehan
Estonian		J. Shlik, A. Aluoja, E. Khil
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Finnish	M. Heikkinen, M. Lijeström, O. Tuominen	M. Heikkinen, M. Lijeström, O. Tuominen
French	Y. Lecrubier, E. Weiller, I. Bonora, P. Amorim, J.P. Lepine	Y. Lecrubier, E. Weiller, P. Amorim, T. Hergueta
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Greek	S. Beratis	T. Calligas, S. Beratis
Gujarati		M. Patel, B. Patel, Organon
Hebrew	J. Zohar, Y. Sasson	R. Barda, I. Levinson, A. Aviv
Hindi		C. Mittal, K. Batra, S. Gambhir, Organon
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Icelandic		J.G. Stefansson
Italian	I. Bonora, L. Conti, M. Piccinelli, M. Tansella, G. Cassano, Y. Lecrubier, P. Donda, E. Weiller	L. Conti, A. Rossi, P. Donda
Japanese		T. Otsubo, H. Watanabe, H. Miyaoka, K. Kamijima, J.Shinoda, K.Tanaka, Y. Okajima
Kannada		Organon
Korean		K.S. Oh and Korean Academy of Anxiety Disorders
Latvian	V. Janavs, J. Janavs, I. Nagobads	V. Janavs, J. Janavs
Lithuanian		A. Bacevicius
Malayalam		Organon
Marathi		Organon
Norwegian	G. Pedersen, S. Blomhoff	K.A. Leiknes , U. Malt, E. Malt, S. Leganger
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Portuguese	P. Amorim	P. Amorim, T. Guterres
Punjabi		A. Gahunia, S. Gambhir
Romanian		O. Driga
Russian		A. Bystritsky, E. Selivra, M. Bystritsky, L. Shumyak, M. Klisinska.
Serbian	I. Timotijevic	I. Timotijevic
Setswana		K. Ketlogetswe
Slovenian		M. Kocmur, M. Kocmur
Spanish	L. Ferrando, J. Bobes-Garcia, J. Gilbert-Rahola, Y. Lecrubier	L. Ferrando, L. Franco-Alfonso, M. Soto, J. Bobes-Garcia, O. Soto, L. Franco, G. Heinze, C. Santana, R. Hidalgo
Swedish	M. Waern, S. Andersch, M. Humble	C. Allgulander, H. Agren M. Waern, A. Brimse, M. Humble.
Tamil		Organon
Telugu		Organon

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Appendix B

Thai | P. Kittirattanapaiboon, S. Mahatnirunkul, P. Udomrat,
P. Silpakit,, M. Khamwongpin, S. Srikosai.
Turkish   T. Örnek, A. Keskiner, I. Vahip | T. Örnek, A. Keskiner, A.Engeler
Urdu | S. Gambhir

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Appendix C - Positive and Negative Symptoms Scale(PANSS)

Positive and Negative Symptoms Scale

Initials:
Date:
Visit:

Positive Symptoms

P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganisation	1	2	3	4	5	6	7
P3	Hallucinatory behaviour	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7

Negative Symptoms

N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	Passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7

Appendix C

General Psychopathology

G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lack of judgement & insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

Appendix D - Clinical Global Impressions Scale (CGI-S)

<u>Clinical Global Impressions Scale</u>

Initials:
Date:
Visit:

SEVERITY OF ILLNESS

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

Normal, not at all ill	☐1
Borderline mentally ill	☐2
Mildly ill	☐3
Moderately ill	☐4
Markedly ill	☐5
Severely ill	☐6
Among the most extremely ill patients	☐7

Appendix E - Abnormal Involuntary Movement Scale (AIMS)

<u>Abnormal Involuntary Movement Scales</u>

Initials:

Date:

Visit:

Instructions: Complete examination procedure before making ratings.
Rate highest severity observed.

Code: 1 None
             2 Minimal, may be extreme normal
             3 Mild
             4 Moderate
             5 Severe

Facial and Oral Movements:

1.   Muscles of facial Expression (e.g., movement of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing)
                                1   2   3   4   5

2.   Lips and Perioral Area (e.g., puckering, pouting, smacking)
                                1   2   3   4   5

3.   Jaws (e.g. biting, clenching, chewing, mouth opening, lateral movement)
                                1   2   3   4   5

4.   Tongue (Rate only increase in movement both in and out of mouth, NOT inability to sustain movement.)
                                1   2   3   4   5

Extremity Movements:

5.   Upper (arms, wrists, hands, fingers). Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine). Do NOT include tremor (i.e., repetitive, regular, rhythmic).
                                1   2   3   4   5

6.   Lower (legs, knees, ankles, toes). (E.g., lateral knee movement, foot taping, heel dropping, foot squirming, inversion and eversion of foot.)

                                1   2   3   4   5

Trunk Movements:

7.   Neck, shoulders, hips (e.g., rocking, twisting, squirming, pelvic gyrations)

$$1 \quad 2 \quad 3 \quad 4 \quad 5$$

Global judgments

8. Severity of abnormal movements:

1. None, normal
2. Minimal
3. Mild
4. Moderate
5. Severe

9. Incapacitation due to abnormal movements:

1. None, normal
2. Minimal
3. Mild
4. Moderate
5. Severe

10. Patient's awareness of abnormal movements (Rate only patient's report)

1. No awareness
2. Aware, no distress
3. Aware, mild distress
4. Aware, moderate distress
5. Aware, severe distress

Dental Status:

11. Current problems with teeth and/or dentures

1. No
2. Yes

12. Does patient usually wear dentures?

1. No
2. Yes

Appendix F - Barnes Akathasia Scale (BARS)

<u>Barnes Akathisia Rating Scale (BARS)</u>

Initials:

Date:

Visit:

Instructions: Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

0   Normal, occasional fidgety movements of the limbs

1   Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, but movements present for less than half the time observed

2   Observed phenomena, as described in (1) above, which are present for at least half the observation period

3   Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness

0   Absence of inner restlessness

1   Non-specific sense of inner restlessness

2   The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still

3   Awareness of intense compulsion to move most of the time *and/or* reports strong desire to walk or pace most of the time

Distress related to restlessness:

0   No distress

1   Mild

2   Moderate

3   Severe

Global Clinical Assessment of Akathisia:

0   *Absent.* No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia

1   *Questionable.* Non-specific inner tension and fidgety movements

2   *Mild akathisia.* Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress.

3   *Moderate akathisia.* Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing

4   *Marked akathisia.* Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.

5   *Severe akathisia.* The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.

Appendix G - Simpson Angus Scale (SAS)

<u>SIMPSON-ANGUS EXTRAPYRAMIDAL SIDE EFFECTS SCALE</u>

Initials:

Date:

Visit:

The exam should be conducted in a room where the subject can walk a sufficient distance to allow him/her to get into a natural rhythm (e.g. 15 paces). Each side of the body should be examined. If one side shows more pronounced pathology than the other, this score should be noted and this taken. Cogwheel rigidity may be palpated when the examination is carried out for items 3, 4, 5, and 6. It is not rated separately and is merely another way to detect rigidity. It would indicate that a minimum score of 1 would be mandatory.

1. **Gait**: The patient is examined as he walks into the examining room, his gait, the swing of his arms, his general posture; all form the basis for an overall score for this item. This is rated as follows:

   0 Normal

   1 Diminution in swing while the patient is walking

   2 Marked diminution in swing with obvious rigidity in the arm

   3 Stiff gait with arms held rigidly before the abdomen

   4 Stooped shuffling gait with propulsion and retropulsion

2. **Arm Dropping:** The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly:

   0 Normal, free fall with loud slap and rebound

   1 Fall slowed slightly with less audible contact and little rebound

   2 Fall slowed, no rebound

   3 Marked slowing, no slap at all

   4 Arms fall as though against resistance; as though through glue

3.   **Shoulder Shaking:** The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:

0 Normal

1 Slight stiffness and resistance

2 Moderate stiffness and resistance

3 Marked rigidity with difficulty in passive movement

4 Extreme stiffness and rigidity with almost a frozen shoulder

4.   **Elbow Rigidity:** The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)

0 Normal

1 Slight stiffness and resistance

2 Moderate stiffness and resistance

3 Marked rigidity with difficulty in passive movement

4 Extreme stiffness and rigidity with almost a frozen elbow

5.   **Wrist Rigidity or Fixation of Position:** The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion and ulnar and radial deviation:

0 Normal

1 Slight stiffness and resistance

2 Moderate stiffness and resistance

3 Marked rigidity with difficulty in passive movement

4 Extreme stiffness and rigidity with almost frozen

6.   **Leg Pendulousness:** The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging form the basis for the score on this item:

0 The legs swing freely

1 Slight diminution in the swing of the legs

2 Moderate resistance to swing

3 Marked resistance and damping of swing

4 Complete absence of swing

7. **Head Dropping:** The patient lies on a well-padded examining table and his head is raised by the examiner's hand. The hand is then withdrawn and the head allowed to drop. In the normal subject the head will fall upon the table. The movement is delayed in extrapyramidal system disorder, and in extreme parkinsonism it is absent. The neck muscles are rigid and the head does not reach the examining table.

0 The head falls completely with a good thump as it hits the table

1 Slight slowing in fall, mainly noted by lack of slap as head meets the table

2 Moderate slowing in the fall quite noticeable to the eye

3 Head falls stiffly and slowly

4 Head does not reach the examining table

8. **Glabella Tap**: Subject is told to open eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:

0 0-5 blinks

1 6-10 blinks

2 11-15 blinks

3 16-20 blinks

4 21 and more blinks

9. **Tremor:** Patient is observed walking into examining room and is then reexamined for this item:

0 Normal

1 Mild finger tremor, obvious to sight and touch

2 Tremor of hand or arm occurring spasmodically

3 Persistent tremor of one or more limbs

4 Whole body tremor

10.   **Salivation:** Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:

0 Normal

1 Excess salivation to the extent that pooling takes place if the mouth is open and the tongue raised

2 When excess salivation is present and might occasionally result in difficulty speaking

3 Speaking with difficulty because of excess salivation

4 Frank drooling

Appendix H - Questionnaire

QUESTIONNAIRES – Cross Sectional Study

Excel	
SPSS	
Inclusion	

Date of interview: _____

1.*RN no:_____

2.*Name:_____

Contact No.:_____ Patient_____Name of relative_____

3.*Date of birth (dd/mm/yyyy) :_____

4. *Age :_____

5.*Sex: Male = 0   Female = 1

6.*Race: Malay = 0   Chinese = 1   Indian = 2   Others =3_____

7.Marital status: Married = 0   Single = 1   Divorced = 2   Widowed = 3

8.Education level: No formal education = 0   Primary = 1   Secondary = 2   Tertiary = 3

9.Occupational: Employed=0   _____

Unemployed=1   Retired = 2   Housewife = 3   Student=4   NA = 5

10.Diagnosis

Schizophrenia =0   Bipolar =1

11.Year of diagnosis_____   12.Age of onset_____   13.* Duration of illness_____

13.Current Medication

No	Name	*start date	*Current dose	*Duration(month)

 Antipsychotics

Clozapine   Risperidone   Amisulpride   Olanzapine

Aripiprazole(Abilify)   Quetiapine   Paliperidone

1

14.Previous medication(past 1 year)

No	Name	Start date	End Date	Last dose	Reason for change

Antipsychotics   Clozapine   Risperidone   Olanzapine   Amisulpride

Aripiprazole   Quetiapine   Paliperidone

15.Female only   On OCP   Yes =1   No=0

16.LMP:_____   Delay   Yes =1   No=0

17.Smoking status

Never smoke = 0   Former smokers ≤ 20 sticks/day = 1   Former smokers ≥ 20 sticks/day = 2

Current smokers ≤ 20 sticks/day = 3   Current smokers ≥ 20 sticks/day = 4

18.Time since quitting for former smokers

≥ 10 years = 0   5 -9 years = 1   1 - 4 years = 2   < 1 year = 3

19.Physical activity (physical exercise at least 30 minutes   e.g. brisk walk, jogging, play games)

Never=0,   Rarely = 1,   1-3 times /month = 2,   1 - 2 times/wk = 3,

3 - 4 times/wk = 4,   ≥ 5 times/wk = 5

20.History of weight gain

Weight before treatment of 1st antipsychotics (estimate) _____kg

Waist circumference before treatment of 1st antipsychotics (estimate) _____cm

Medical History

21. Hypertension   Yes=1   No=0   if yes, go to Q22

22. Hypertension before diagnosis of mental illness   Yes=1   No=0

23. Diabetes mellitus   Yes=1   No=0   if yes , go to Q24

24. Diabetes mellitus before diagnosis of mental illness   Yes=1   No=0

24a. Female only : History of gestational diabetes   Yes=1   No=0

2

Appendix H - Questionnaire

Family History

25. Hypertension   Yes=1   No=0

26. Diabetes mellitus   Yes=1   No=0

27. Obesity   Yes=1   No=0

28. Parent obese   Yes=1   No=0

29. Siblings obese   Yes=1   No=0

Physical Examination

30. Weight:_____kg

31. Height:_____cm

32. *BMI: _____

33. Waist circumference:_____cm

Male >90cm,   Yes=1   No=0

Female >80cm,   Yes=1   No=0

34. Hip circumference _____ cm

35. *Waist-hip ratio_____

36. Blood pressure_____mmHg

37. *Weight gain > 7%   Yes=1   No=0

Blood investigation

38. Random blood sugar

☐ Fasting :_____mmol/l   ≥ 5.6 mmol/l   Yes=1   No=0

☐ Not fasting :_____mmol/l   Duration after meal _____ minutes

    ≥ 7.0 mmol/l   Yes=1   No=0

39. *History of screening before starting 1st antipsychotic treatment :   Yes=1   No=0

Weight   Yes=1   No=0

Height   Yes=1   No=0

BMI: Yes=1   No=0

Waist circumference   Yes=1   No=0

Blood pressure   Yes=1   No=0

Random blood sugar   Yes=1   No=0

3

Fasting blood sugar	Yes=1	No=0
Hb$_A$1c	Yes=1	No=0
Fasting lipid profile	Yes=1	No=0
ECG	Yes=1	No=0

40.*History of screening before changing to another antipsychotic :   Yes=1   No=0

Weight	Yes=1	No=0
Height	Yes=1	No=0
BMI:	Yes=1	No=0
Waist circumference	Yes=1	No=0
Blood pressure	Yes=1	No=0
Random blood sugar	Yes=1	No=0
Fasting blood sugar	Yes=1	No=0
Hb$_A$1c	Yes=1	No=0
Fasting lipid profile	Yes=1	No=0
ECG	Yes=1	No=0

41.*History of monitoring after initiation of antipsychotics   Yes=1   No=0

Weight	Yes=1	No=0
Height	Yes=1	No=0
BMI:	Yes=1	No=0
Waist circumference	Yes=1	No=0
Blood pressure	Yes=1	No=0
Random blood sugar	Yes=1	No=0
Fasting blood sugar	Yes=1	No=0
Hb$_A$1c	Yes=1	No=0
Fasting lipid profile	Yes=1	No=0
ECG	Yes=1	No=0

4

42.*Results

Medication: antipsychotics				
Parameters/Date				
Weight				
Height				
Waist circumference				
Blood pressure				
Random blood sugar				
Fasting blood sugar				
Hb_A1c				
Fasting lipid profile -Total				
LDL-C				
HDL-C				
TG				
ECG				

*History of mental illness

History of hospitalization due to relapse   Yes=1   No=0

Medication								
Date								

Medication					
No. of relapse					

5

Appendix I - Approval Letter from Ethical Committee/ Government Authorities

UNIVERSITI MALAYA
KUALA LUMPUR
PUSAT PERUBATAN UM

JAWATANKUASA ETIKA PERUBATAN
PUSAT PERUBATAN UNIVERSITI MALAYA
ALAMAT: LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA
TELEFON: 03-79494422 samb. 3209 FAKSIMILI: 03-79494638

NAME OF ETHICS COMMITTEE/IRB: Medical Ethics Committee, University Malaya Medical Centre ADDRESS: LEMBAH PANTAI 59100 KUALA LUMPUR	ETHICS COMMITTEE/IRB REFERENCE NUMBER: 715.66
PROTOCOL NO: TITLE: Randomized Controlled Trial Of The Safety And Efficacy Of Ziprazidone Vs Aripiprazole In The Treatment Of Schizophrenia With Metabolic Syndrome And Diabetes Mellitus	
PRINCIPAL INVESTIGATOR : Dr. Mas Ayu Said TELEPHONE: KOMTEL:	SPONSOR:

The following item [✓] have been received and reviewed in connection with the above study to be conducted by the above investigator.

[ ] Borang Permohonan Pindaan Penyelidikan   Ver date:
[ ] Study Protocol   Ver date:
[ ] Investigator Brochure   Ver date:
[ ] Patient Information Sheet   Ver date:
[ ] Consent Form   Ver date:
[✓] Notification;
   • Change the Principal Investigator (Prof. Madya Ahamd Hatim Sulaiman)
   • Payment for hospitalization & Treatment of sides effects for patient who enrolled in Clinical Trial
[✓] Investigator(s) CV's (Prof. Madya Ahamd Hatim Sulaiman)

and have been [✓]

[✓] Approved
[ ] Conditionally approved (identify item and specify modification below or in accompanying letter)
[ ] Rejected (identify item and specify reasons below or in accompanying letter)

Comments:

Date of approval: 22th APRIL 2009

....
PROF. LOOI LAI MENG
Chairman
Medical Ethics Committee

Appendix I – Ethics Approval

PEJABAT TIMBALAN KETUA PENGARAH KESIHATAN
OFFICE OF THE DEPUTY DIRECTOR-GENERAL OF HEALTH
(PENYELIDIKAN & SOKONGAN TEKNIKAL)
(RESEARCH & TECHNICAL SUPPORT)
KEMENTERIAN KESIHATAN MALAYSIA
MINISTRY OF HEALTH MALAYSIA
Aras 12, Blok E7, Parsel E, Presint 1
Level 12, Block E7, Parcel E, Precinct 1
Pusat Pentadbiran Kerajaan Persekutuan
Federal Government Administrative Centre
62590 PUTRAJAYA

Tel : 03 88832543
Faks : 03 88895184

JAWATANKUASA ETIKA & PENYELIDIKAN
PERUBATAN
KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 Kuala Lumpur

Ruj. Kami : (2) dlm.KKM/NIHSEC/08/0804/P09-

Tarikh : 19 Januari 2010

Prof Madya Dr Ahmad Hatim Sulaiman
Jabatan Psikologi
Fakulti Perubatan
Universiti Malaya

Tuan,

NMRR-09-814-4650
Metabolic Syndrome and Diabetes Mellitus among Schizophrenic Patients with Atypical Antipsychotics

Lokasi projek : Hospital Bahagia Ulu Kinta/ Hospital Permai Johor/ Hospital Mesra Kota Kinabalu/ Hospital Sentosa Kuching/ Hospital Pulau Pinang/ Hospital Tengku Ampuan Afzan/ Hospital Tentera Melaka

Dengan hormatnya perkara di atas adalah dirujuk.

2. Jawatankuasa Etika & Penyelidikan Perubatan (JEPP), Kementerian Kesihatan Malaysia (KKM) mengambil maklum bahawa projek tersebut adalah projek usahasama antara Universiti Malaya, Kementerian Kesihatan Malaysia dan Hospital Angkatan Tentera Malaysia.

3. Sehubungan dengan itu, Jawatankuasa Etika & Penyelidikan Perubatan (JEPP), Kementerian Kesihatan Malaysia (KKM) tiada halangan, dari segi etika, ke atas pelaksanaan kajian tersebut. JEPP mengambil maklum bahawa kajian tersebut tidak mempunyai intervensi klinikal ke atas subjek dan hanya melibatkan pengumpulan data melalui *secondary data*. Segala rekod dan data subjek adalah SULIT dan hanya digunakan untuk tujuan kajian dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi. Kebenaran daripada Pengarah hospital di mana kajian akan dijalankan mesti diperolehi terlebih dahulu sebelum kajian dijalankan. Tuan perlu akur dan mematuhi keputusan tersebut.

5. Laporan tamat kajian dan sebarang penerbitan dari kajian ini hendaklah dikemukakan kepada Jawatankuasa Etika & Penyelidikan Perubatan selepas tamatnya kajian ini.

Sekian terima kasih.

BERKHIDMAT UNTUK NEGARA

Saya yang menurut perintah,

(DATO' DR CHANG KIAN MENG)
Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia

Appendix J - Research Grant

UMRG/RG048/09HTM

13 April 2009

Puan Mas Ayu Said
Jabatan Perubatan Kemasyarakatan dan Pencegahan
Fakulti Perubatan, Universiti Malaya.

Y. Bhg. Profesor / Datuk / Dato' / Datin / Dr. / Tuan / Puan,

PERUNTUKAN GERAN PENYELIDIKAN UNIVERSITI MALAYA (UMRG) 2009 DAN KATALALUAN

Dengan hormatnya perkara di atas adalah dirujuk.

Sukacita dimaklumkan permohonan UMRG Y. Bhg. Profesor / Datuk / Dato' / Datin / Dr. / Tuan / Puan telah diluluskan oleh Timbalan Naib Canselor (Penyelidikan & Inovasi) atas perakuan AJK Kluster *Health and Translational Medicine (HTMed)*.

Berikut adalah maklumat bagi projek Y. Bhg. Profesor / Datuk / Dato' / Datin / Dr. / Tuan / Puan yang telah diluluskan :

No. Akaun	: RG048/09HTM
Tajuk	: Randomised Controlled Trial Of Safety And Efficacy Of Ziprazidone Vs Aripiprazole In Schizophrenia With Metabolic Syndrome And Diabetes Mellitus
Katalaluan	: BUY5ju
Jangkamasa	: 1 Tahun (1-04-2009 hingga 31-03-2010)

Vot	Perkara	Jumlah Kelulusan (RM)	Vot	Perkara	Jumlah Kelulusan (RM)
Vote 11000	Gaji & Upahan	12,000.00	Vote 26000	Bekalan, & Pembaikan	66,630.00
Vote 14000	Elaun Lebih Masa	-	Vote 27000	Bekalan & Bahan Penyelidikan	2,270.00
Vote 21000	Perjalanan & Sara Hidup	2,000.00	Vote 28000	Penyelenggaraan & Pembaikan Kecil	-
Vote 23000	Perhubungan & Utiliti	-	Vote 29000	Perkhidmatan Ikhtisas & Lain-Lain	14,100.00
Vote 24000	Sewaan	-	Vote 35000	Peralatan	3,000.00
Jumlah Peruntukan Yang Diluluskan Tahun 1 : RM100,000.00					

Berhubung dengan perkara ini, Y. Bhg. Profesor / Datuk / Dato' / Datin / Dr. / Tuan / Puan diminta memaklumkan kepada unit ini sama ada Y. Bhg. Profesor / Datuk / Dato' / Datin / Dr. / Tuan / Puan menerima atau tidak tawaran di atas dengan mengisi borang penerimaan tawaran IPPP/UPGP/ (UMRG)2009 terlampir dan serahkan kembali selewat-lewatnya pada **24 April 2009 (Jumaat). Jika pihak kami tidak menerima sebarang maklum balas sehingga tarikh tersebut tawaran ini akan terbatal dengan sendirinya dan akaun *e-Finance* tidak dapat diakses.**

Unit Pengurusan Geran Penyelidikan
Institut Pengurusan dan Pemantauan Penyelidikan
A205 Bangunan IPS, Universiti Malaya, 50603 Kuala Lumpur, Malaysia
Tel: (603) 7967 4522 / 4647 / 4652 / 4653 / 4654 / 4675 / 4521 / 6952
Faks: (603) 7967 4648
Emel : ketua_upd_ippp@um.edu.my • http://www.ippp.um.edu.my

MS ISO 9001:2000 REG. NO.AR 2760

Appendix J – Research Grant

Segala urusan perbelanjaan (pembelian & pembayaran) dan semakan akaun **mestilah menggunakan sistem kewangan baru melalui laman web : http://www.ippp.um.edu.my/ eFinance**. Manual penggunaan sistem boleh didapati di dalam laman web tersebut. Sebarang pertanyaan mengenai sistem kewangan ini boleh diajukan kepada **Cik Aiza Zilla binti Abdul (03- 79674521)**.

Semua cadangan pembelian hendaklah dipersetujui oleh Pengarah/ Ketua Pusat/ Kumpulan Penyelidikan dan Pengerusi Kluster (bagi pembelian melebihi RM10,000 sahaja) sebelum proses pemerolehan dijalankan. Kesemua tuntutan perbelanjaan hendaklah dikemukakan kepada Unit Pengurusan Geran Penyelidikan (UPGP), Institut Pengurusan dan Pemantauan Penyelidikan (IPPP), Universiti Malaya melalui Pengarah/ Ketua Pusat/ Kumpulan Penyelidikan dan Ketua Jabatan/ Bahagian. Tuntutan mestilah sampai ke Unit ini tidak lewat dari satu bulan selepas aktiviti/pembelian dijalankan. Tuntutan selepas tempoh ini tidak dapat diluluskan. Projek penyelidikan ini hendaklah dilaksanakan dengan baik untuk memenuhi semua KPI penyelidikan yang telah ditetapkan oleh pihak universiti. Geran penyelidikan ini perlu habis digunakan sekurang-kurangnya 80% dari peruntukan dalam tahun 2009.
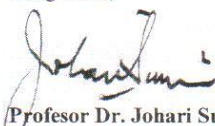
Tuan/Puan perlu kemukakan laporan kepada Unit seperti berikut;

1. Laporan Status Kemajuan Projek (6 bulan)   : **30 September 2009**
2. Laporan Akhir Projek   : **31 Mac 2010**

Untuk makluman Y. Bhg. Profesor / Datuk / Dato' / Datin / Dr. / Tuan / Puan sekiranya laporan ini tidak dikemukakan maka ianya akan menjejaskan permohonan peruntukan UMRG Y. Bhg. Profesor / Datuk / Dato' / Datin / Dr. / Tuan / Puan di masa akan datang.

Sekian.

Yang benar,

Profesor Dr. Johari Surin
Ketua,
Unit Pengurusan Geran Penyelidikan
Institut Pengurusan dan Pemantauan Penyelidikan
Universiti Malaya

s.k.   1. Pengerusi
        Health and Translational Medicine (HTMed)
        Jabatan Perubatan
        Fakulti Perubatan, Universiti Malaya.

       2. Dekan Fakulti

       3. Ketua Jabatan

Appendix J – Research Grant

UNIVERSITI MALAYA

UM.TNC2/RC/HTM/261/ RG048/09HTM

16 April 2010

Dr. Mas Ayu Said
Jabatan Perubatan Kemasyarakatan dan Pencegahan
Fakulti Perubatan
Universiti Malaya

Tuan/ Puan,

Tawaran Pelanjutan Peruntukan Geran Penyelidikan Universiti Malaya (UMRG) bagi Fasa 1/2009 (Tahun 2)
No. Akaun Projek : RG048/09HTM

Dengan segala hormatnya saya merujuk kepada perkara di atas.

2.   Sukacita dimaklumkan bahawa tuan/puan telah ditawarkan pelanjutan untuk geran UMRG bagi Tahun 2 dengan jumlah peruntukan yang diluluskan adalah sebanyak **RM32,600**. Tempoh projek tuan/puan adalah mulai **1 April 2010 – 31 Mac 2011.**

3.   Sehubungan dengan itu, tuan/puan adalah diminta untuk mengesahkan penerimaan tawaran dengan membuat pecahan peruntukan berjumlah **RM32,600**   mengikut *vote* yang telah disenaraikan di dalam **Lampiran A**. Sila kemukakan borang penerimaan tawaran yang telah diisi kepada Pejabat Kluster Penyelidikan selewat-lewatnya pada **30 April 2010.**

4.   Untuk makluman tuan/puan, agihan peruntukan bagi tahun berikutnya tertakluk kepada prestasi dan laporan penyelidikan projek tersebut. Tuan/puan adalah diingatkan untuk menghantar laporan penyelidikan projek pada tarikh yang telah dinyatakan di bawah dan kemukakan kepada Pejabat Kluster Penyelidikan Health and Translational Medicine (HTM).
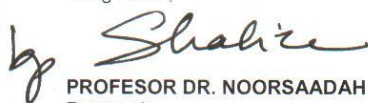
   a)   Laporan Kemajuan Projek Tahun 2 (6 bulan) : **30 September 2010**
   b)   Laporan Kemajuan Projek Tahun 2 (12 bulan) : **31 Mac 2011**

Sekiranya laporan penyelidikan tersebut tidak diterima oleh Kluster Penyelidikan pada tarikh yang telah ditetapkan maka ia akan menjejaskan agihan peruntukan bagi tahun berikutnya.

5.   Bersama ini dilampirkan keputusan penilaian akhir tahun projek tuan/puan bagi tahun 1 untuk makluman dan perhatian tuan/puan. Keputusan dibuat adalah berdasarkan penilaian ke atas Laporan Kemajuan dan Laporan Akhir projek serta peratusan perbelanjaan peruntukan sehingga 31 Mac 2010.

Sekian, terima kasih.

Yang benar,

PROFESOR DR. NOORSAADAH ABD RAHMAN
Pengarah
Institut Pengurusan dan Pemantauan Penyelidikan

s.k.   Timbalan Naib Canselor (Penyelidikan & Inovasi)
        Pengerusi Kluster Penyelidikan Health and Translational Medicine (HTM)

Appendix K - Oral and Poster Presentation

		Sitemap	Contact	Legal Disclaimer	Privacy	General Conditions	search

28th CINP World Congress of
Neuropsychopharmacology
CINP – The International College of Neuropsychopharmacology
3 – 7 June 2012 // Stockholm, Sweden

Welcome to Stockholm

President & Committee → | Online Scientific Programme → | General Information →

Tuesday, 5. June 2012

No.:	P-08 - Poster Session
Session title:	Schizophrenia
Time:	17.00-18.00
Room:	Exhibition Hall A
087	**Prevalence of metabolic syndrome among schizophrenia patients treated with monotherapy atypical antipsychotics in Malaysia**
	Ahmad Hatim Sulaiman	Author
	Mas Ayu Said	Co-Author
	Mohd Hussain Habil	Co-Author

Objective

The objective of this study was to determine the prevalence of metabolic syndrome(MetS), hypertension and diabetes mellitus(DM) among schizophrenia patients treated with monotherapy atypical antipsychotics.

Methods

The study was conducted at 4 mental institutions and 4 general hospitals in Malaysia. 527 patients were screened during study period and 485 patients fulfilled the DSM-IV criteria for schizophrenia. 325 schizophrenia patients agreed to be interviewed but only 274 consented for fasting blood investigations and metabolic syndrome profile. The definition of MetS was based on Modified National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) with Asians values for waist circumference.

Results

Out of 325 patients, 186 patients(57.2%) received monotherapy atypical antipsychotics. 64/186 on risperidone, 61/186 patients were on olanzapine, 28/186 patients were on paliperidone, 14/186 were on clozapine, 8/186 on aripiprazole, 7/186 on quetiapine and 4/186 on amisulpride. The prevalence of hypertension and DM among schizophrenia patients after initiation of monotherapy antipsychotics was 5.7%(95%CI 1.9-15.4) and 5.7%(95%CI 1.9-15.4)in olanzapine, 7.5%(95%CI 3.0-17.9) and 5.5% (95%CI 1.9-14.9)in risperidone, 7.1%(95%CI 2.0-22.7) and 11.5%(95%CI 4.0-29.0)in paliperidone, 16.7%(95%CI 3.0-56.4)of DM in quetiapine and 14.3%(95%CI 2.6-51.3)of DM in aripiprazole. None of amisulpride patients developed hypertension and DM. 53.2% of overall patients had MetS. While 83.3% in clozapine, 66.7% in quetiapine, 53.8% in paliperidone, 52.8% in olanzapine, 43.4% in risperidone and 14.3% in aripiprazole developed MetS. None of patients on amisupride has MetS.

Conclusion

The prevalence of MetS was high among schizophrenia patients treated with monotherapy atypical antipsychotics in Malaysia. Urgent measures are needed to address the issue.

Appendix K – Oral and Poster Presentation

Appendix K – Oral and Poster Presentation
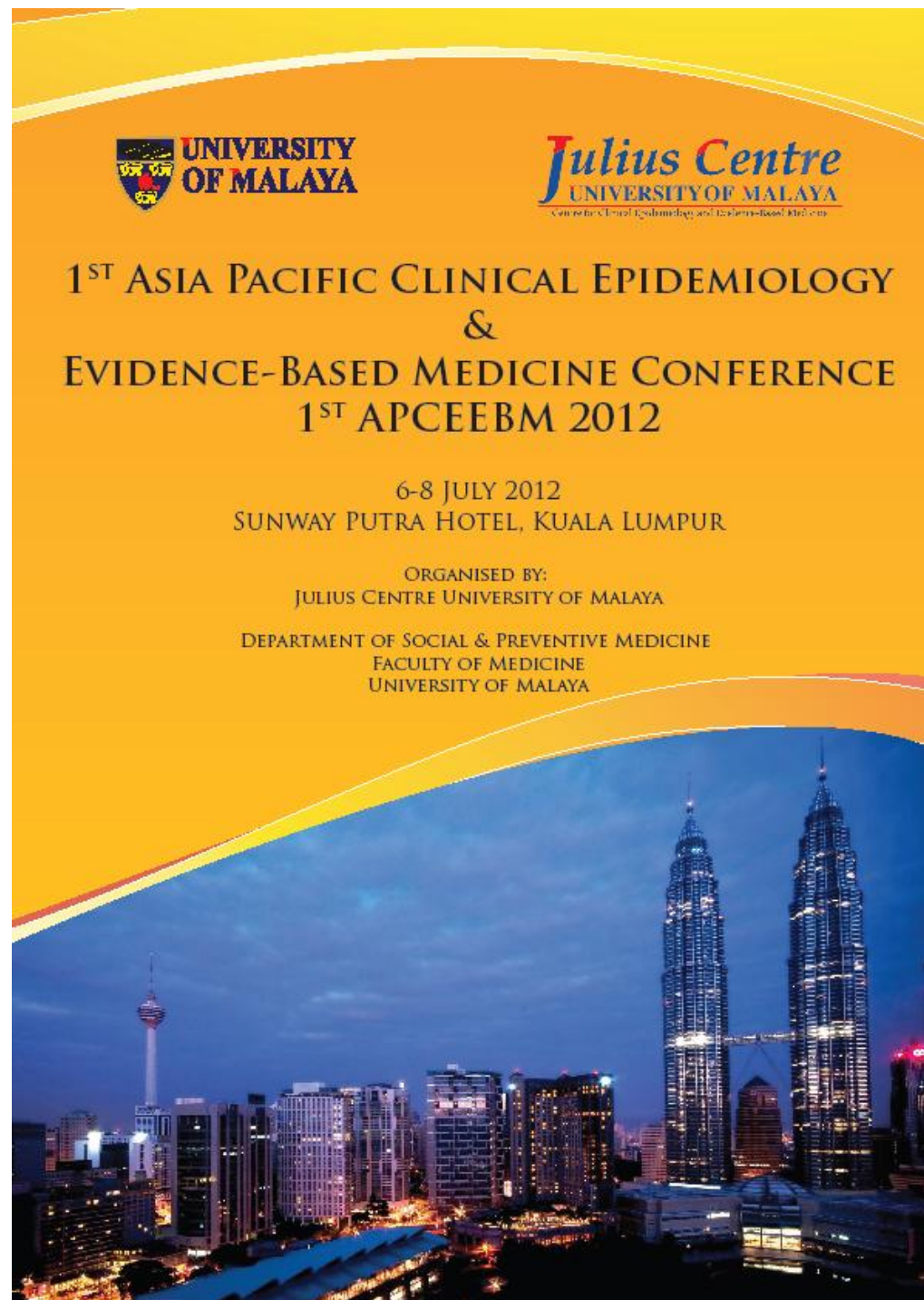
OR 2.36, 95% CI (1.90-2.94); 60 years old and above as reference

Conclusion: The prevalence of smoking among Malaysian males remained high in spite of several population level interventions over the past decade. Tobacco will likely remain a primary cause of premature mortality and morbidity in Malaysia.

PT205
COMPARATIVE EFFECTIVENESS OF ARIPIPRAZOLE AND ZIPRASIDONE IN THE IMPROVEMENT OF METABOLIC SYNDROME COMPONENTS AND ATHEROGENIC DYSLIPIDEMIA IN SCHIZOPHRENIA PATIENTS: A RANDOMIZED, DOUBLE-BLIND, 6-MONTH STUDY

Said MA, Sulaiman AH, Habil MH, Bulgiba AM
University of Malaya

Objectives: To determine improvement of metabolic syndrome components and lipid profiles when previously treated with other antipsychotics.

Methods: A 6-month randomized double-blind clinical trial was conducted at four mental institutions and four general hospitals in Malaysia. 175 patients participated in the study. Metabolic measurements for waist circumference, blood pressure, fasting blood sugar, HDL, triglycerides, total cholesterol and LDL were taken. The definition of metabolic syndrome components were based on Modified National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) with Asian values for waist circumference.

Results: For metabolic syndrome components and dyslipidemia, there were significant difference in Least Squares mean change for multiple comparisons with Bonferonni correction $p < 0.008$ in waist circumference and total cholesterol for study visit 1 to 6 months between aripiprazole and ziprasidone. For MMRM analysis of metabolic syndrome components and dyslipidemia, there were statistically significant in the time effect for waist circumference and total cholesterol. These indicate significant reductions in LS mean change over time for both parameters. However there was no statistically significant for intervention x time interaction effect for all parameters.

Conclusion: Aripiprazole and ziprasidone were equally effective in the improvement of waist circumference and total cholesterol level in schizophrenia patients.

PT206
HISTOLOGICAL OBSERVATION OF THE HIPPOCAMPUS AND FRONTAL CORTEX OF EXPERIMENTAL SPRAGUE-DAWLEY RATS FED WITH LEAD IN A DOSE RELATED MANNER

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Universiti Kebangsaan Malaysia (UKM)

Objectives: During recent times, lead poisoning cases have been on the rise. The present study aimed to look into the histological changes occurring in the brain following lead ingestion in a dose-related manner.

Methods: Eighteen male Sprague-Dawley rats weighing 150-200g were randomly divided into 3 groups. A control (CTRL) group was fed with distilled water. The PB2 and PB4 groups were fed with 0.2% and 0.4% lead acetate in distilled water respectively, for 30 days. The hippocampus and frontal cortex were subjected to light microscopic examination.

Results: It was observed that there was apoptosis on neurons of the hippocampus and frontal cortex occurred in a dose-related manner after 30 days of lead ingestion. Compared to CTRL, PB2 showed the presence of apoptotic neurons accompanied with disorganized neuronal cells. PB4 showed a significant increase of apoptotic cells in both hippocampus and frontal cortex. However, significant histological changes between the 2 experimental groups were not observed.

Conclusion: Lead ingestion in a dose-related manner is capable of causing histopathological changes in the hippocampus and frontal cortex in rats. The cause of lead toxicity is to be borne in mind in day-to date life where one runs the risk of getting exposed to lead.

Appendix L - Publication

The following papers have been published from this thesis:

<u>**Journals**</u>

1. Mas Ayu Said, Ahmad Hatim Sulaiman, Mohd Hussain Habil, Srijit Das, Abdul Kadir Abu Bakar, Rosliwati Md. Yusoff, Loo Tsui Huei, Shamshunnisah Abu Bakar. Metabolic syndrome and cardiovascular risk among schizophrenia patients receiving antipsychotics in Malaysia. Singapore Medical Journal, 2012.53(12):801-807

2. Mas Ayu Said, Ahmad Hatim Sulaiman, Mohd Hussain Habil, Wan Zafidah, Haslina Mohd Yusof, Badiah Yahya, Ramli Mohd Ali, Ananjit Singh, Sapini Yaccob, Mohd Shah, Badli Mahmud, Awang Bulgiba, Noran Naqiah Hairi. Metabolic syndrome and monotherapy antipsychotic treatment among schizophrenia patients in Malaysia. Preventive Medicine,2013.Doi:10.1016/j.ypmed.2013.01.005. [Epub ahead of print]

Appendix L – Publication

Metabolic syndrome and cardiovascular risk among patients with schizophrenia receiving antipsychotics in Malaysia

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INTRODUCTION This study aimed to determine the prevalence of metabolic syndrome and risk of coronary heart disease (CHD) in patients with schizophrenia receiving antipsychotics in Malaysia.

METHODS This cross-sectional study, conducted at multiple centres, involved 270 patients who fulfilled the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR diagnostic criteria for schizophrenia, were on antipsychotic medications for at least one year, and were screened for metabolic syndrome. Patients receiving mood stabilisers were excluded. Metabolic syndrome was defined according to the National Cholesterol Education Program ATP III criteria modified for Asian waist circumference. Risk for cardiovascular disease was assessed by using Framingham function (all ten-year CHD events).

RESULTS The prevalence of metabolic syndrome was 46.7% (126/270). Among all the antipsychotics used, atypical antipsychotics (monotherapy) were most commonly used in both the metabolic and non-metabolic syndrome groups (50.8% vs. 58.3%). The ten-year risk for CHD was significantly higher in patients with metabolic syndrome. The proportion of patients with high/very high risk for CHD (Framingham ≥ 10%) was greater in patients with metabolic syndrome than in those with non-metabolic syndrome (31.5% vs. 11.0%, odds ratio 3.9, 95% confidence interval 2.0–7.6; p < 0.001). The mean body mass index was higher in patients with metabolic syndrome than in those without (29.4 ± 5.1 kg/m² vs. 25.0 ± 5.6 kg/m²; p < 0.001).

CONCLUSION Patients with schizophrenia receiving antipsychotics in Malaysia have a very high incidence of metabolic syndrome and increased cardiovascular risk. Urgent interventions are needed to combat these problems in patients.

INTRODUCTION

Metabolic syndrome comprises a spectrum of medical disorders associated with an increased risk of developing type 2 diabetes mellitus and cardiovascular disease (CVD).[1] Metabolic syndrome affects a great number of people and it is estimated that approximately 20%–25% of the world's adult population suffers from it.[2] The reported prevalence of metabolic syndrome in Asians is lower (5%–16%).[3-5] However, the incidence of metabolic syndrome in Malaysia is much higher compared to other Asian countries.[6] According to the World Health Organization, National Cholesterol Education Program (NCEP) ATP III, International Diabetes Federation and Harmonized metabolic syndrome definitions, the overall crude prevalences of metabolic syndrome in Malaysia are 32.1%, 34.3%, 37.1% and 42.5%, respectively.[6] Metabolic syndrome not only entails serious health complications but also places individuals at a greater risk of other serious medical conditions such as CVD.[7]

The pathophysiology of metabolic syndrome is extremely complex and is not fully understood. Insulin resistance and central obesity are considered to be important underlying causes of metabolic syndrome.[8,9] Some individuals may be at greater risk of developing metabolic syndrome due to medications that cause weight gain or changes in blood pressure, cholesterol and blood sugar levels.[10] Atypical antipsychotics have been reported to be associated with the increased risks of hyperglycaemia and impaired glucose levels, and consequently, an increased risk of developing metabolic syndrome.[11] It has also been shown that psychiatric disorders, including schizophrenia, are associated with an elevated risk of developing diabetes mellitus regardless of antipsychotic use.[12] Patients with schizophrenia are at a greater risk for metabolic dysfunctions than other individuals due to a number of reasons, including an inactive lifestyle, poor dietary choices as well as the side effects of antipsychotic medications.[13]

Cohn et al used the NCEP ATP III criteria to assess metabolic syndrome in 240 patients with schizophrenia or schizoaffective

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Appendix L – Publication

disorder, and reported a gender-based prevalence of 42.6% in men and 48.5% in women.[14] They also reported comparable incidence among patients under (43.8%) and over (45.8%) 45 years of age. Using the same definition of metabolic syndrome, studies have described the prevalence of metabolic syndrome in inpatients with schizophrenia to range between 27%–29%[15,16] and in outpatients to be between 25%–35%.[17,18]

In Southeast Asia, especially in Malaysia, there is a paucity of data on the prevalence of metabolic syndrome and cardiovascular risk among patients with schizophrenia. A local study on 51 patients with primary psychotic and mood disorders by Rahman et al found the prevalence of metabolic syndrome to be 37.2% in these patients.[19] In the present study, we aimed to determine the prevalence of metabolic syndrome in patients with schizophrenia receiving antipsychotics in Malaysia as well as the risk of coronary heart disease (CHD) in these patients.

METHODS

The study was conducted at four mental institutions (Hospital Bahagia Ulu Kinta, Perak; Hospital Permai Johor Bahru, Johor; Hospital Sentosa Kuching, Sarawak; Hospital Mesra Kota Kinabalu, Sabah), two army hospitals (Terendak Army Hospital, Melaka; Navy Hospital Lumut, Perak) and two general hospitals (University Malaya Medical Centre [UMMC], Kuala Lumpur; Hospital Sg Petani, Kedah) from June 2008 to September 2011.

The study population comprised patients with schizophrenia between 18–65 years of age who fulfilled the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR diagnostic criteria for schizophrenia. The patients must have received antipsychotic treatment for at least one year. Patients receiving mood stabilisers were excluded from the study, as it could have confounded the parameters of weight gain and metabolic syndrome.[20,21] One patient on lithium and three others on sodium valproate were excluded. Out of 527 patients who were screened during the study period, 485 patients fulfilled the DSM-IV-TR criteria for schizophrenia. 325 patients with schizophrenia agreed to be interviewed and underwent part assessment for metabolic syndrome parameters. However, only 270 patients gave final consent for fasting blood investigations and full metabolic syndrome profile. All participants were outpatients. There was no difference between the group of patients who consented to participation and those who did not, in terms of sociodemographics or diagnosis.

The prevalence of metabolic syndrome was estimated using the NCEP criteria (the 2001 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults) modified for the Asian waist circumference[22] based on the presence of three or more of the following components – abdominal obesity (waist circumference: men ≥ 90 cm; women ≥ 80 cm), hypertriglyceridaemia (fasting triglyceride concentration > 150 mg/dL), dyslipidaemia (fasting high-density lipoprotein [HDL] cholesterol: men < 40 mg/dL; women < 50 mg/dL), hypertension (systolic/diastolic blood pressure,

> 130/85 mmHg) and hyperglycaemia (fasting glucose concentration > 100 mg/dL).

Waist circumference was measured at the midpoint between the lower rib margin (12th rib) and the iliac crest. Participants were asked to stand with feet together and arms in a relaxed position at either side during measurement. A tape was then held in a horizontal position and wrapped around the waist, loose enough for the recorder to place one finger between the tape and the participant's body. Patients were asked to breathe normally and measurements were taken to the nearest 0.1 cm at the end of a normal exhalation. It was ascertained that participants did not contract the abdominal muscles during measurements.

Blood pressure was measured using a digital sphygmomanometer (Omron Digital Automatic Blood Pressure Monitor Model HEM-907, Omron Healthcare Co Ltd, Kyoto, Japan) on both the right and left arms following a rest of five minutes in a seated position, with the arm supported at heart level. Each arm was measured twice and measurements from the arm with the highest readings were used to calculate the average systolic and diastolic blood pressures. To minimise variability in anthropometric measurements between recorders and study centres, the main investigators from each institution attended an investigators meeting, held prior to the start of the study. Procedures were standardised and appropriate training was provided as part of the meeting. Training for the remaining members of the research team was subsequently carried out by the main investigators at their respective institutions. All anthropometric measurements for the duration of the study were carried out by these trained team members.

The Framingham[23] function was used to estimate the overall risk of fatal or nonfatal CHD (including any type of angina, myocardial infarction, other types of coronary ischaemia, congestive heart failure, intermittent claudication or peripheral arterial ischaemia) over ten years. The Framingham function is a mathematical probability model obtained using multivariate analysis from follow-up studies of individuals in the general population, in which the incidence of a fatal or nonfatal CHD event is related to the individual risk factors of each participant. Risk of CHD was calculated from the values meant for age, gender, total cholesterol, HDL cholesterol, blood pressure, diabetes mellitus status and smoking status. Patients were classified according to the probability of presenting a high/very high risk for fatal or nonfatal CHD (Framingham ≥ 10%) within ten years.

Sociodemographic and clinical data were recorded for all participants in addition to detailed information on lifestyle, smoking and occupational status. Patients were classified into two groups – metabolic syndrome and non-metabolic syndrome – according to the criteria mentioned above. The mean, standard deviation, median and interquartile range were calculated for continuous variables, and the frequency and percentage of patients were used to estimate the prevalence of cardiovascular risk factors and the components of metabolic syndrome. Individual

Appendix L – Publication

Table I. Characteristics of patients with schizophrenia (n = 270).

Characteristic	No. of patients (%)		p-value*
	Metabolic disease (n = 126)	Non-metabolic disease (n = 144)	
Mean age ± SD (yrs)	40.5 ± 11.3	39.5 ± 11.8	0.472§
Age group (yrs)			
< 20‡	2 (1.6)	2 (1.4)	0.500
20–29	18 (14.3)	34 (23.6)	
30–39	44 (34.9)	40 (27.8)	
40–49	29 (23.0)	32 (22.2)	
50–59	26 (20.6)	27 (18.8)	
≥ 60	7 (5.6)	9 (6.2)	
Mean BMI ± SD (kg/m²)	29.4 ± 5.1	25.0 ± 5.6	< 0.001§¶
BMI group (kg/m²)			
Underweight‡ (< 18.5)	0 (0)	14 (9.7)	
Normal weight‡ (18.5–24.9)	25 (19.8)	70 (48.6)	< 0.001¶
Overweight (25–29.9)	50 (39.7)	35 (24.3)	
Obese (≥ 30)	51 (40.5)	25 (17.4)	
Gender			
Male‡	74 (58.7)	100 (69.4)	0.747
Female	52 (41.3)	44 (30.6)	
Occupation			
Employed‡	33 (26.1)	55 (38.2)	0.003¶
Unemployed	83 (65.9)	67 (46.5)	
Housewife	6 (4.8)	5 (3.5)	
Not specified	4 (3.2)	17 (11.8)	

*Chi-square test. ‡Reference group. §Patients who were underweight (BMI < 18.5 kg/m²) were excluded, and only the data of those categorised as normal, overweight and obese were used for chi-square analysis. §t-test. ¶p < 0.05 was statistically significant.
BMI: body mass index; SD: standard deviation

prevalence of cardiovascular risk factors and the prevalence of metabolic syndrome components were estimated by calculating the corresponding 95% confidence intervals. Framingham risk scores in the metabolic syndrome and non-metabolic syndrome patient groups were compared using parametric (Student's t-test) or nonparametric (Mann-Whitney U test) tests, according to the distribution of variables. The risk score of patients were further classified as low (Framingham < 10%) or high/very high (Framingham ≥ 10%) ten-year risk of CHD. The categorical risk scores were compared using chi-square test. A p-value < 0.05 was considered statistically significant.

The least squares mean of Framingham risk scores were also compared according to patient age groups with and without metabolic syndrome. The multiple comparisons were analysed using two-way interaction in three-way analysis of variance (ANOVA), with Bonferroni correction and adjustment for gender. Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows version 16.0 (SPSS Inc, Chicago, IL, USA). Ethics approval for the study was obtained in advance from the Medical Research and Ethics Committee, Ministry of Health Malaysia, and University Malaya Medical Centre Ethics Committee.

RESULTS

The prevalence of metabolic syndrome in patients with schizophrenia was 46.7% (126/270). The mean body mass index (BMI) showed a statistically significant difference between patients with metabolic syndrome and non-metabolic syndrome. The mean BMI for metabolic syndrome patients was higher than

that for the non-metabolic syndrome group (29.4 ± 5.1 kg/m² vs. 25.0 ± 5.6 kg/m²). A majority of patients with metabolic syndrome were overweight (39.7% vs. 24.3%) and obese (40.5% vs. 17.4%) compared to those in the non-metabolic group (Table I).

Table II presents the antipsychotics and other concomitant medications that were given to patients during the study. Among all antipsychotics used, atypical antipsychotics (monotherapy) were used the most in both metabolic syndrome and non-metabolic syndrome group patients (50.8% vs. 58.3%), followed by typical antipsychotics (monotherapy), also in both patient groups (21.4% vs. 20.8%). Among patients receiving typical antipsychotics (monotherapy) treatment, chlorpromazine (33.3%) was given the most to patients in the metabolic syndrome group, followed by sulpiride and perphenazine (18.5% each). Among patients receiving atypical antipsychotics (monotherapy) treatment, olanzapine (42.2%) was given most frequently to patients in the metabolic syndrome group followed by risperidone (32.8%). None of the patients on amisulpride had metabolic syndrome (Table II).

Table III shows statistically significant differences for all metabolic syndrome components, except low-density lipoprotein (LDL) cholesterol, between patients in the metabolic syndrome and non-metabolic syndrome groups. The median values of fasting blood glucose, triglycerides and glycated haemoglobin were also significantly different between patients in the metabolic syndrome and non-metabolic syndrome groups (Mann-Whitney U test). Among all the metabolic syndrome components, abnormal waist circumference was the commonest among patients in the metabolic syndrome and non-metabolic syndrome

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Appendix L – Publication

Table II. Treatment with antipsychotics and other medications in patients with schizophrenia.

Treatment	Patients No. (%)		p-value*
	Metabolic disease (n = 126)	**Non-metabolic disease (n = 144)**	
Current antipsychotics			
Atypical antipsychotics (monotherapy)†	64 (50.8)	84 (58.3)	0.339
Typical antipsychotics (monotherapy)	27 (21.4)	30 (20.8)	
Combination of typical and atypical antipsychotics	15 (11.9)	11 (7.7)	
Combination of typical antipsychotics	14 (11.1)	9 (6.2)	
Combination of atypical antipsychotics	6 (4.8)	10 (7.0)	
Typical antipsychotics (monotherapy)			
Chlorpromazine	9 (33.3)	10 (33.3)	
Sulpiride	5 (18.5)	6 (20.0)	
Perphenazine	5 (18.5)	5 (16.7)	
Haloperidol†	3 (11.2)	5 (16.7)	0.960
Stelazine	2 (7.4)	1 (3.3)	
Intramuscular fluanxol	2 (7.4)	1 (3.3)	
Intramuscular modecate	1 (3.7)	2 (6.7)	
Atypical antipsychotics (monotherapy)			
Olanzapine†	27 (42.2)	26 (31.0)	0.390
Risperidone	21 (32.8)	29 (34.5)	
Paliperidone	11 (17.2)	16 (19.0)	
Clozapine	2 (3.1)	1 (1.2)	
Quetiapine	1 (1.6)	2 (2.4)	
Aripiprazole	2 (3.1)	6 (7.1)	
Amisulpride	0 (0)	4 (4.8)	
Concomitant medication			
Anticholinergics	41 (32.5)	44 (30.6)	0.726
Benzodiazepine	25 (19.8)	22 (15.3)	0.324
Antidepressants	16 (12.7)	19 (13.2)	0.904
Other medication			
Antidiabetic medication	8 (6.3)	5 (3.5)	0.271
Blood pressure-lowering medication	6 (4.8)	6 (4.2)	0.813
Lipid-lowering medication	6 (4.8)	10 (6.9)	0.449

*Chi-square test. †Reference group.

groups (98.4% vs. 50.7%), followed by HDL cholesterol (72.6% vs. 30.9%); fasting blood glucose was the least common in the two patient groups (51.6% vs. 6.2%) (Table III).

31.5% of patients in the metabolic syndrome group had a high/ very high ten-year risk of CHD, while the corresponding figure for patients in the non-metabolic syndrome group was 11.0%. The difference in incidence of high/very high ten-year risk of CHD was statistically significant between the two groups (p < 0.001). Also significant was the difference in the median Framingham risk scores of the two patient groups (p < 0.001). The mean Framingham risk score for the metabolic syndrome group was 7.6 (i.e, 8/100 people with this level of risk were likely to have a heart attack in the next ten years) while that for the non-metabolic syndrome group was 5.0 (i.e. 5/100 people with this level of risk might have a heart attack in the next ten years) (Table IV).

There was a greater increase in the mean scores of CHD risk for patients of all age groups in the metabolic syndrome group compared to those in the non-metabolic syndrome group. There was a significant difference in the mean score of CHD risk for patients of all age groups except those over 60 years of age (Fig. 1).

DISCUSSION
Our study was aimed at estimating the prevalence of metabolic syndrome in patients with schizophrenia in the local population who were being treated with antipsychotic medications for at least one year. Our results showed that 46.7% of patients fulfilled the criteria for metabolic syndrome, as defined by NCEP ATP III guidelines. This incidence is considerably higher than the reported prevalence of metabolic syndrome in both the general Malaysian (34.3%)[6] and Asian populations (5%–16%).[3-5]

The higher prevalence of metabolic syndrome in patients with schizophrenia has frequently been reported.[14,24] For instance, a study by Cohn et al[14] found that the prevalence of metabolic syndrome in men and women with schizophrenia was 42.6% and 48.5%, respectively, using the same criteria. Similarly, a Japanese study by Sugawara et al reported a 48.1% incidence of metabolic syndrome in outpatients with schizophrenia.[24]

The reasons for a higher rate of metabolic syndrome being associated with schizophrenia are many. Certain lifestyles (such as sedentary habits and intake of high-fat and high-carbohydrate diets) that are frequently seen in people with severe mental illness are associated with metabolic syndrome.[25,26] Schizophrenia may predispose individuals to physiological changes that increase the risk of metabolic syndrome. For instance, abnormalities in glucose regulation along with a pattern of insulin resistance have been described in schizophrenic patients even prior to the development of illness or the use of antipsychotic agents.[27,28] Some antipsychotics are associated with a high occurrence of the development of metabolic syndrome. These medications may cause weight gain or changes in blood pressure, cholesterol and blood sugar levels.[10]

Original Article

Table III. Metabolic syndrome components according to metabolic syndrome status in patients with schizophrenia.

Component	Metabolic disease (n = 126)		Non-metabolic disease (n = 144)		Total (n = 270)		p-value*
	No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI	
Waist circumference (men ≥ 90 cm; women ≥ 80 cm)	124 (98.4)	94.4–99.6	73 (50.7)	42.6–58.7	197 (73.0)	67.4–77.9	< 0.001[‡]
HDLC[†] (men < 40 mg/dL; women < 50 mg/dL)	90 (72.6)	64.1–79.7	42 (30.9)	23.7–39.1	132 (50.8)	44.7–56.8	< 0.001[‡]
Triglyceride[†] (≥ 150 mg/dL)	84 (67.7)	59.1–75.3	21 (15.4)	10.3–22.5	105 (40.4)	44.7–56.8	< 0.001[‡]
BP (≥ 130/85 mmHg)	77 (61.1)	52.4–69.2	36 (25.0)	18.6–32.7	113 (41.9)	36.1–47.8	< 0.001[‡]
Fasting blood glucose (≥ 100 mg/dL)	65 (51.6)	42.9–60.1	9 (6.2)	3.3–11.5	74 (27.4)	22.4–33.0	< 0.001[‡]
Laboratory test parameter							
Fasting blood glucose (mg/dL)							
Mean ± SD	110.5 ± 37.9	103.9–117.2	89.2 ± 21.3	85.7–92.7	99.2 ± 31.9	95.3–103.0	
Median (IQR)	100.8 (88.2–113.4)		86.4 (81.0–91.8)		90.0 (82.8–100.8)		< 0.001[‡,§]
Triglycerides (mg/dL)							
Mean ± SD	214.1 ± 57.0	185.5–242.6	116.9 ± 57.0	107.2–126.6	163.2 ± 127.9	147.6–178.9	
Median (IQR)	171.8 (125.8–245.3)		113.8 (81.5–138.2)		132.9 (97.4–186)		< 0.001[‡,§]
HbA1c (%)							
Mean ± SD	6.4 ± 1.7	6.1–6.7	5.5 ± 0.7	5.4–5.6	5.9 ± 1.3	5.8–6.1	
Median (IQR)	5.9 (5.6–6.5)		5.4 (5.2–5.8)		5.6 (5.3–6.1)		< 0.001[‡,§]
Mean TC ± SD (mg/dL)	216.1 ± 46.5	207.8–224.3	202.2 ± 41.3	195.2–209.2	208.8 ± 44.3	203.4–214.2	0.011[‡,¶]
Mean LDLC ± SD (mg/dL)	136.6 ± 40.4	129.1–144.0	131.1 ± 40.4	124.2–138.0	133.6 ± 40.4	128.6–138.6	0.287[¶]
HDLC ± SD (mg/dL)							
Men	37.9 ± 6.8	36.3–39.5	46.0 ± 13.0	43.3–48.6	42.5 ± 11.5	40.7–44.2	< 0.001[‡,¶]
Women	44.5 ± 10.7	41.5–47.5	52.8 ± 13.6	48.5–57.1	48.2 ± 12.7	45.5–50.8	0.001[‡,¶]
Other parameters							
Mean waist circumference ± SD (cm)							
Men	102.4 ± 9.8	100.1–104.7	87.5 ± 13.8	84.7–90.2	93.9 ± 13.9	91.9–95.8	< 0.001[‡,¶]
Women	96.7 ± 10.8	93.7–99.7	88.6 ± 13.7	84.4–92.8	91.7 ± 13.1	89.4–94.0	0.002[‡,¶]
Mean systolic BP ± SD (mmHg)	127.0 ± 16.7	124.0–130.0	117.4 ± 17.4	114.5–120.2	121.6 ± 18.2	119.7–123.6	< 0.001[‡,¶]
Mean diastolic BP ± SD (mmHg)	83.8 ± 12.7	81.6–86.1	77.1 ± 11.9	75.1–79.1	80.7 ± 13.0	79.3–82.1	< 0.001[‡,¶]

*Chi-square test. [†]For triglycerides and HDLC (n = 260). [‡]p < 0.05 was statistically significant. [§]Mann-Whitney U test. [¶]t-test.
CI: confidence interval; BP: blood pressure; HbA1c: glycated haemoglobin; IQR: interquartile range; TC: total cholesterol; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; SD: standard deviation

Table IV. Cardiovascular risk factors and coronary heart disease risk (Framingham) according to metabolic syndrome status in patients with schizophrenia.

Variable	Metabolic disease (n = 126)		Non-metabolic disease (n = 144)		Total (n = 270)		p-value*
	No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI	
Cardiovascular risk factors							
Age (men ≥ 40 years; women ≥ 45 years)	58 (46.0)	37.6–54.7	64 (44.4)	36.6–52.6	122 (45.2)	39.4–51.2	0.794
Smoker	29 (23.0)	16.5–31.1	47 (32.6)	25.5–40.7	76 (28.1)	23.1–33.8	0.079
Diabetes mellitus (known diagnosis or glucose ≥ 126 mg/dL)	26 (20.6)	14.5–28.5	6 (4.2)	1.9–8.8	32 (11.9)	8.5–16.3	< 0.001[§]
TC[†] (≥ 200 mg/dL)	80 (64.5)	55.8–72.4	68 (50.0)	41.7–58.3	148 (56.9)	50.9–62.8	0.018[§]
HDLC[†] (men < 45 mg/dL; women < 50 mg/dL)	99 (79.8)	71.9–86.0	78 (57.4)	49.0–65.4	177 (68.1)	62.2–73.4	< 0.001[§]
Mean systolic BP[‡] ± SD (men ≥ 140 mmHg; women ≥ 130 mmHg)	28 ± 22.2	15.9–30.2	22 ± 15.3	10.3–22.1	50 ± 18.5	14.3–23.6	0.143
Mean diastolic BP[‡] ± SD (men ≥ 90 mmHg; women ≥ 80 mmHg)	42 ± 33.3	25.7–42.0	20 ± 13.9	9.2–20.5	62 ± 23.0	18.4–28.3	< 0.001[§]
Ten-year risk of CHD (Framingham)							
Mean ± SD	7.6 ± 6.4	6.5–8.8	5.0 ± 4.4	4.3–5.8	6.3 ± 5.6	5.6–7.0	
Median (IQR)	6.5 (2.5–11.0)		4.0 (1.0–7.0)		4.0 (1.0–9.0)		< 0.001[§,¶]
Patients with high/very high (Framingham ≥ 10%) ten-year risk of CHD (Framingham)	39 (31.5)	23.9–40.1	15 (11.0)	6.8–17.4	54 (20.8)	16.3–26.1	< 0.001[§]

*Chi-square test. [†]For total and HDLC (n = 260). [‡]In patients with diabetes mellitus, cardiovascular disease or kidney disease. [§]p < 0.05 was statistically significant. [¶]Mann-Whitney U test.
CI: confidence interval; BP: blood pressure; CHD: coronary heart disease; IQR: interquartile range; TC: total cholesterol; HDLC: high-density lipoprotein cholesterol; SD: standard deviation

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Studies have shown that atypical antipsychotics are associated with an increased risk of hyperglycaemia and impaired glucose levels, which consequently increase the risk of metabolic syndrome.[11,29,30] Among the patients in our study who had metabolic syndrome, 42% of them were on olanzapine, 32.8% were on risperidone and 17.2% were on paliperidone.

We found that the presence of metabolic syndrome in schizophrenic patients was associated with CHD risk. A significant difference was observed in the cardiovascular risk of patients with and without metabolic syndrome. Our results were similar to a study in Spain by Bobes et al,[17] which reported high cardiovascular risk, as defined by the Framingham score, in patients treated with antipsychotic drugs. Correll et al, who studied 367 adult patients being treated with atypical antipsychotics, found that metabolic syndrome was present in 137 (37.3%) patients and it was significantly associated with a ten-year risk of CHD.[31] Similarly, Holt el al found that 12% of patients in their study with serious mental illness had a > 20% ten-year risk of CHD.[32]

We observed a statistically significant difference in all metabolic syndrome components, except LDL cholesterol, between patients in the metabolic syndrome and non-metabolic syndrome groups. The mean fasting blood sugar level in the metabolic syndrome group was clearly impaired (110.5 mg/dL) although it was normal in the non-metabolic syndrome group (89.2 mg/dL). Men in the non-metabolic syndrome group had normal mean HDL cholesterol levels compared to those in the metabolic syndrome group. Furthermore, the mean triglyceride level in the metabolic syndrome group was nearly double that in the non-metabolic syndrome group (214.1 mg/dL vs. 116.9 mg/dL).

The most common findings in our patients with metabolic syndrome were abnormal waist circumference (98.4%), low HDL cholesterol (72.6%), raised triglycerides (67.7%) and elevated blood pressure (61.1%). Elevated fasting blood glucose was the least frequent abnormality. Our results substantiate those by Kato et al, who found that the most common metabolic syndrome criteria were abnormal waist circumference, dyslipidaemia and elevated blood pressure, while the least prevalent metabolic component was elevated fasting blood glucose.[33]

The mean BMI was significantly higher in patients with metabolic syndrome (29.4 ± 5.1 kg/m²) in our study than those with non-metabolic syndrome (25.0 ± 5.6 kg/m²; $p < 0.05$). When patients were categorised according to weight, a significantly higher proportion of overweight (39.7% vs. 24.3%) and obese (40.5% vs. 17.4%) patients were seen in the metabolic syndrome group than in the non-metabolic syndrome group. Our results were similar to that of the CLAMORS study, where general obesity and abdominal adiposity were high in outpatients with schizophrenia who had metabolic syndrome.[17] The study by Bobes et al recorded a two-fold higher rate of obesity in outpatients with metabolic syndrome when compared to those with non-metabolic syndrome (55.2% vs. 22.7%).[17] The high prevalence of obesity and abdominal adiposity among patients
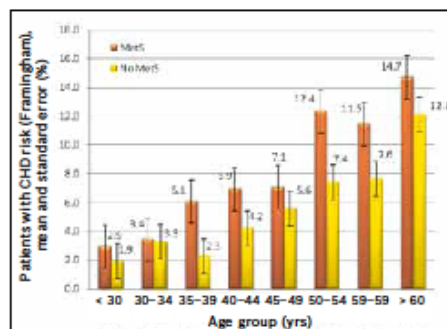
Fig. 1 Risk of coronary heart disease (Framingham) according to patients' age group and metabolic syndrome (MetS) status.

with schizophrenia who had metabolic syndrome in our study was also in agreement with the results of the CATIE study.[34]

Despite finding higher rates of metabolic syndrome in patients with schizophrenia, the present study is not without limitations. First, as this was a cross-sectional study, the causal pathway of metabolic syndrome in patients with schizophrenia could not be inferred from our study even though it was frequent in our population. Second, a reference population without psychopathology was not to be found although the incidence of metabolic syndrome in adult Malaysians was available from a nationwide survey.[6]

In conclusion, we found that the prevalence of metabolic syndrome in patients with schizophrenia receiving antipsychotic therapy in Malaysia is very high. Our data adds to the mounting body of evidence that suggests that patients with schizophrenia are at an increased risk of developing metabolic syndrome. Our findings highlight the need for urgent formulation of comprehensive interventional measures aimed at combating problems faced by this patient cohort.

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Brief Original Report

Metabolic syndrome and antipsychotic monotherapy treatment among schizophrenia patients in Malaysia

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ABSTRACT

Objective. The objective of this study is to determine the prevalence of metabolic syndrome among schizophrenia patients receiving antipsychotic monotherapy in Malaysia.

Method. A cross-sectional study was conducted at multiple centres between June 2008 and September 2011. Two hundred and five patients who fulfilled the DSM IV-TR diagnostic criteria for schizophrenia and who had been on antipsychotic medication for at least one year, were screened for metabolic syndrome. Patients receiving a mood stabilizer were excluded from the study. Metabolic syndrome was defined by using the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Treatment Panel III (ATP III) modified for Asian waist circumference.

Results. In the first-generation antipsychotic (FGA) group, the highest prevalence of metabolic syndrome was among patients treated with trifluoperazine and flupenthixol decanoate (66.7% each). For the second-generation antipsychotic (SGA) group, the highest prevalence of metabolic syndrome was among patients treated with clozapine (66.7%). The component with the highest prevalence in metabolic syndrome was waist circumference in both FGA and SGA groups except for aripiprazole in SGA.

Conclusion. The prevalence of metabolic syndrome in schizophrenia patients receiving antipsychotic monotherapy in Malaysia was very high. Intervention measures are urgently needed to combat these problems.
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Introduction

Metabolic abnormalities have historically been associated with illnesses such as schizophrenia (Meduna et al., 1942). Metabolic syndrome comprises a spectrum of medical disorders that increase the risk of developing type-2 diabetes and cardiovascular disease. The pathophysiology of the metabolic syndrome is extremely complex and remains to be fully elucidated. Currently, both insulin resistance and central obesity are considered to be the significant underlying causes of this syndrome (Anderson et al., 2001; Nesto, 2003). While the metabolic syndrome itself poses potentially serious health complications, it also places individuals at an increased risk for other serious medical conditions, such as cardiovascular disease (Kondo et al, 2011).

Schizophrenia patients are at greater risk for metabolic dysfunctions than other individuals due to a number of reasons, including inactive lifestyle, poor dietary choices, and side effects of antipsychotic medications (Cohn, 2009). Second-generation antipsychotic (SGA) or atypical antipsychotic may cause gain in weight or changes in blood pressure and cholesterol and blood sugar level and may subsequently increase the risk for metabolic syndrome (Fenton and Chavez, 2006).

In Malaysia, there is paucity of data on the prevalence of metabolic syndrome among schizophrenia patients. This study aims to determine the prevalence of metabolic syndrome among schizophrenia patients receiving antipsychotic monotherapy in Malaysia.

Materials and methods

Study population

This multicentre, cross-sectional pharmaco-epidemiological study was conducted at four mental institutions and four general hospitals between

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June 2008 and September 2011. The study comprised of patients aged between 18 years and 65 years old who fulfilled the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR diagnostic criteria for schizophrenia (APA, 2000). The patients must have been treated with antipsychotic monotherapy for at least one year. Patients receiving a combination of antipsychotic drug therapy and mood stabilizer were excluded from the study.

Out of 527 patients who were screened during the study period, 485 were schizophrenia patients. 247 patients who were on antipsychotic monotherapy treatment fulfilled the inclusion criteria and agreed to be interviewed. However only 205 patients (83%) gave their consent and came back for fasting blood investigations and full metabolic syndrome profile.

Data collection

A face-to-face interview with a structured questionnaire was conducted. Data on sociodemographic variables and current antipsychotic drug treatment were collected. During the visit, height, weight, sitting blood pressure and waist circumference were measured. Waist circumference was measured at the midpoint between the lower rib margin and the iliac crest using a Seca 201 circumference measuring tape held firmly in a horizontal position. All patients were informed to fast at a minimum of 8 h prior to this study visit. A fasting blood sample was taken for fasting blood sugar and fasting lipid profile.

Outcome measures

The outcome was the prevalence of metabolic syndrome and its components according to the monotherapy treatment. Metabolic syndrome prevalence was estimated using the criteria of the National Cholesterol Education Program (NCEP), the 2001 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Treatment Panel III (ATP III) modified for Asian waist circumference (Grundy et al., 2005), assessing the presence of three or more of the following components: abdominal obesity (waist circumference ≥ 90 cm in males and ≥ 80 cm in females), hypertriglyceridemia (fasting triglyceride concentration ≥ 150 mg/dL), dyslipidemia (fasting HDL cholesterol: < 40 mg/dL in men; < 50 mg/dL in women), hypertension (systolic/diastolic blood pressure ≥ 130/85 mm Hg), and hyperglycemia (fasting glucose concentration ≥ 100 mg/dL).

Statistical analyses

Patients were described by the type of antipsychotic medication received, namely FGA or SGA. The prevalence of metabolic syndrome and its components was described according to drug treatment. Mean and standard deviation were calculated for continuous variables and frequency and percentage for categorical variables. Pearson's chi-square test was used to determine the possible association between sociodemographic variables and the type of antipsychotic medication.

Results

The mean age showed a statistically significant difference between schizophrenia patients treated with FGA and SGA. For the antipsychotics used, SGA monotherapy was used more often compared to FGA monotherapy (75.5% vs. 24.5%). Among patients receiving FGA monotherapy treatment, chlorpromazine (31.7%) was given the most, followed by perphenazine (21.7%). Among patients receiving SGA monotherapy, risperidone was given most frequently (34.3%), followed by olanzapine (32.6%) (Table 1).

In the FGA group, the highest prevalence of metabolic syndrome was among patients treated with trifluoperazine and flupenthixol decanoate (66.7% each). For the SGA group, the highest prevalence of metabolic syndrome was among patients treated with clozapine (66.7%), followed by those with olanzapine (50.9%). The component with the highest prevalence in metabolic syndrome was waist circumference in both FGA and SGA groups except for those on aripiprazole in the SGA group. The prevalence of fasting blood glucose was the lowest in all drugs in both FGA and SGA groups (Table 2).

Table 1
Demographics and characteristics of schizophrenia patients.

Characteristics	FGA (n = 60) n (%)	SGA (n = 187) n (%)	p value
Age (year) mean ± SD (n = 247)	43.0 (11.6)	38.1 (11.4)	p = 0.005[a]
Age group (n = 347)			
<20	0 (0)	4 (2.1)	p = 0.166
20–29	7 (11.7)	46 (24.6)	
30–39	19 (31.7)	60 (32.1)	
40–49	14 (23.3)	37 (19.8)	
50–59	16 (26.7)	31 (16.6)	
>60	4 (6.7)	9 (4.8)	
BMI (kg/m²) mean ± SD (n = 247)	27.0 (6.0)	26.7 (5.9)	p = 0.717[a]
BMI (n = 247)			
Underweight (<18.5)	5 (8.3)	13 (7.0)	p = 0.265
Normal (18.5–24.9)	19 (31.7)	68 (36.4)	
Overweight (25–<30)	14 (23.3)	60 (32.1)	
Obese (≥30)	22 (36.7)	46 (24.6)	
Sex (n = 247)			
Male	40 (66.7)	110 (58.8)	p = 0.279
Female	20 (33.3)	77 (41.2)	
Antipsychotic treatment (n = 347)			
Typical antipsychotics (monotherapy)			
Chlorpromazine	19 (31.7)		
Perphenazine	13 (21.7)		
Sulpiride	11 (18.3)		
Haloperidol	8 (13.3)		
Trifluoperazine	3 (5.0)		
Flupenthixol decanoate	3 (5.0)		
Fluphenazine decanoate	3 (5.0)		
Atypical antipsychotics (monotherapy)			
Risperidone		64 (34.3)	
Olanzapine		61 (32.6)	
Paliperidone		29 (15.6)	
Clozapine		14 (7.5)	
Quetiapine		7 (3.7)	
Aripiprazole		8 (4.2)	
Amisulpride		4 (2.1)	
NCEP-ATP III; number of criteria (n = 205)			
0	4 (7.0)	13 (8.8)	p = 0.355
1	11 (19.3)	37 (25.0)	
2	15 (26.3)	34 (23.0)	
3	15 (26.3)	39 (26.4)	
4	12 (21.1)	21 (14.1)	
5	0 (0)	4 (2.7)	

Chi square test. NCEP-ATP III: National Cholesterol Education Program — Adults Treatment Panel III.
[a] t-Test.

Discussion

Our study aimed to estimate the prevalence of metabolic syndrome and its components in schizophrenia patients in the local population who were being treated with antipsychotic monotherapy for at least one year. Our results showed that the prevalence of metabolic syndrome was high in schizophrenia patients treated with antipsychotic monotherapy. Some of the prevalence of drug treatment reported was considerably greater than the 34.3% prevalence of metabolic syndrome found in the general Malaysian population (Mohamud et al., 2011).

Our results were consistent with the findings from the CLAMORS study (Bobes et al., 2007) and the CATIE study (McEvoy et al., 2005) in which the prevalence of general obesity and abdominal adiposity was also high in their schizophrenia outpatients with metabolic syndrome. The higher prevalence of central obesity among schizophrenia patients reflected that both FGA and SGA predisposed individuals to physiological changes and increased the risk of having metabolic syndrome (Anderson et al., 2001; Nesto, 2003). Our study showed that elevated fasting blood glucose was the least frequent abnormality. Our results substantiate those of Falissard et al. (2011), who also found that the least prevalent metabolic component was elevated fasting blood glucose in FGA and SGA groups compared to other metabolic components.

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Table 2
Prevalence of metabolic syndrome and its components according to drug treatment.

FGA (n=57)	Chlorpromazine (n=19)	Sulpiride (n=11)	Perphenazine (n=10)	Haloperidol (n=8)	Trifluoperazine (n=3)	Flupenthixol decanoate (n=3)	Fluphenazine decanoate (n=3)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Prevalence of metabolic syndrome	9 (47.4)	5 (45.5)	5 (50.0)	3 (37.5)	2 (66.7)	2 (66.7)	1 (33.3)
Metabolic syndrome component							
Waist circumference (male ≥ 90 cm, female ≥ 80 cm)	13 (68.4)	10 (90.9)	9 (90.0)	4 (50.0)	3 (100)	3 (100)	3 (100)
HDL (male < 40 mg/dL, female <50 mg/dL)	10 (52.6)	6 (54.5)	6 (60.0)	4 (50.0)	1 (33.3)	2 (66.7)	1 (33.3)
Triglyceride (≥150 mg/dL)	8 (42.1)	4 (36.4)	5 (50.0)	3 (37.5)	1 (33.3)	1 (33.3)	1 (33.3)
BP (≥ 130/85 mm Hg)	6 (31.6)	3 (27.3)	6 (60.0)	1 (12.5)	2 (66.7)	2 (66.7)	2 (66.7)
Fasting glucose (≥ 100 mg/dL)	6 (31.6)	3 (27.3)	1 (10.0)	2 (25.0)	2 (66.7)	1 (33.3)	0 (0)

SGA (n=148)	Olanzapine (n=53)	Risperidone (n=50)	Paliperidone (n=27)	Clozapine (n=3)	Quetiapine (n=3)	Aripiprazole (n=8)	Amisulpride (n=4)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Prevalence of metabolic syndrome	27 (50.9%)	21 (42.0)	11 (40.7)	2 (66.7%)	1 (33.3%)	2 (25.0%)	0 (0)
Metabolic syndrome component							
Waist circumference (male ≥ 90 cm, female ≥ 80 cm)	41 (77.4)	36 (72.0)	21 (77.8)	3 (100)	3 (100)	1 (12.5)	1 (25)
HDL (male <40 mg/dL, female <50 mg/dL)	31 (58.5)	23 (46.0)	10 (37.0)	1 (33.3)	1 (33.3)	3 (37.5)	0 (0)
Triglyceride (≥150 mg/dL)	20 (37.7)	18 (36.0)	9 (33.4)	1 (33.3)	1 (33.3)	4 (50.0)	0 (0)
BP (≥ 130/85 mm Hg)	24 (45.3)	18 (36.0)	10 (37.0)	2 (66.7)	1 (33.3)	3 (37.5)	1 (25.0)
Fasting glucose (≥ 100 mg/dL)	15 (28.3)	12 (24.0)	9 (33.4)	1 (33.3)	1 (33.3)	1 (12.5)	0 (0)

The strength of this study was ensuring the prevalence of metabolic syndrome in antipsychotic monotherapy treatment, by eliminating the masked effect of patients receiving multiple antipsychotic medications. The quality of secondary data has been done thoroughly for patient's antipsychotic monotherapy treatment. This study also included all eligible patients from a naturalistic clinical setting in order to reduce selection bias.

Despite finding higher rates of metabolic syndrome in schizophrenia patients with FGA and SGA monotherapy treatment, our findings should be interpreted with limitations in mind. First, our study showed that the prevalence of metabolic syndrome was higher in FGA monotherapy than in SGA monotherapy. This finding could be by chance mainly due to cross-sectional study design. Second, due to the small number of patients in some monotherapy treatments, the prevalence of metabolic syndrome needed to be interpreted with caution.

Many studies showed that the presence of metabolic syndrome was associated with high coronary heart disease risk (Correll et al., 2006; Holt et al., 2010). Abnormalities of either waist circumference or blood pressure warrant screening for other components of metabolic syndrome. Mental health professionals should consistently measure and monitor waist circumference and blood pressure, two components of metabolic syndrome, which are easily assessed in clinical setting. From this study aripiprazole and amisulpride have a more favourable metabolic profile. They could be considered as treatment options for schizophrenia patients with high metabolic risk.

In conclusion, the prevalence of metabolic syndrome in schizophrenia patients receiving antipsychotics in Malaysia was very high. Our data adds to the mounting evidence that schizophrenia patients treated with either monotherapy FGA or monotherapy SGA are at increased risk for developing metabolic syndrome. Screening and comprehensive intervention measures are needed to combat these problems.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Author's contributions

MAS, AH and MHH contributed in the study concept and designing the research protocol. MAS, AH, WZ, HMY, BY, RMA, AS, SY, MS, BM, AB, and NNH contributed in conceptualising the research and data collection. MAS and AH contributed in data analysis, interpretation of data and writing the manuscript. AB, MHH and NNH contributed in critically editing the manuscript. All authors read and approved the final manuscript.

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Appendix L – Publication

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Appendix M - Blinding of Study Drugs

Blinding

Dose Label	Aripiprazole	Ziprazidone
1	10mg daily	40mg bd
2a	15mg daily	40mg om, 60mg on
2b	20mg daily	60mg bd
3a	25mg daily	60mg om, 80mg on
3b	30mg daily	80mg bd

Dose can be adjusted base on your judgment (efficacy and tolerability) - flexible

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