A LONGITUDINAL COMPARISON OF THE METABOLIC CHARACTERISTICS OF OUTPATIENTS WITH FIRST EPISODE PSYCHOSIS TAKING SECOND GENERATION ANTIPSYCHOTICS; AN INTERIM ANALYSIS

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR

THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Pharmacology and Therapeutics)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

April 2015

Abstract

Background. Second generation antipsychotics (SGAs) are used widely for the treatment of schizophrenia and other psychotic disorders. Despite the efficacy of these compounds, they have been associated with a number of adverse events such as weight gain and type II diabetes.

Methods. In this study we have performed an interim analysis of a four-month long clinical trial to evaluate the effects of SGA drugs on weight gain in patients with first episode psychosis. A completer's analysis was performed approximately mid-way through the trial. Anthropometric measures were collected at baseline and again at four months. Physical activity and eating patterns were measured through the international physical activity questionnaire (IPAQ) and three factor eating questionnaire (TFEQ). Secondary outcomes that were investigated include the effects on psychopathology using the positive and negative syndromes scale (PANSS) and the Calgary depression scale (CDS), effects on global functioning through the social and occupational functioning scale (SOFAS), quality of life as assessed by the short-form 36 (SF-36). Adherence to medication was assessed through the medication adherence rating scale (MARS). A simple t-test (p=<.05) was used to detect differences in anthropometric data, the PANSS, and the CDS. Repeated measures one-way analysis of variance (ANOVA) (p=<.05) was utilized for analysis of SF-36, TFEQ, IPAQ, and MARS.

Findings. At baseline, patients taking antipsychotics weighed significantly more than the control group. Significant increases in waist circumference were observed in patients taking antipsychotics at four months. Significant differences in BMI and heart rate were detected between groups at four months. Significantly lower SF-36 summary

scores were detected between groups with significant improvements in mental health summary scores in the antipsychotic group. CDS scores also improved significantly.

Conclusion. At four months of treatment with SGAs, patients may show measurable changes in metabolic parameters that could eventually lead to metabolic syndrome.

Preface

Ethics approval for this study was obtained from the University of British Columbia Children's and Women's Research Ethics Board (UBC C&W REB) REB number H12-01611 approval date Nov 19th 2012 which was required for conducting research at the C&W facility. Ethics approval was also obtained from Vancouver Coastal Health Research Institute (VCHRI) CREB REB number V12-01611 that was required for the recruitment of patients from the Vancouver/Richmond Early Psychosis Intervention (EPI) program.

The author's specific contributions to the identification of the research study, involvement, and analysis of the research are discussed later.

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Acknowledgements

- First and foremost I would like to thank my supervisor Dr Alasdair Barr, for his dedication to my success in this program. My journey in this program has not been easy. Through the highs and lows Dr Barr has supported me consistently with encouragement, hope, and support. I consider him not just a supervisor but also a mentor and a friend and will forever be grateful to him for his contributions to my academic success.
- Secondly, I would like to thank Dr Ric Procyshyn. In addition to serving as a member of my committee, he has helped me through this program thought being a mentor and teacher. I consider him a role model both professionally and personally.
- Dr Heidi Boyda has served as a fellow graduate student and later a postdoctoral fellow in the lab. I had the honor of working alongside Heidi in this study where we served as members of the research team. In addition to providing me with the required training to complete this project, she has given me encouragement and support through teaching and education in all aspects of this degree. I am forever grateful to her hard work and patience.
- Lurdes Tse, a graduate of the program and current medical student worked in collaboration with, Heidi and myself, to undertake and carry out the study. In addition to serving as a vital member of the research team, she has provided me with much encouragement and wisdom. I owe her special thanks for her mentoring and patience in teaching. Conducting this highly sophisticated,

complex clinical trial would not have been possible without such strong team collaborations between Heidi, Lurdes, and myself.

- Committee members Dr Sastry Bhagavatula (Chair), and Dr Bernard Macleod, I would like to thank for through ongoing support, assistance, and feedback in this program.
- Others I would like to acknowledge are fellow graduate students Hyun-Kyoung Koo, Tim Fung, Wynne Leung, program secretary, and friends Jane Hambley and Primo Villanueva for your ongoing social support.

Dedication

To my Grandmother, Myrtle A. Whitney

1931-2014

Chapter 1: Introduction

1.1 Metabolic Syndrome

1.1.1 Definition

Metabolic Syndrome is defined as a group of physical symptoms that together predispose patients and lead to chronic health conditions such as type II diabetes mellitus, stroke, coronary heart disease (CHD), and other cardiovascular diseases and health problems (National Institutes of Health (NIH), 2014). Metabolic syndrome has also been referred a syndrome X, dysmetabolic syndrome, obesity syndrome, insulin resistance syndrome, and hypertriglyceridemic waist (NIH, 2014).

There are different definitions of metabolic syndrome according to different institutions. The World Health Organization (WHO) in 1999 defined metabolic syndrome as having glucose intolerance, impaired glucose tolerance, or diabetes mellitus and/or insulin resistance in addition to two or more of the following: (1) impaired glucose regulation or diabetes (2) insulin resistance which is defined as: under hyperinsulinemic euglycemia, or glucose uptake which is below the lowest quartile of the population that is being investigated) (3) arterial blood pressure greater than or equal to 140/90 mmHg, (4) increased triglyceride levels (greater than or equal to 1.7 mmol) and or low HDL cholesterol levels (less than 0.9 mmol in men and 1.0 mmol in women), (5) abdominal obesity (defined as a waist-hip ratio greater than 0.9 in men and 0.85 in women) and or a BMI greater than 30. (6) microalbuminemia (defined as a urinary albumin excretion

rate of greater than or equal to 20 micrograms/min or and albumin-creatinine ratio greater than or equal 30mg/gram (WHO, 1999).

1.1.2 Prevalence

According to the Canadian Health Measures Survey (CHMS) (2009-2011), 1 in 5 Canadians between the ages of 18-79 had metabolic syndrome (Statistics Canada, 2014). This prevalence rate is consistent with a 2011 survey of the Canadian Medical Association (Riediger & Clara, 2011). According to this CHMS survey, 22% of Canadians meet the criteria for metabolic syndrome (Statistics Canada, 2014). The prevalence of metabolic syndrome in Canada was found to increase with age; 10% of Canadians ages 18-39 were found to meet the criteria for metabolic syndrome compared to 40% of Canadians ages 60-79 (Statistics Canada, 2014). The rates of metabolic syndrome in Canada were found to be similar in males and females (Statistics Canada, 2014).

Although exact mechanisms of metabolic syndrome have not completely understood (Riediger & Clara, 2011), studies have shown that the prevalence of metabolic syndrome tends to be higher in people with mental illness than the general population, regardless of their specific diagnosis (Mackin et. al., 2007). Specifically, the study by Mackin et. al. (2007) that surveyed 90 subjects with mental illness and 92 control subjects found that patients with mental illness had higher BMIs (average of 29.9 which indicates overweight), higher rates of dylipidemias, glucose homeostasis disorders, higher waist circumference, and waist hip ratios (that indicate higher visceral adiposity) (Mackin et. al.,2007).

Decreased physical activity combined with poor dietary intake may be contributing factors to the higher risk of cardiovascular disease seen in patients with schizophrenia (Hert et. al., 2009). In addition, the use of antipsychotic medications may increase risk factors of cardiovascular disease, including, weight gain (Hert et. al., 2009).

After diagnosis of metabolic syndrome is made, treatment should begin with a risk assessment for cardiovascular disease and type 2 diabetes (Alberti et. al., 2006). Treatment regimens primarily involve lifestyle modifications such as (1) increased physical activity and (2) diet modification that decreases saturated fat, sodium, increase fiber, and decrease caloric intake with a goal of 5-10% loss of total body weight in 12 months (Alberti et. al., 2006). Hert et. al. (2009) suggests a focus on prevention, which target weight gain, diet, and lifestyle as soon as antipsychotic therapy is initiated. See appendix I for further information on treatment for clozapine associated weight gain.

1.1.3 Diagnostic Criteria and Symptomology

Diagnosis of metabolic syndrome is based on a set of specific criteria. Although each symptom may occur on its own, they are more commonly found together (NIH, 2014). In order to be diagnosed with metabolic syndrome, 3 or more of the following risk factors must be presenting the individual (see table 1).

Table 1.1 Diagnostic Criteria of Metabolic Syndrome according to National Institutes of Health (2014)

Diagnostic Criteria for Metabolic Syndrome
≥3 of the following risk factors indicate Metabolic Syndrome
Abdominal Obesity
≥35 inches for women
≥40 inches for men
Hypertriglyceridemia
≥150mg/dL
or
taking lipid lowering agents
Low HDL
<50mg/dL for women
<40mg/dL for men
Hypertension or High Blood Pressure
≥130/85mmHg
or
taking antihypertensive medication
**Note, single systolic or diastolic elevation still places patients' at risk for metabolic syndrome*
Hyperglycemia (Fasting)
≥100mg/dL
or
taking antidiabetic medication

Source: (NIH, 2014)

1.1.4 Prediabetes

The Canadian Diabetes Association (CDA) (2013) defines prediabetes as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or an gylcated hemoglobin (A1C) value of 6.0-6.4% (CDA, 2013) (see table 1.2). These risk factors place individuals at a higher risk for developing diabetes than the general population (CDA, 2013). According to a 2005-2008 U.S. survey over a third (35%) of Americans over the age of 20 and half (50%) of those over the age of 65 were found to have prediabetes (Center for Disease Control (CDC), 2011).

Table 1.2 Canadian Diabetes Association Clinical Practice Guidelines Expert Committee (2013) criteria for the diagnosis of prediabetes.

Test	Result	Prediabetes category
FPG (mmol/L)	6.1–6.9	IFG
2hPG in a 75 g OGTT (mmol/L)	7.8–11.0	IGT
A1C (%)	6.0–6.4	Prediabetes

2hPG, 2-hour plasma glucose; *A1C*, glycated hemoglobin; *FPG*, fasting plasma glucose; *IFG*, impaired fasting glucose; *IGT*, impaired glucose tolerance; *OGTT*, oral glucose tolerance test.

Source: (CDA, 2013)

1.1.5 Type II Diabetes mellitus

Diabetes is defined as a disease whereby the body is unable to produce functional insulin (Canadian Diabetes Association (CDA), 2014). Insulin is a hormone produced by beta cells in the pancreas that is integral to the regulation and utilization of glucose levels in the blood. Insufficient or non-functioning insulin results in abnormally high levels of glucose in the blood that result in a number of acute and chronic negative

effects on body systems (CDA, 2014). There are three major types of diabetes; type 1, 2, and gestational (CDA, 2014).

Type 1 diabetes is defined as a type of diabetes that occurs when the body is unable to produce insulin (CDA, 2014). Type 2 diabetes is defined as that in which insulin is produced but in insufficient amounts or is produced but is non-functional (CDA, 2014). Gestational diabetes is a type of diabetes that can temporarily affect pregnant women during their pregnancy (CDA, 2014). Of those diagnosed with diabetes, approximately 10-15% of persons have type 1 diabetes and approximately 85-90% have type 2 (Smith et. al., 2008).

Although disturbances in blood glucose have been reported in patients with schizophrenia prior to the use of antipsychotic medications (Haupt & Newcomer, 2001). Various SGAs have been linked to the incidence of type II diabetes (Gianfrancesco et. al., 2002). Patients taking SGAs have been identified as a high-risk group for developing type two diabetes (Lean & Pajonk, 2003). Fortunately, antipsychotic induced diabetes us usually revisable if them medication is stopped.

1.1.6 Impaired glucose tolerance

Impaired glucose tolerance is a condition whereby the glucose levels in the blood remain high to levels that are above normal but not high enough to constitute diagnosis of diabetes (Nathan et. al., 2007). An individual is said to have impaired glucose tolerance if their plasma glucose concentration (between 140-200 mg/dl) for two hours after the administration of a 75-gram oral glucose tolerance test (OGTT) in the presence of fasting plasma glucose of less than 126 mg/dl (Nathan et. al., 2007).

1.1.7 Insulin resistance

Insulin resistance is a condition that results in abnormally high glucose levels in the blood due to a decrease in the uptake of circulating glucose by cells (National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 2014). This lack of glucose uptake occurs because the cells do not respond normally to insulin.

1.1.8 Obesity and Weight Gain

1.1.8.1 Definition

The World Health Organization (WHO) (2014) defines obesity (and overweight) as “abnormal or excessive fat accumulation that presents a risk to health”. Specifically, WHO (2013) classifies a person as obese if they have a BMI of greater than or equal to 30 (WHO, 2013). Those whom have a BMI of greater than or equal to 25 but less than 30 are defined as overweight (WHO, 2013). Obesity places persons at risk for many comorbid conditions including coronary heart disease, stroke, hypertension or high blood pressure, diabetes type II, gallbladder disease, breast, colon, and endometrial cancer, sleep apnea and psychological issues such as low self esteem and depression (Health Canada, 2006). Obesity is also associated with various metabolic abnormalities such as insulin resistance, diabetes, dyslipidemia, and cardiovascular disease (Newcomer, 2005).

Table 1.3. Weight Classification System

Health Canada (2006) Weight Classification System (Body Mass Index
Underweight (≤18.4)
Normal weight (18.5-24.5)
Overweight (between 25 and 29.9)
Obese (≥30)

Source: (Health Canada, 2006)

Table 1.4. Health Risk Classification According to Body Mass Index (BMI).

Classification	BMI Category (kg/m^2)	Risk of developing health problems
Underweight	< 18.5	Increased
Normal Weight	18.5 - 24.9	Least
Overweight	25.0 - 29.9	Increased
Obese class I	30.0 - 34.9	High
Obese class II	35.0 - 39.9	Very high
Obese class III	>= 40.0	Extremely high

Source: Health Canada. Canadian Guidelines for Body Weight Classification in Adults. Ottawa: Minister of Public Works and Government Services Canada; 2003

Figure 1. Estimation of BMI Chart

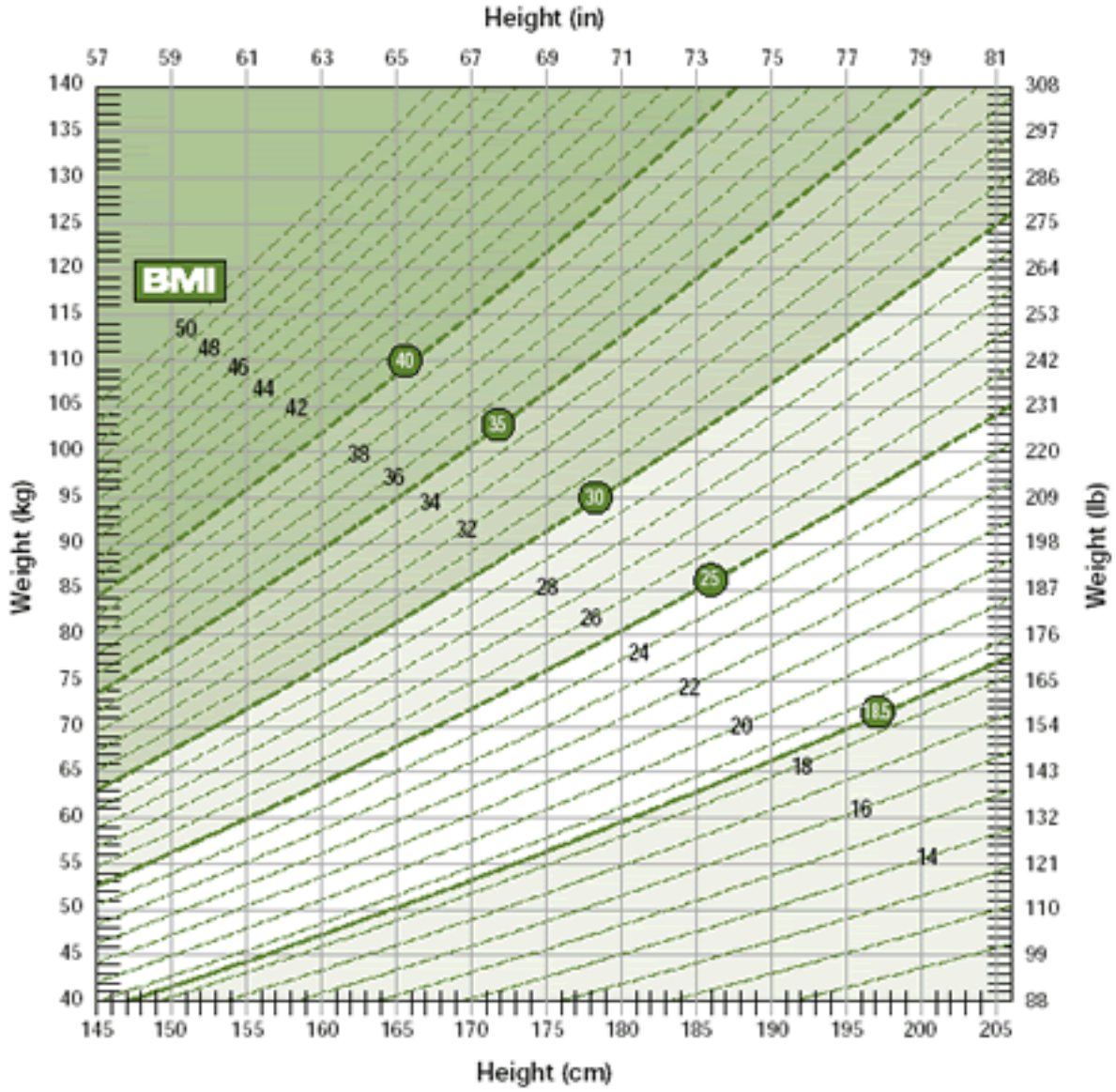


Figure 1. Estimation of BMI Chart. The above chart (Fig. 1) is used to estimate BMI. In order to estimate BMI, find the location where weight (y-axis) and height (x-axis) intersect (Health Canada, 2003). The number on the dashed line closest to the intersection point is the estimated BMI (Health Canada, 2003). BMI can also be calculated by dividing weight in kilograms by height in meters: BMI = Weight (Kg) / Height $(m)^2$ (Health Canada, 2003).

Source: Health Canada. Canadian Guidelines for Body Weight Classification in Adults. Ottawa: Minister of Public Works and Government Services Canada; 2003.

1.1.8.2 Prevalence

High rates of obesity are seen in both Canada and the U.S. In 2008, over 1/3 of Canadians were found to be overweight (see Table 1.3) and ¼ of those surveyed were found to be obese (Statistics Canada, 2014). The rates of obesity have increased 1% from a 2005 survey (Statistics Canada, 2014). In a 2011 survey of obesity and overweight rates within British Columbia, Canada was found to have the lowest rates of overweightness (30%) and obesity (14%) and Newfoundland and Labrador had the highest overweight (40%) and obesity (29%) (Statistics Canada, 2014). Internationally, among G7 countries, Canada was ranked as having the third highest rates of obesity with the U.S. having the highest and France having the lowest (Statistics Canada, 2014). In a 2010 study of prevalence rates in the U.S. between 1999-2000, 68% of the U.S. population was found to be overweight (BMI ≥ 25) and 35% were found to be obese (BMI ≥ 30) (Flegal et. al., 2010). Rates of overweight and obesity tend to be higher in those with advanced age (ages 45-54) than younger populations (Statistics Canada, 2014).

1.1.8.3 Attributing Factors

According to the National Institutes of Health (NIH) (2014), obesity occurs when the caloric intake exceeds the calories that are utilized over time (NIH, 2014). Caloric intake usually fluctuates from day to day, however, if overtime calorie input (food)

exceeds caloric output (e.g. exercise, day to day activities) than weight gain will result. When an individuals' caloric intake is below that which is required by the body, over time, the person may lose weight (NIH, 2014). When the caloric intake of the individual is in balance, over time, than the persons weight will usually stay the same (NIH, 2014).

In addition to the imbalance of caloric intake and output described, other factors also play a role in weight gain and obesity. These include, but are not limited to decreased physical activity, environmental factors, medical conditions, genetic influences, medication, insufficient rest, age, emotional influences (Wright & Aronne, 2012).

1.2 Summary of Schizophrenia and Psychotic Disorders

1.2.1 Definition

Psychotic disorders are defined as a group of mental disorders that includes abnormal changes in thinking and perceptions and a loss of touch with reality (American Psychiatric Association (APA), 2013; NIH, 2014). Primary symptoms include delusions (false beliefs) and hallucinations (false perceptions) (NIH, 2014). Schizophrenia is type of psychotic disorder (APA, 2013). According to the DSM-5, schizophrenia belongs to a larger group of psychotic disorders known as schizophrenia spectrum and other psychotic disorders that include schizophrenia, schizotypal (personality) disorder, and other psychotic disorders (APA, 2013). There are a variety of psychotic disorders and disorders that may lead to psychotic symptoms (APA, 2013). For the purposes of this thesis, only schizophrenia will be explored in greater detail.

1.2.2 Epidemiology

Schizophrenia is the most common type of psychotic disorder that effects approximately 1% of the Canadian population (Public Health Agency of Canada (PHAC), 2014) and 0.7% of the population worldwide (Saha et. al., 2005). Approximately 20-30% of all patients treated for schizophrenia may be resistant to treatment (Conley & Kelly, 2001). In a Finnish population survey study of the prevalence of psychotic disorders in the general population, schizophrenia was found to be the most common followed by schizoaffective disorder, schizophreniform, delusional disorder, bipolar I disorder, psychotic symptoms related to major depressive disorder, substance induced psychosis, and psychotic symptoms secondary to a medical condition respectively (Perälä et. al., 2007).

1.2.3 Clinical Diagnosis and Treatment

Diagnosis of schizophrenia is based on specific criteria of symptoms in the Diagnostic and Statistical Manual of Mental Disorders version 5 (table 3.)

Table 1.5. Diagnostic criteria for Schizophrenia (DSM-5, 2013)

DSM-V Diagnostic criteria for schizophrenia
1. ≥ 2 of the following symptoms present during a considerable amount of time in 1-month unless successfully treated. ≥ must be I), II), or III). **I) Delusions** **II) Hallucinations** **III) Disorganized speech** **IV) Grossly disorganized**

DSM-V Diagnostic criteria for schizophrenia
V) Negative Symptoms
2. Decreased level of functioning (e.g. in work, relationships, self care) compared to the level prior to the onset of symptoms or compared to the expected level of functioning.
3. Symptoms of disturbance must be present for at least 6 months. Within the 6-month window, the individual must have experienced symptoms from criteria 1. and may include prodromal or residual symptoms. The prodromal/residual periods maybe observed as negative symptoms or ≥2 of the symptoms listed in section 1. in an "attenuated" form (e.g. odd beliefs , unusual perceptual experience).
4. Bipolar disorder with psychotic features and schizoaffective disorder have been ruled out due to the following 2 reasons I) the absence of any manic or major depressive episode occurring together with active-phase symptoms, or II) if episodes of mood abnormalities have occurred during active phase symptoms, than they have only been present for a small amount of the total active and residual periods.
5. Symptoms are not secondary to a medical condition (e.g. brain tumor) or substance (e.g. LSD, anesthetics).
6. If the patient has been diagnosed with a communication disorder or autism spectrum disorder where the onset was in childhood than a diagnosis of schizophrenia can be given only if marked delusions, hallucinations, are present in addition to the other diagnostic criteria of schizophrenia are also present for ≥1 month or <1 month if the symptoms have been treated successfully.
**Note, there are further specifies for schizophrenia (e.g. first episode, with catatonia). See the DSM-V for greater detail on diagnoses*
Table 3 has been adapted from the American Psychiatric Association: DSM-V. 2013. Diagnostic Criteria for Schizophrenia.

Source: (APA, 2013)

1.1.4 Diagnostic and Statistical Manual of Mental Disorders (DSM)

The DSM is a manual used by health care professionals and researchers in Canada and the United States that provides information and specific guidelines on the diagnosis of psychiatric disorders (American Psychiatric Association (APA), 2014). The DSM provides definitions, diagnostic criteria, symptomology that define types of psychiatric disorders (APA, 2014). The DSM provides guidelines on assessment and diagnoses of psychiatric disorders but not instructions on treatments (APA, 2014). Treatments for psychiatric disorders are specific to the individual diagnoses, therefore, the DSM does provide information required to make accurate psychiatric diagnoses that will then determine which treatments are administered (APA, 2014). The most recent version of the manual is the DSM-5 (APA, 2014).

1.3 Second Generation Antipsychotics

SGAs, also referred to as atypical antipsychotics are a group of newer antipsychotic drugs that are claimed to have a broader efficacy, lower propensity to induce EPS, and benefit in the treatment of negative symptoms and depression (Leucht et. al., 2009).

1.3.1 Pharmacology of Second Generation Antipsychotics

Mechanism of action of SGAs is generally understood to involve an interaction between the antagonism of serotonin 5-HT2A receptors and dopamine D2 receptors

(Kuroki et. al., 2008). Most new SGAs share the common mechanism of having a higher degree of antagonism for 5HT2A receptors than D2 receptors (Kuroki et. al., 2008). See appendix II for specific pharmacology of common SGAs.

1.3.2 Clinical Indications of Second Generation Antipsychotics

SGAs are used for a multitude of psychiatric disorders including Tourette's disorder, bipolar disorder, conduct disorder, attention deficit hyperactivity disorder (ADHD), eating disorders, disruptive behavior disorder (DBD), anxiety disorders, sleep disorders, and depression (Linton et. al. 2013, Procyshyn et. al., 2014, Whitney et. al., 2015).

1.3.3 Safety and Tolerability

1.3.3.1 Antipsychotic Induced Metabolic Syndrome

Rates of obesity, glucose disregulation, cardiovascular disease, and diabetes have been found to be present more frequently in patients with schizophrenia than the general population (Meyer et. al., 2005). These could be related to negative symptoms of schizophrenia (e.g. lack of motivation) or psychotic symptoms resulting in an inability to work and a sedentary lifestyle. Weight Gain may be related to lower income and consumption of fast food (Beebe, 2008). In addition to the preexisting risk factors for metabolic syndrome that is seen in schizophrenia, the use of antipsychotic medications have also been associated with an increased risk of metabolic disturbances

(Newcomer, 2005). The prevalence of metabolic syndrome is said to be 35-40% in patients with schizophrenia. As previously mentioned, the use of SGAs places patients in a high-risk category for developing type 2 diabetes (Lean & Pajonk, 2003). In addition, the use of SGAs increase patients' risk of weight gain which is a risk factor for type 2 diabetes and increases the likelihood of ones chances of developing metabolic syndrome (Lean & Pajonk, 2003).

1.3.3.2 Mechanisms of Antipsychotic Induced Weight Gain

Antipsychotic induced weight gain is a complex process that may have multiple causal mechanisms (Rege, 2008). As discussed, antipsychotic medications act on a variety of receptors including dopamine histamine, and serotonin of which, all may result in weight gain (Reynold et. al., 2006; Baptista et. al., 1999). There is still no clear understanding of the exact causal mechanisms behind antipsychotic induced weight gain, however many theories exist. It is suspected that there are multiple pathways and that each may contribute to the metabolic disregulation and weight gain. Theories of antipsychotic induced weight gain can be explained though describing their effects at these various receptors.

1.3.3.2.1 Dopamine Hypothesis

In a review article by Goudie et. al. (2005), the authors describe a dopaminergic hypothesis of antipsychotic induced weight gain and suggest that, in light of research that obese people may have a "dopamine deficiency" which may lead to a

compensation by excess food intake. There is evidence that the antagonistic effects at dopamine receptors could contribute to weight gain (Baptista et. al., 1987). For example, sulpride, a potent D2 and D3 antagonist showed a linear relationship with the dose of the drug and weight gain in rats (Baptista et. al., 1987).

1.3.3.2.2 Serotonin hypothesis

There is evidence that SGAs effects on serotonergic systems may contribute to weight gain. For example, when mice were mutated to express nonfunctional 5-HT2C receptors they become obese as a result of uncontrolled feeding behavior (Tecott et. al., 1995). Experiments in rats have shown that olanzapine and 5-HT2C-receptor antagonist result in significant increases in weight (Kirk et. al., 2009). Goudie et. al. (2005), described that the serotonergic hypothesis insufficient at explaining the marked weight gain seen in SGAs because olanzapine is known to have a low affinity for 5-HT2C.

1.3.3.2.3 Histamine hypothesis

The role of histamine receptors in antipsychotic induced weight gain is well described in the literature (Kroez et. al., 2003). Experiments in mice have shown large increases in the activity of the enzyme AMPK, a hypothalamic orexigenic-stimulating enzyme with the largest increases in response to clozapine and olanzapine. The stimulation of this enzyme was linked to the antagonism at histaminergic receptor H1R (Kim et. al., 2006). Wirshing and colleagues showed a correlated between short-term weight gain and affinity of antipsychotic to histamine H1 receptors with the greatest weight gain seen in clozapine and olanzapine (Wirshing et. al., 1999). Goudie et. al.

(2005), suggests this is an incomplete hypothesis because ziprasidone has a high affinity for H1 yet has a lower propensity to induce weight gain (Richelson & Souder, 2000).

1.4 Significance of Study

Numerous studies have discussed antipsychotic induce weight gain (Bai et. al., 2011; Hummer et. al., 1995; Kroez et. al., 2003), however, this is the first ever study that has looked at the distribution of visceral versus subcutaneous fat using MRI. The primary goal of the clinical trial is to look at the distribution of visceral versus subcutaneous fat.

For the purposes of this interim analysis, data analysis will consist only of anthropometric measures, physical assessments, questionnaires, and psychiatric tests. This valued information will form as an interim analysis to gain insight into the progression of the entire clinical trial that will utilize MRI and blood work in addition to data utilized for this thesis. Interim analyses are an important part of a clinical trial as it provides useful insight into the progression into the outcome of the clinical trial. In addition to providing useful insight into the progression of the clinical trial, this data will also be useful to see where differences exist. For example it will be useful to note any major differences in waist circumference as this will indicate a change in visceral fat. Recently published literature has suggested that visceral fat magnitude may be a much more accurate predictor of insulin resistance and glucose intolerance than subcutaneous fat (Usui et. al., 2009). It is therefore vital that research exploring this

connection between antipsychotic induced metabolic disregulation and visceral fat distribution is carried out.

1.4.1 Role of Visceral Fat

It is well documented in the literature that rates of obesity, diabetes mellitus, and insulin resistance are higher in patients with schizophrenia than the general population (Ryan & Thakore, 2002). The side effect of weight gain is arguably the most discussed component of metabolic disregulation in the literature and is also the most pronounced.

It is well documented that second generation antipsychotics are associated with marked weight gain (Newcomer, 2005). Interestingly, it has also been reported that patients with schizophrenia, both drug naive and those treated with antipsychotics, have been shown to have a large increases in visceral fat when compared healthy controls (Thakore et. al., 2002). It is therefore pertinent that research investigating the association between visceral fat and SGA use is carried out.

1.5 Hypotheses and Specific Aims

The purpose of this study was to explore the metabolic changes over four months in a group of patients with first episode psychosis in the early stages of treatment with SGAs. In addition, changes in psychopathology would be evaluated in response to drug treatment over time, as well as subjective perceptions of mental and physical health, eating patterns, physical activity, and overall social and occupational functioning, and compare the results to those seen in a group of healthy control participants.

Table 1.6 Study Hypotheses

Study Hypotheses
I) **Hypothesis I.** There will be no significant differences between participants taking antipsychotics and those not taking antipsychotics at baseline. II) **Hypothesis 2.** At four months, significant increases in weight, WC, and BMI will be seen in participants taking antipsychotics. III) **Hypothesis 3.** At four months, participants taking antipsychotics will show significant decreases in physical activity and significant changes in eating patterns. IV) **Hypothesis 4.** At four months, participants taking antipsychotics will show significant improvements in psychopathology, global functioning, and quality of life. V) **Hypothesis 5.** At four months, there will be no significant changes in control participants.

It was hypothesized that there will be no significant differences between groups in any variables at baseline. This is because participants in the antipsychotic group were newly started on SGAs so metabolic effects may not yet be measurable. Moreover, it was hypothesized that a significant increase in weight, WC, and BMI at the four month follow up as well as decreased levels of physical activity, changes in eating patterns in the antipsychotic group with no significant differences in the control group. Furthermore, it was hypothesized that significant improvements in quality of life, global

functioning, and psychopathology would be seen in the antipsychotic group with no changes in the control group.

Chapter 2: Methods

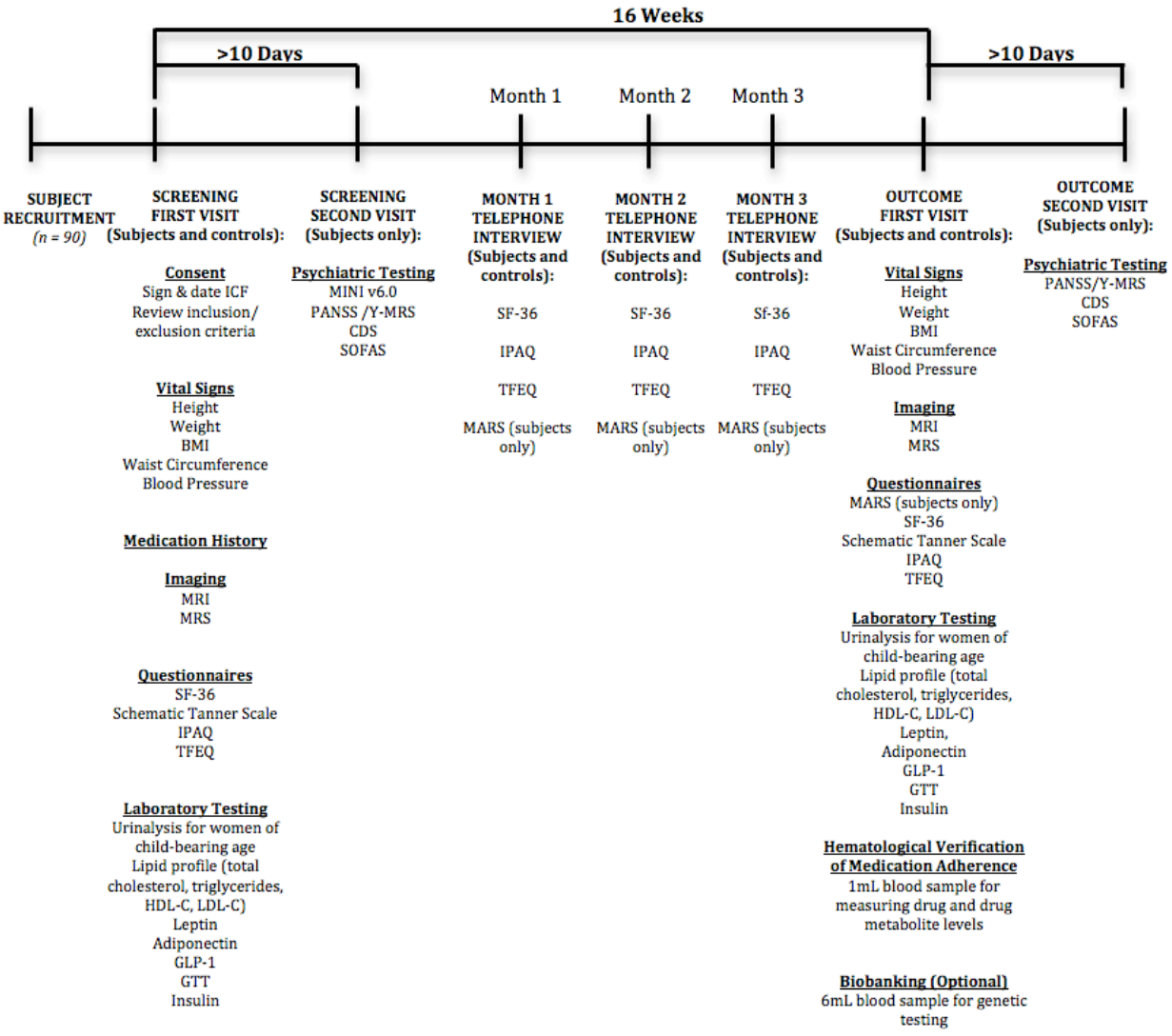
2.1 Trial Design

The study that was conducted was part of a larger clinical trial that looked at comparing high metabolic risk second-generation antipsychotic drugs and a low metabolic risk drug aripiprazole. This thesis will consist of an interim analysis of a clinical trial but will not include MRI or blood work data. Specifically, a comparison between all second-generation antipsychotics with controls has been done and an analysis only of the questionnaires (TFEQ, IPAQ), psychiatric scales (PANSS, CDS), and anthropometric measures (blood pressure, weight etc.) were carried out.

The clinical trial is titled “A longitudinal comparison of Aripiprazole vs. Higher Metabolic Risk Antipsychotic Drugs on Adiposity Using MRI”, abbreviated “the CALM study”. This is a longitudinal study with naturalistic intake. It is a four-month long clinical trial whereby participants receive MRI scans and interviews at the beginning of the study and again after 4 months. Interviews are conducted throughout the study at regular time points.

In addition to MRI, participants also received magnetic resonance spectroscopy (MRS) scans which to evaluate hepatic lipid content. In addition, relevant blood work has been conducted on both treatment groups and controls at baseline and again at four months to supplement the MRI/MRS imaging.

Figure 2. Trial Design Diagram.



Source: (Retrieved from CALM study protocol version 2.0 Sept 2 2014.)

2.1.1 Data Collection

As discussed, this was a four-month long study whereby a series of clinical assessments were conducted with human participants. In this section, the schedule of assessments beginning with the first contact with a participant and ending with the last contact will be discussed. In the following section the “graduate student” and “researcher” refer to myself, the author. I, as the graduate student, was part of an interdisciplinary team who carried out this clinical trial. I was responsible for the data collection used in this thesis. As a registered nurse with foundations in psychiatry, this provided me with unique qualifications to carry out data collection procedures that would not have been possible without intense training and education by other individuals.

2.1.2 Initial Contact

The initial contact between the graduate student and the potential participant begins when the individual is referred to the study by one of the following means: 1) the individual contacts the graduate student after hearing about the study from a flyer, co patient, friend, family member, or other means 2) the individual has implied interest in the study to one of the psychiatrists at their community mental health team (Vancouver/Richmond early psychosis intervention (EPI) program). Once the individual has consented to the study, the participant is then scheduled for the initial set of baseline assessments.

2.1.3 Baseline Assessment

The first assessment was termed the “first visit” and was done after the consented participant had been determined to meet the inclusion and exclusion criteria. This initial baseline assessment was completed as soon as possible after the consent process was complete. The purpose of the baseline assessment was to review the informed consent process once again, perform baseline anthropometric measures (height, weight, waste circumference), vital signs (blood pressure (orthostatic), heart rate), MRI and MRS, blood work (oral glucose tolerance test (OGTT), lipids, leptin, adiponectin, insulin, and glucagon like peptide 1 (GLP-1), medical history, and questionnaires (short form-36 (SF-36), international physical activity questionnaire (IPAQ), three factor eating questionnaire (TFEQ)).

All baseline and four-month follow up assessments were conducted at the University of British Columbia (UBC) Hospital. Physical assessments, medical history and questionnaires were conducted in a designated research room in the department of psychiatry. MRI/MRS were conducted at the MRI 3T research center connected to UBC hospital. Blood collection/phlebotomy was carried out by the graduate student or by technicians at UBC hospital laboratory services. Processing of blood work, which includes centrifugation of samples and separation into aliquots, was conducted in secure facilities at UBC department of anesthesiology, pharmacology, and therapeutics medical sciences block C. After the plasma had been separated and the samples had been placed into separate vials, they were then stored in a -80 degrees Celsius freezer in secure laboratory at the same location.

Baseline assessments were conducted in the morning and lasted approximately six hours from beginning to end (0700-1300). Participants were asked to begin fasting approximately ten to twelve hours prior to the baseline assessments, blood work, and MRI/MRS. Specifically, the participant is asked to have only water after midnight the night prior. Baseline anthropometric measures and vital signs were done initially followed by blood collection or MRI/MRS scans.

2.1.4 Second Assessment (in person clinical interview)

In the second assessment, an approximately three-hour long clinical interview was conducted whereby a series of psychiatric scales that evaluate the mental health and psychiatric symptoms of patients were administered. The graduate student, along with other members of the research team was responsible for conducting the clinical interviews. Second assessments were scheduled approximately 7-10 days after the baseline assessments. The second assessment was for participants taking antipsychotic medications only. The psychiatric scales administered in the second visit include the mini international neuropsychiatric interview (MINI), positive and negative syndromes scale (PANSS), social and occupational functioning scale, and the Calgary depression scale (CDS). The interviews were conducted in a place of the participants choice, usually a coffee shop or the participants home, wherever they would feel most comfortable. Furthermore, answers to the psychiatric scales were also interpreted and reviewed by two individuals to ensure inter rater reliability and accuracy.

2.1.5 Ongoing Assessments (monthly telephone questionnaires)

At three time points throughout the 4 months, participants were contacted via telephone for three 20-30 minute telephone interviews. These interviews were conducted at approximately one month, two months, and again at three months from the baseline assessment. The purpose of the telephone interviews was to assess any changes in overall health, physical activity, medication adherence, and eating patterns over the course of the study. Questionnaires that were administered as part of the telephone interviews were the SF-36, TFEQ, IPAQ, and the MARS. MARS were not administered to those in the control group.

2.1.6 Third Assessment (Four-month follow up)

At approximately four months from the baseline assessment, participants were asked to meet for the second clinical assessment involving MRI, anthropometric assessments, vital signs, and blood work. All participants (patients and controls) undergo the third assessment. The third assessment is nearly identical in structure to the baseline assessment. Contrasting from the baseline assessment, participants taking antipsychotics were asked to provide an additional vial of blood collected with the regular blood work in order to assess medication adherence. Furthermore, participants were invited to participate in an optional biobanking component of the study, if informed consent is obtained, the participant is asked to provide an additional three milliliters of blood which was stored in the -80 freezer and be used for future studies.

2.1.7 Final Assessment (second clinical interview)

The second clinical interview was identical to the first clinical interview. Similar to the first clinical interview, the second clinical interview applied to participants taking antipsychotic medications only. Psychiatric scales that were administered in the second clinical interview were the PANSS, SOFAS, and CDS. The purpose of the second clinical interview was to evaluate the mental health and psychiatric symptoms at two time points, early in antipsychotic treatment (within twenty-four weeks) and after four months.

2.2 Study Population and Characteristics

The complete trial will consist of ninety participants of whom all will undergo assessment through magnetic resonance imaging (MRI) at baseline and again at 4 months. For the CALM study, thirty will be controls (age and gender matched), thirty will be treated with high metabolic risk atypical antipsychotic drugs, and thirty with aripiprazole (low risk metabolic group). Individuals were deemed eligible to participate in the study if they were (1) 12 years or older with a diagnosis of bipolar disorder or 15 years of age or older with a diagnosis of a non-affective psychosis, (2) the individual has experienced recent admission to hospital or enrollment in community based psychiatric treatment or follow up services related to first episode psychosis or first episode bipolar disorder (inpatient or outpatient) (3) the individual must be treated with some type of antipsychotic medication (4) at the time of consent the individual must have been under

treatment of the antipsychotic for 24 weeks or less (5) the individual had to have been able to give informed consent or assent thought informed parental consent. The individual was deemed ineligible to participate in the study if: (1) they had been taking antipsychotic medication for greater than 24 weeks or their total lifetime exposure to antipsychotic medication exceeds 24 weeks. (2) the individual was not eligible to receive an MRI. For example, if the individual may have any metal in their body e.g. from tattoos, piercings (that cannot be removed), recent surgery, metalwork etc. or if the individual had morbid obesity or claustrophobia. Patients who had surgery within the passed six months were not eligible enter the MRI scanner and participate in the study (3) the individual had been diagnosed previously with any of the following disorders/conditions: diabetes mellitus, mental retardation (specifically that with an IQ of less than seventy). (4) If the individual were pregnant or within three months postpartum (5) if the individual were not proficient in written, spoken, and comprehension of English (6) the individual had undergone chemotherapy within the previous four weeks preceding the baseline assessment or the sixteen week follow-up interview.

For the purposes of this interim analysis, the treatment group will be defined as participants in the study whom are currently taking antipsychotic medication. The control group is defined as participants who are not currently taking any antipsychotic medication.

2.3 Data Collection Protocol

2.3.1 Consent Process

Individuals were screened either in person or over the phone to determine if they were eligible to enter the study. Prior to the baseline assessment visit, all participants must have had signed and dated the consent forms. No less than seven days prior to the baseline assessment visit the potential participant was met for an in-person meeting with a research associate. The purpose of this meeting is to ensure that the potential participant understands the protocol, expectations, risks and benefits of the study. This meeting also provides an opportunity for the individual to ask questions before deciding to enter the study. After the meeting, the individual was scheduled for another follow-up meeting whereby the individual may ask any further questions they may have had before entering the study. The follow-up meetings occured approximately 24 hours after the initial meetings. The participant, as well as the graduate student or research associate was required to sign and date the consent forms. Two copies of the consent were signed and one was given to the participant and the other kept in a secure location for record by the researchers.

2.3.2 Anthropometric Measures and Vital Signs

During the initial baseline assessment visits and at the four-month follow-up visits, all participants including controls and those taking antipsychotic medications had the following assessments performed. Anthropometric and vital sign assessments began with measuring the patients' height and weight. With shoes removed, the

participant was asked to stands tall on the scale while height and weight was measured. Height is measured to the nearest 0.1 centimeter and weight to the nearest 0.1 kilogram. Weight was taken at approximately the same time of day at each study visit to avoid fluctuations within subjects. Waist circumference was measured though measuring the median between the top of the iliac crest and the bottom of the costal margin in the mid-axillary line. To obtain orthostatic blood pressure and heart rate, the participant was asked to lay supine for five minutes before having the blood pressure and heart rate measures. The participant was then asked remain in the standing position for two minutes before having their blood pressure and heart rate measured again. The same automatic blood pressure and heart rate monitor was used for all participants.

2.3.3 Psychiatric Scales (clinical Interviews) and Questionnaires

At the baseline assessment, month one, month two, month three, the four-month follow-up visit, and the final clinical interview, a series of questionnaires and or psychiatric assessments were carried out.

Questionnaires were administered to all participants (patients and controls) at five time points throughout the study; the baseline assessment, month one, month two, and month three telephone interviews and at the four-month follow-up visit.
The first set of questionnaires took place at the baseline assessment during the two hour window between the first and second blood draw of the oral glucose tolerance test (OGTT), the questionnaires were then repeated over the phone at approximately one

month into the study, and again at two months, three months, and in person at the four-month follow up visit. The following is brief description of the questionnaires that were administered.

2.3.3.1 Mini International Neuropsychiatric Interview (MINI)

The MINI was used at the two clinical interviews with participants who were taking antipsychotic medications only. The purpose of the MINI is to provide a guided clinical interview to establish if a participant meets the criteria for a spectrum of psychiatric diagnoses. It is an abbreviated, thirty-minute, structured clinical interview that allows for the diagnosis of DSM-IV and ICD-10 Axis I disorders. The MINI is divided into modules that correspond to a diagnostic category. For example, module A evaluates whether the individual meets criteria for a past or current major depressive episode (MDE), module B for suicidality, and module C for dysthymia etc. There are a total of twenty-four modules (A-X). Although the MINI is designed to take approximately thirty-minutes, the clinical interviews lasted approximately two to four hours. Length of the clinical interviews was dependent on the cognitive process and ability of the participant. The MINI was the first psychiatric test that was administered during the clinical interviews because, depending on the outcome of the MINI, either the PANSS or the Y-MRS were administered.

2.3.3.2 Three-factor Eating Questionnaire (TFEQ)

The three-factor eating questionnaire is a short test that evaluates three dimensions of eating behavior; cognitive restraint in eating (factor one), disinhibition of control (factor two), and susceptibility to hunger (factor three). The first factor, cognitive restraint in eating, measures the conscious mechanisms of limiting food intake. Factor two, disinhibition of control, evaluates disinhibition type behaviors in eating. Factor three, susceptibility to hunger, evaluates the general sensations of hunger and the associated behavioral consequences. The test is comprised of fifty-one questions that are a combination of true and false, and multiple choice scaled questions. Items of the questionnaire are scored as binary functions. Each of the 51 questions is scored as ordinal data and assigned zero or one). Maximum score for the TFEQ is 20-16-15 corresponding to factor one, two, and three respectively with a minimum score of 0-0-0.

2.3.3.3 Short Form 36 (SF-36)

The SF-36 is a tool used to assess general physical and mental health as perceived by the individual. The SF-36 is structured to assess eight dimensions of health. The eight dimensions are: physical functioning (assesses limitations in performing physical activities), role-physical (assesses bodily pain), general health, vitality (assess general energy levels and fatigability), social functioning (assesses impact of physical and emotional problems on social functioning), role-emotional (assess the limitations in role act), and mental health (overall perceptions of mental health).

2.3.3.4 International Physical Activity Questionnaire (IPAQ)

The IPAQ is a short questionnaire that quantifies the amount of physical activity performed by the individual. Levels of physical activity are calculated in terms of vigorous, moderate, mild physical (e.g. walking), and sedentary activities (sitting). There are two forms of the IPAQ that are available; the long form and the short form. The short form was used for this study.

2.3.3.5 Medication Adherence Rating Scale (MARS)

The MARS is short questionnaire composed of ten yes or no questions that is used to assess adherence to antipsychotic medications. The MARS evaluates three components of medication adherence; behaviors relate to medication adherence, attitudes about taking medications, and thirdly, adverse events associated with antipsychotic medication and their attitudes towards these effects. One point is given for each of the ten questions of the MARS. A score of five or greater indicates that the participant is likely adhering to their medication.

2.3.3.6 Positive and Negative Syndromes Scale (PANSS)

The PANSS is a tool used in clinical practice and in research that measures the positive and negative symptoms of psychosis. The PANSS is composed of three separate rating subscales: positive scale, negative scale, and a general psychopathology scale. The positive and negative scale is composed of seven sections

that are rated on a scale of severity from one (absence of symptoms) to seven (extreme). The third subscale used to rate general psychopathology is composed of sixteen sections that are also rated on a scale of severity from one to seven. The thirty sections are then totaled to give total score for the PANSS with a minimum score of thirty and a maximum of two-hundred-ten. The information required to accurately score the PANSS was obtained through the structured clinical interview and information received from primary care staff and family members. The graduate student and research assistants, whom were trained by a licensed and practicing psychiatrist, were the ones who administered and score the PANSS.

2.3.3.7 Calgary Depression Scale (CDS)

The CDS is a tool used to evaluate depressive symptoms in patients with schizophrenia separate from the negative symptoms associated with schizophrenia. The CDS is a short, one-page questionnaire composed of nine symptoms associated with depression (for example, depression, hopelessness, self depreciation). Each section is rated on a scale of 0-3 from absent to severe respectively.

2.3.3.8 Social and Occupational Functioning Scale (SOFAS)

The SOFAS is a scale that is used to measure limitations in functioning related to mental or physical limitations. The criteria will only apply if the participant is

experiencing limitations in functioning directly related to mental or physical health problems (maybe add more here)

2.3.5 Honorarium

Honorariums for participation in the study were allocated as follows; seventy-five dollars was given to all participants for compensation of the baseline assessment and four month follow up. Compensation was given at the end of each assessment. Fifty dollars was given to participants in the antipsychotic group after completion of each of the two clinical interviews. For all participants who complete the telephone interviews, ten dollars was given for the first and second telephone interview and fifteen dollars was allocated for the third.

2.4 Primary Outcome: Assessing Weight Gain Over Time

Weight gain was assessed manually though physical assessments at baseline and again at four months. A manual column scale was used to assess height and weight. Differences were calculated after the four-month follow up. WC was measured manually in centimeters using a standard measuring tape at baseline and four-month follow-up visits. BMI was calculated manually (weight in kilograms by height in meters: BMI = Weight (Kg) / Height $(m)^2$ (see figure 1.) (Health Canada, 2003). A minimum of two individuals was required to perform physical assessments in both control and participants taking antipsychotics. Research assistants were required to have special training in both physical assessments and patient communication. The graduate student's baccalaureate training and clinical experience in nursing have served as a

vital prerequisite for performing physical assessments and served as served as an important intellectual contribution to this aspect of the study. The graduate student was responsible for obtaining height, weight, and WC while other members of team would simultaneously be responsible for the processing of blood and urinalysis samples at the nearby UBC laboratory. The role of the graduate student and research assistants was interchanged depending on patient preference, knowledge base, participant rapport, and safety.

2.5 Secondary Outcomes

Secondary outcomes that were investigated include orthostatic blood pressure and pulse measurements, which may be affected by antipsychotic treatment. Changes in psychopathology were assessed through the PANSS and CDS. Changes in physical activity and eating patterns were evaluated through the IPAQ and TFEQ respectively. Changes in subjective quality of life and perceptions of mental and physical health were measured through the SF-36. Lastly, adherence to medication was assessed though the MARS. The graduate student, along with other members of the research team, were responsible collecting secondary outcome data. The graduate student was responsible for the measurement of pulse and orthostatic blood pressure while another member of the research team would be responsible for processing samples at the nearby UBC laboratory. The graduate student was responsible for administration of the SF-36, TFEQ, IPAQ, and MARS during the baseline and four month follow-up assessments while another member of the team would be responsible for the processing of samples. As previously mentioned, roles may interchange depending on patient preference,

rapport, knowledge base, and safety. The graduate student and research team were responsible for administration and scheduling of telephone interviews throughout the study. The graduate student as well as another member of the research team was required to perform clinical interviews (MINI, PANSS assessment, CDS, and SOFAS) and for interpretation of the results to maintain inter-rater reliability.

Due to the frequency of telephone interview assessments (three per participant), consenting processes, clinical interview assessments and interpretation (two per participant in the antipsychotic group), baseline, and follow up assessments, telephone interview appointments would often conflict with clinical interviews, baseline/follow-up assessments, and consenting. In this case the graduate student or other members of the research team would be required to perform the telephone interview while the other members of the team (or graduate student) performed the other assessments.

2.6 Statistical Analysis

Statistical analysis was performed using IBM Statistics Package for the Social Sciences (SPSS) version 22.0. Age, height, weight, WC, BMI, PANSS scores, CDS scores, SOFAS scores, orthostatic blood pressure, and pulse measurements were analyzed using a students t-test ($p \leq 0.05$). Independent samples t-test was used for analysis between groups and paired samples t-test used for within groups analysis. A chi-squared test was used to detect differences in gender ($p \leq 0.05$). t-tests were used for statistical analysis because the type of data that was analyzed was continuous variables that show normality. Repeated measures one way analysis of variance (ANOVA) was used for analysis of the TFEQ, IPAQ, SF-36, and MARS ($p \leq 0.05$). This

test was determined to be appropriate because it will show the differences over time as well as interaction effects between two groups (treatment and control). A completer's analysis was utilized because it was an appropriate for interim analysis of a clinical trial that may take four years to complete. The completer's analysis was also useful because results may change by the end of the trial, therefore further statistical tests may not be beneficial. The graduate student was responsible for learning to utilize SPSS software, running, analyzing, and interpreting the statistical analysis of the data. The graduate student contributed intellectually to statistical analysis through the choices of statistical tests in collaboration with Dr Barr. Further intellectual contributions include interpretation of data both raw and that which was generated though statistical analysis. Solely the graduate student drew data interpretation and conclusions.

Chapter 3: Results

Table 3.1 Complete list of variables included in statistical analysis.

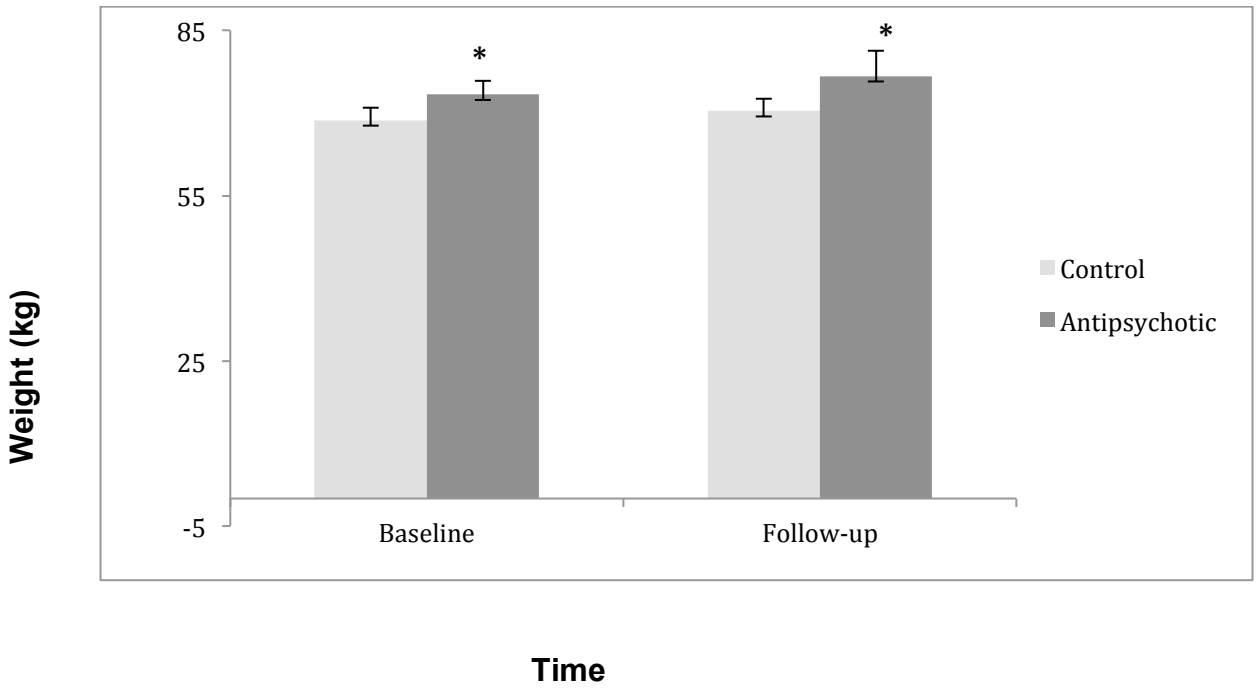
Baseline assessment	First clinical interview	Telephone interview I	Telephone interview II	Telephone interview III	Four month follow-up	Second clinical interview
Height Weight BMI Waist circumference Orthostatic blood pressure laying HR laying systolic laying diastolic standing HR laying systolic standing diastolic **SF-36** Physical functioning Role physical Bodily pain Gen health Vitality Social functioning Role emotional Mental health MH summary Physical health summary **IPAQ** Mild PA Moderate PA Vigorous PA Total PA **TFEQ** Level of cognitive restraint Level of disinhibition Susceptibility to hunger MARS (antipsychotic group)	PANSS CDS SOFAS	**SF-36** Physical functioning Role physical Bodily pain Gen health Vitality Social functioning Role emotional Mental health MH summary Physical health summary **IPAQ** Mild PA Moderate PA Vigorous PA Total PA **TFEQ** Level of cognitive restraint Level of disinhibition Susceptibility to hunger MARS (antipsychotic group)	**SF-36** Physical functioning Role physical Bodily pain Gen health Vitality Social functioning Role emotional Mental health MH summary Physical health summary **IPAQ** Mild PA Moderate PA Vigorous PA Total PA **TFEQ** Level of cognitive restraint Level of disinhibition Susceptibility to hunger MARS (antipsychotic group)	**SF-36** Physical functioning Role physical Bodily pain Gen health Vitality Social functioning Role emotional Mental health MH summary Physical health summary **IPAQ** Mild PA Moderate PA Vigorous PA Total PA **TFEQ** Level of cognitive restraint Level of disinhibition Susceptibility to hunger MARS (antipsychotic group)	Height Weight BMI Waist circumference Orthostatic blood pressure laying HR laying systolic laying diastolic standing HR laying systolic standing diastolic **SF-36** Physical functioning Role physical Bodily pain Gen health Vitality Social functioning Role emotional Mental health MH summary Physical health summary **IPAQ** Mild PA Moderate PA Vigorous PA Total PA **TFEQ** Level of cognitive restraint Level of disinhibition Susceptibility to hunger MARS (antipsychotic group)	PANSS CDS SOFAS

Table 3.2 Mean (SD) values, sample sizes (n), and statistical analysis of anthropometric data at baseline and four months. P-values are given for between subjects at baseline, at four months, and longitudinally for both groups.

Variable Mean (SD)	Baseline Assessment			Four month follow-up		
	Control Group (n=20)	Antipsychotic Group (n=34)	P Value	Control Group (n=15)	Antipsychotic Group (n=21)	P Value
Age (Years)	23.7(2.9)	22.8(3.8)	.2*			
Sex, Male N(%)	11(55)	21(63.6)	.5	9(60)	12(57)	.9
Weight (kg)	68.7(10.1)	73.4(14.6)	**.02***	70.4(8.8)	79.3(17.7)	**.03*** .5** **.001****
Height (m)	1.7(0.11)	1.71(0.10)	.68*	1.7(0.9)	1.71(0.11)	.8* .10** .4***
Body Mass Index (BMI) (kg/m^2)	23.5(3.1)	25(4.3)	.13*	24.2(2.8)	26.2(6.7)	**.04*** .17** **.005****
Waist Circumference (cm)	82.8(8.7)	90.3(11.6)	.09*	84.6(7.8)	96.3(13)	.08* .38** **.01****

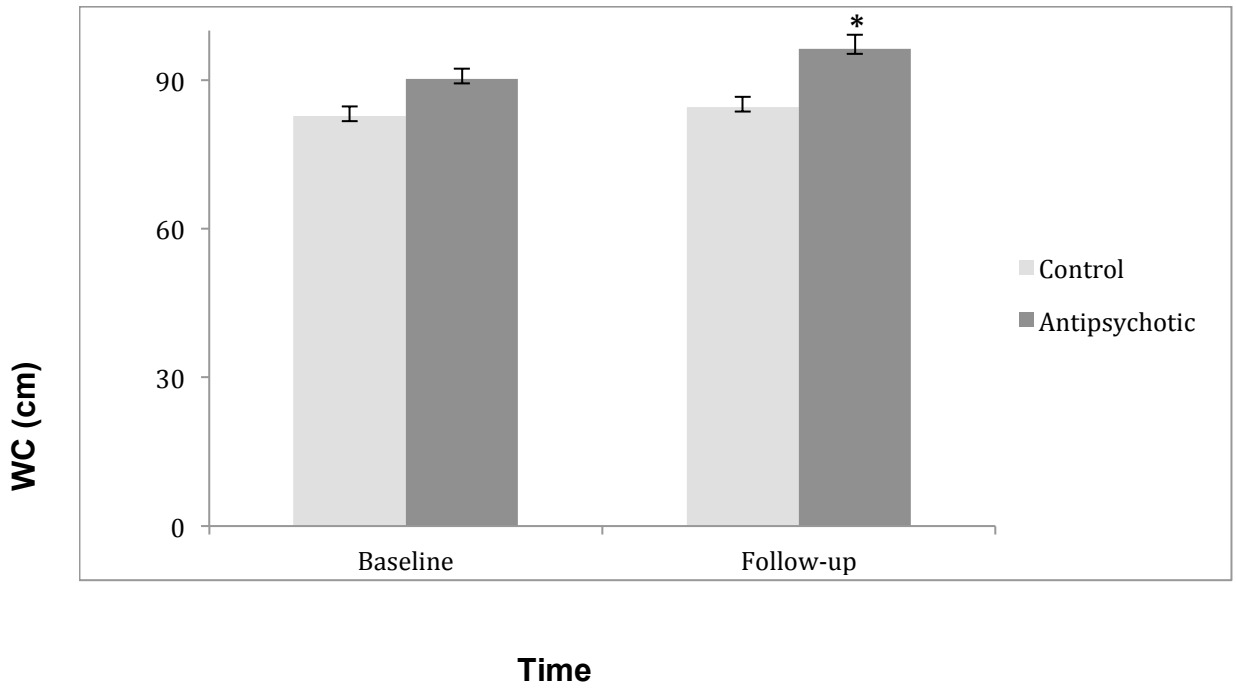
[a] Significance values: Independent samples t test=*, Paired samples t test: Controls=**, antipsychotic group=***.

Figure 3. Mean weight (Kg) at baseline and four month follow-up.



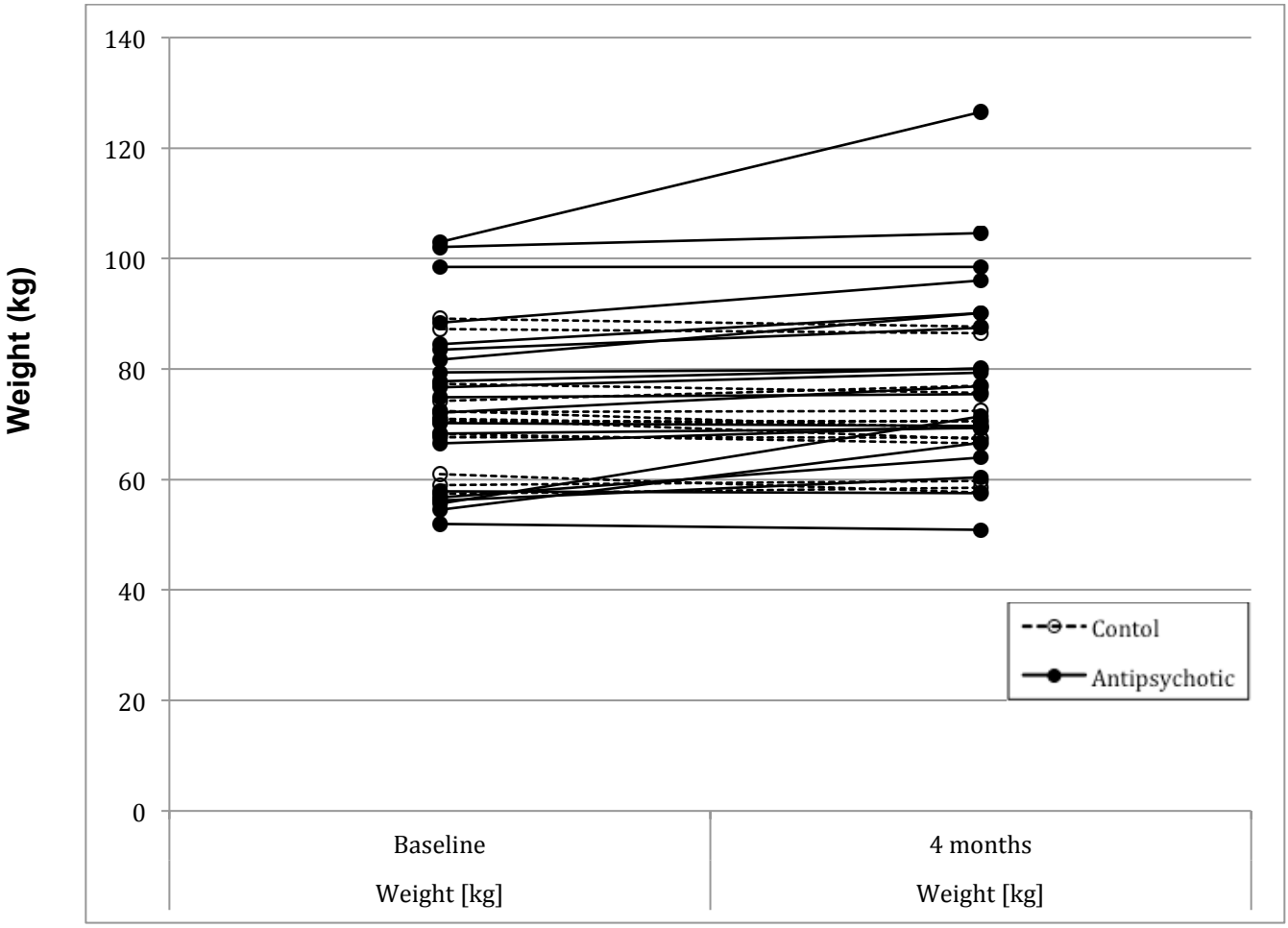
[a]Values represent group means ± standard error of the mean (SEM). *P<.05

Figure 4. Mean WC at baseline and four month follow-up.



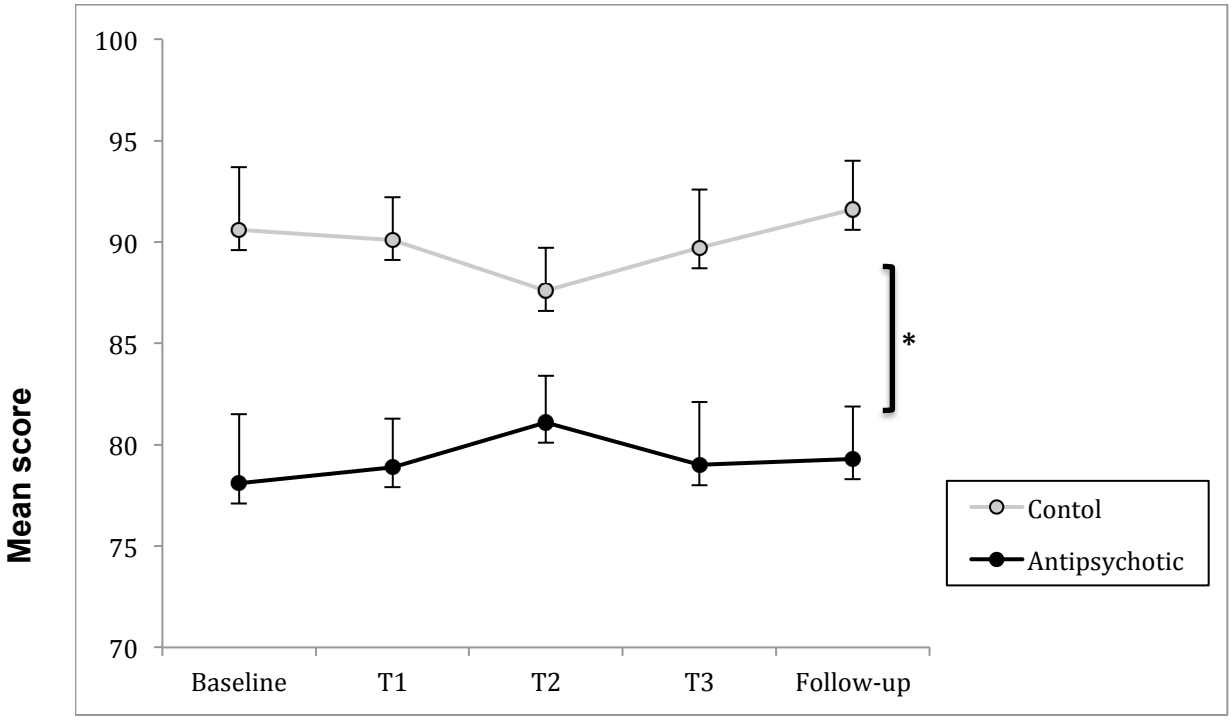
[a]Values represent group means ± standard error of the mean (SEM). *P<.05

Figure 5. Weight gain between baseline and four month follow-up.



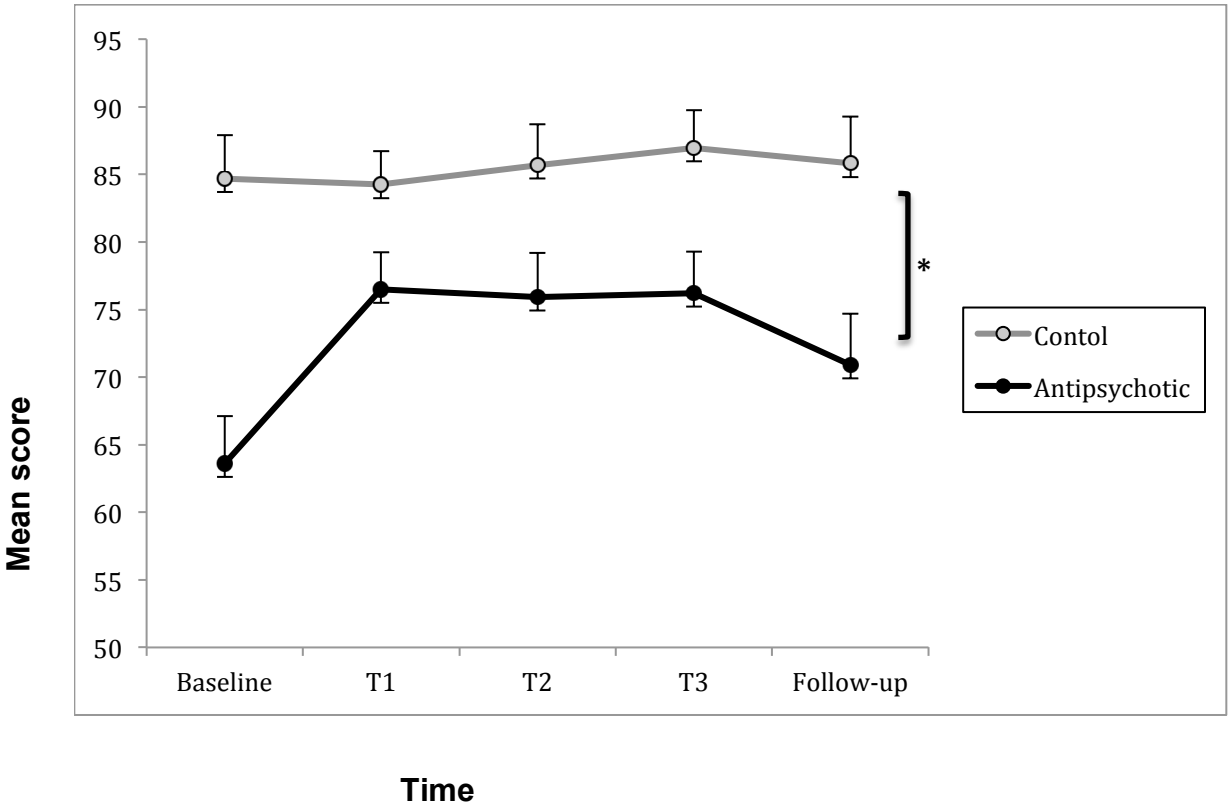
[a] Graph depicts weight in kilograms (Kg) of control participants and those taking antipsychotic medication. Only participants who completed the baseline assessment and four month follow-up were included in the illustration.

Figure 6. SF-36 Physical Health Summary.



[a]T1 = Telephone interview 1; T2 = Telephone interview 2, T3 = Telephone interview 3;
[a]Values represent group means ± standard error of the mean (SEM). *P<.05

Figure 7. SF-36 Mental Health Summary.



[a]T1 = Telephone interview 1; T2 = Telephone interview 2, T3 = Telephone interview 3;
[a]Values represent group means ± standard error of the mean (SEM). *P<.05

Table 3.3 Mean (SD) data and sample sizes (N) of orthostatic blood pressure and pulse measurements of control and antipsychotic participants at baseline and at four months.

Baseline				Four-month follow-up		
Variable Mean(SD)	**Controls (n=20)**	**Antipsychotic group (n=33-34)**	**P Value**	**Controls (n=14-15)**	**Antipsychotic group (n=20)**	**P Value**
Supine						
Systolic BP (mmHg)	111.1(16.4)	112.8(10.9)	.41*	110.1(13)	112(13.6)	.52* .86** .79***
Diastolic BP	71.5(9.5)	69.7(8.4)	.59*	72.9(8.4)	69.9(10.4)	.55* .96** .85***
Pulse (BPM)	63.5(12.4)	64(12.1)	.95*	58.6(8.4)	61.5(13.3)	.07* .08** .3***
Standing						
Systolic BP	119.1(16.4)	112(14.9)	.42*	114.6(11.3)	110.6(16.6)	.24* .13** .25***
Diastolic BP	85.4(16.6)	78.6(13.2)	.49*	79.4(7.6)	75.3(8.5)	.85* .11** .6***
Pulse	79.9(13.6)	85.8(17.8)	.14*	77.1(7.4)	82.8(17.4)	.005* .14** .04***

[a] P values are given for between subjects at baseline and at four months, and longitudinally for both groups. Significance values: Independent samples t test=*, Paired samples t test: Controls=**, antipsychotic group=***.

Table 3.4 Mean (SD) values and sample sized (n) of the Short Form 36 (SF-36) in the control group (C) and antipsychotic group (A) and at baseline, month one, two, and three telephone interviews, and four-month follow up visit.

Variable	Baseline		Month I		Month II		Month III		Four-month follow-up		
Mean (SD)	**C (n=13)**	**A (n=11)**	**C (n=13)**	**A (n=11)**	**C (n=13)**	**A (n=11)**	**C (n=13)**	**A (n=11)**	**C (n=13)**	**A (n=11)**	**P value**
Physical Functioning	96.9 (6)	92.7 (14.9)	98.1 (4.8)	83.6 (20.9)	96.5 (5.6)	91.8 (15.2)	98.5 (5.5)	90.9 (14.8)	98.5 (4.3)	89.6 (15.7)	
Role -Physical	95.2 (8.5)	71.6 (28.6)	96.6 (5.5)	80.7 (16.2)	91.3 (10.7)	90.9 (11.6)	92.8 (10.5)	86.4 (17.2)	97.1 (6)	80.1 (17.4)	
Pain	94.2 (9.5)	85.2 (14.1)	92.7 (11.1)	87.7 15.3	88.8 (9.3)	92.3 (9.5)	91.9 (13.1)	93.1 (13)	96 (8.1)	97 (7.1)	
General Health	75 (16.3)	71.8 (14)	74.2 (13)	74.1 (13.9)	73.9 (15.2)	68.2 (14)	75.8 (14)	71.4 (16.1)	75 (13.8)	71.8 (15.2)	
Role Emotional	96.2 (6.5)	69.7 (22.4)	91 (14.2)	78.8 (18.4)	94.9 (8.7)	90.9 (16)	96.2 (8.1)	84.1 (19.9)	96.2 (11.6)	81.8 (18.9)	
Vitality	66.8 (18.1)	54 (17.5)	67.3 (11.7)	63.1 (13.2)	68.3 (9.7)	51.7 (18.1)	70.2 (14.9)	59.7 (12)	68.8 (13.5)	58 (12.2)	
Social Functioning	93.3 (13.1)	61.4 (16.3)	97.1 (7.4)	86.4 (13.1)	94.2 (11)	87.5 (15.5)	96.2 (93.4)	83 (20.4)	94.2 (11)	73.9 (22)	
Mental Health	82.7 (12)	69.6 (16.8)	81.5 (9)	77.7 (11)	85.8 (8.9)	73.6 (16.4)	85.4 (11.8)	78.2 (11)	84.2 (10.8)	70 (16.1)	
Physical Health Summary	90.6 (3.1)	78.1 (3.4)	90.1 (2.2)	83.9 (2.4)	87.6 (2.1)	85.8 (2.3)	89.8 (2.9)	85.5 (3.1)	91.6 (2.4)	84.6 (2.6)	.42* **.03****
Mental Health Summary	84.7 (3.2)	63.6 (3.5)	84.2 (2.5)	76.5 (2.8)	85.8 (3)	75.9 (3.7)	89 (2.8)	76.2 (3)	85.8 (3.5)	71 (3.8)	**.04*** **.09g*** **.00****

[a] Significance values: Repeated measures ANOVA significance values: within subjects*, between subjects**. Interaction effects: group = g, time = t. C = control group, A = antipsychotic group.

Table 3.5 Mean (SD) values of the international physical activity questionnaire (IPAQ) in the control group at baseline, month one, two, and three telephone interviews, and four-month follow-up visit.

Variable Mean (SD)	Baseline (n=13)		Month I (n=13)		Month II (n=13)		Month III (n=13)		Four month follow-up (n=13)		
	C	A	C	A	C	A	C	A	C	A	P
Walking	1524.7 (1737.2)	2760.8 (2501.3)	1306.3 (1950.6)	1320 (1644.1)	1182.9 (1121.3)	941.8 (775.2)	2293.5 (3254.1)	2009.2 (2780.6)	1863.2 (2433.5)	1756.6 (2520.1)	
Moderate physical activity	341.5 (253.8)	266.2 (401.1)	498.5 (477.1)	696.9 (867.9)	678.5 (508.8)	495.4 (547.9)	700 (627.1)	927.7 (1304.6)	696.9 (560.5)	646.2 (603.7)	
Vigorous physical activity	566.2 (381.2)	926.2 (1543.1)	830.8 (616.7)	600 (1104.2)	1680 (992.9)	923.1 (891.8)	1240 (973.7)	1163.1 (1232)	1181.5 (689.1)	935.4 (1246.7)	
Total physical activity	2432.4 (554.1)	3952.9 (554.1)	2635.5 (572.8)	2616.9 (572.8)	3541.4 (456.75)	2360.2 (456.75)	4233.5 (1023.8)	4099.96 (1023.8)	3741.7 (456.1)	3338.2 (756.1)	**0.1*** **0.9****

[a] Repeated measures ANOVA significance values: within subjects=*, between subjects=**. C = control group, A = antipsychotic group.

Table 3.6 Mean (SD) values and statistical analysis of the Three Factor Eating Questionnaire (TFEQ) the in the control group at baseline, month one, two, and three telephone interviews, and four-month follow up visit.

Factor Mean (SD)	Baseline		Month I		Month II		Month III		Four month follow-up		
	C (n=13)	A (n=12)	C (n=13)	A (n=12)	C (n=13)	A (n=12)	C (n=13)	A (n=12)	C (n=13)	A (n=12)	P Value
I-Cognitive restraint	7.1 (1.3)	8.9 (1.4)	7.5 (1.2)	8.7 (1.3)	6.6 (1.0)	6.5 (1.0)	7.3 (1.4)	9 (1.5)	7.385 (1.4)	9.8 (1.5)	.06* .4**
II-Disinhibion	4.8 (3)	5.9 (2.2)	4.2 (3.5)	6.1 (4.4)	3.5 (2.5)	4.8 (3.5)	3.8 (3.3)	4.3 (2.8)	3.5 (2.8)	5.8 (3.3)	.09* .2**
III-Susceptibility to hunger	3.6 (2.4)	5.4 (4)	3.6 (2.8)	5.6 (3.7)	4 (2.6)	4.6 (3.1)	3.6 (2.7)	4.4 (3.4)	3.2 (3)	5 (3.6)	.8* .2**

[a] Repeated measures ANOVA significance values: within subjects=*, between subjects=**. C = control group, A = antipsychotic group.

Table 3.7 Mean (SD) values for the Medication Adherence Rating Scale (MARS) of participants in the antipsychotic group at month one, two, and three telephone interviews, and four-month follow-up visit.

	Month I	Month II	Month III	Four-month follow up	P Value
MARS Score Mean (SD) (n=13)	8 (2)	8 (2)	8 (2)	8 (2)	.8

Table 3.8 Mean (SD) values for the positive scale, negative subscale, and general psychopathology subscale and total scored Positive and Negative Syndromes Scale for participants taking antipsychotics at the first and second clinical interview.

	Clinical Interview I (n=17)	**Clinical Interview II (n=17)**	**P value**
Positive Scale	17 (6)	14(5)	
Negative Subscale	20(7)	33(11)	
General Psychopathology Subscale	41(9)	35(13)	
Total PANSS Score Mean (SD)	77 (18)	68 (23)	**.2**

Table 3.9 Mean (SD) values Calgary Depression Scale (CDS) in the antipsychotic group at the first and second clinical interview.

Variable	**Clinical Interview I Mean (SD)**	**Clinical Interview II**	**P Value**
Total Score	4.45(4.22)	2.65(2.64)	**.05**

Table 3.10 Mean (SD) values for the Social and Occupational Functioning Scale (SOFAS) of participants in the antipsychotic group at the first and second clinical interview.

	Clinical Interview I Mean (SD)	**Clinical Interview II**	**P Value**
SOFAS Score	60(13.9)	62(14.8)	0.7

3.1 Anthropometric measures at baseline

At the baseline assessment, a significant difference in weight was seen between control participants (68.7±10.1) and antipsychotic drug treated participants (73.4±14.6), t(52) = 5.91, p=0.02 (**Table 3.2, Figure 3**). At baseline, participants taking antipsychotic medications weighed on average 4.6 kilograms (kg) more than control participants. A trend difference was also seen in waist circumference (WC) at baseline. Antipsychotic treated participants (90.3±11.6) had greater waist WCs than control participants (82.8±8.7), t(52) = 2.9, p = .09. Age, height, BMI, sitting and standing blood pressures and pulse measurements were not significantly different between control participants and participants taking antipsychotic medications at baseline.

3.2 Anthropometric measures at four months

At the four month follow-up a significant difference in weight was seen between control participants (70.4±8.8) and participants taking antipsychotics (79.3±17.7), t(34) = -1.784, p < .05. At four months, participants taking antipsychotic medications weighed an average of 8.9 kg more than control participants. A significant difference in BMI was found between control participants (24.2±2.8) and participants taking antipsychotics (27±5.4) at four months t(34) = -1.9, p=.04. On average, participants taking antipsychotic medications had a 2-point higher (8.2%) BMI than control participants. A trend in WC was seen at four months between controls (84.6±7.8) and antipsychotic participants (96.3±13), t(34) =3.243, p=0.08. On average, control participants had 11.7 cm smaller WCs than participants taking antipsychotic medications. Standing pulse measurements were found to be significantly different at four months between control

participants (77.1±7.4) and those taking antipsychotics (82.8±17.4), t(32) = 8.903, p=.005. On average, participants taking antipsychotic medications had 5.6 beats per minute (BPM) higher pulse measurements than control participants.
Furthermore, a trend was seen in supine pulse measurements at four months between control participants (58.6±8.4) and those taking antipsychotics (61.5±13.3) t(32) =3.608, p=.07. Participants in the control group had slightly higher pulse measurements, although not statistically significant.

3.3 Within-subjects at baseline and four months

Significant differences in WC were seen within participants taking antipsychotics at baseline (90.3±11.6) and at four months (96±13), t(20) = -2.937, p = .08 (**see Figure 4**). On average, antipsychotic treated participants showed a 5.6 cm increase in waist circumference at the four month follow up. A significant difference was seen between standing pulse measurements in the antipsychotic group (85.8±17.8) and four months (82.8±17.4), t(18) = 2.219, p = .04. Lastly, a significant difference was seen when comparing baseline weight (73.4±15.7) with weight at four months (79.3±17.7), t(20) = -3.732, p < .005 in the antipsychotic group. Over the course of four months, participants taking antipsychotic medications gained an average of 5.5 kg.

3.4 Weight gain over time

To test for the presence of weight gain over time, the difference in weight between four months and baseline was calculated (weight at four months – weight at baseline). Gain in BMI and WC was also calculated. Only participants who had

completed both the baseline assessment and the four-month follow-up were included in the analysis. A t-test was used to detect significance between the control group (n=15) and those taking antipsychotics (n=21). We found that the weight gain in participants taking antipsychotics was significantly greater than the control participants ($t(34) = -3.56$, $p < .05$). In addition, we found significantly greater BMI ($t(34) = -2.96$, $p = .005$) in participants taking antipsychotics compared to control participants. Gain in WC did not reach statistical significance. When the weight gain was normalized it was also found to be statistically significant ($t(34) = -3.53$, $p < .05$).

3.5 Short Form 36 (SF-36) Mental and Physical Health Summary

Between subjects analysis revealed significant differences between control participants (n=13) and participants taking antipsychotics (n=11) in physical health summary results of the SF-36 (**Table 3.4, Figure 6**) $F(1, 22) = 5.54$, $p < .05$. Patients taking antipsychotics reported lower physical health scores than participants not on antipsychotics. No other significant differences in physical heath summary results were found. Significant differences in the mental health summary were found through within subjects analysis over time $F(4, 88) = 2.657$, $p < 0.05$. A significant increase in mental health summary scores over time was seen in participants taking antipsychotic medication (**Figure 7**). A trend was seen though within subjects analysis by group $F(4, 88) = 2.657$, $p = 0.09$. Furthermore, significant differences were also found through between subjects analysis of the mental health summary when comparing control participants (n=13) and those taking antipsychotics (n=11) $F(1,22) = 17.83$, $p < .05$.

Control subjects had significantly higher mental health summary scores than those taking antipsychotics. No other significant differences were found in mental health summary scores.

3.6 Three Factor Eating Questionnaire (TFEQ)

Within subjects analysis of factor one revealed a trend differences by time $F(4,92) = 2.347$, $p = 0.06$ (**Table 3.6**). Within subjects analysis revealed a trend differences over time of factor two of the TFEQ $F(4, 92) = 2.088$, $p = 0.09$ (**Table 3.6**). No further significant differences were found though analysis of the TFEQ through within or between subjects analysis of the TFEQ in either group.

3.7 International Physical Activity Questionnaire (IPAQ)

No significant differences were found through analysis of the IPAQ in either group over time. A trend, however, was seen through within subjects analysis over time $F(4, 96) = 2.018$, $p = .1$ (**Table 3.5**).

3.8 Positive and Negative Syndromes Scale (PANSS)

For analysis of the PANSS a paired samples t-test was used to test for differences within the same group at two time points, clinical interview one at the beginning of the study and the second four months later. No significant differences were found though analysis of the PANSS (**Table 3.8**).

3.9 Calgary Depression Scale (CDS)

Again, paired samples t test was used to test for differences within the CDS. Significantly lower CDS scores were found at the second clinical interview (4.5±4.42) compared to clinical interview one (2.7±2.6) $t(19) = 2.1$, $p = 0.05$ (**Table 3.9**).

3.10 Social and Occupational Functioning Scale (SOFAS)

A paired samples t test was also used to test for significance between clinical interview one (60±13.9) and clinical interview two (62±14.8). No significant differences were seen in the SOFAS scores. Analysis of the SOFAS, did, however, reveal a trend increase in SOFAS score at the second clinical interview $t(19) = -.358$, $p = 0.07$ (**Table 3.10**).

Chapter 4: Discussion

4.1 Findings

In this study we have undertaken an interim analysis of a four month long clinical trial. A completers analysis was used for statistical analysis.

This interim analysis shows that patients with first episode psychosis newly started on a SGA tend to weigh more than people with no history of psychiatric illness and SGA treatment. This is contrary to the hypothesis that at baseline there would be no significant differences in weight. In addition to weighing more, patients with first episode psychosis on SGAs tend to have greater waist circumferences at the beginning of the study.

Although this contrasts to our hypothesis that there would be no significant differences in weight or waist circumference at baseline, it is not unexpected that a sample of patients with mental illness would greater weight and waist circumferences than those with no history of psychiatric illness. As such, there are a number of factors, in addition to antipsychotic drug treatment, that place those with mental illness at a greater risk of weight gain than those without (Thakore et. al., 2002; Hennekens et. al., 2005). The disease process of schizophrenia can result in a number of symptoms that lead to weight gain. For example, poor diet, smoking, and decreased physical activity have been found to be more prevalent in people with schizophrenia (Brown et. al., 1999), increasing their risk of obesity. At four month follow-up, patients taking antipsychotics appeared to gain weight over the course of the study. This is consistent

with the hypothesis and is an expected finding given the potential of SGAs to induce weight gain.

Changes in heart rate were also noted at four months with slightly significant differences between controls and those taking antipsychotics. Given that there were no significant differences at baseline, we can conclude that that this is related to the effects of antipsychotic medications. Moreover, heart rate variability has been reported as an effect of antipsychotics (Silke et. al., 2002). At four month follow up, a trend difference was seen in WC with slightly greater WC observed in patients taking antipsychotics compared to controls. We hypothesize that, by completion of the entire clinical trial (n=90), differences in WC between groups will reach statistical significance. Although WC differences were not significantly different than controls at four months, participants taking antipsychotics did show a significant increase in WC from their measurements at baseline. Given that WC is an indicator of visceral fat deposition (Thakore et. al., 2002), this is consistent with our hypothesis that the weight gain seen in patients taking antipsychotics could be largely visceral. Given these findings, the benefit of analysis through abdominal MRI is especially useful in exploring the locality and magnitude of visceral fat deposition in patients taking antipsychotic medications. Although a significant difference in weight was expected to be seen within the antipsychotic group, the weight gain seen over the course of four months did not reach statistical significance. A trend difference in weight was seen in the antipsychotic group with a mean weight gain of 2.5 kg. We hypothesize that, by the end of the clinical trial, which would create a larger sample size, significant differences in weight will be seen in the antipsychotic group.

In order to assess weight gain over time, the difference in weight at baseline and four months was calculated in participants who had completed the baseline assessment and four-month follow-up. We found that participants taking antipsychotics had significantly more weight gain at four months of the study than did control participants. Furthermore, we found an overall weight loss in control participants at four months of the study. Additionally, a corresponding gain in BMI was also found in BMI at four months. Gain in WC was also calculated, however, it was not statistically significant. Overall, we found that, after four months of the study, participants taking antipsychotic medication gained an average of 5.5 kg.

There are a number of confounders that may have affected the significant gain in weight in participants taking antipsychotics. These include, starting weight, duration of antipsychotic treatment. Participants who had a lower BMI at the beginning of the study may have had a higher likelihood of weight gain than participants who were already at a high BMI. In order to be eligible for the study, the duration of antipsychotic treatment was limited to no longer than twenty-four weeks (six months) of initial treatment with the drug. Based on our results that significant weight gain was found over four months of the study, it is likely that the length of time that the participant has been on the antipsychotic may be a confounder. Specifically, participants that have been on the antipsychotic for longer may experience less weight gain than those who are in earlier stages of antipsychotic treatment.

The results of the study found significant differences in subjective quality of life assessed by the SF-36. Patients taking antipsychotic medications rated their physical and mental heath as lower than the control participants. The SF-36 has been shown to

be an accurate tool to measure quality of life in patients with schizophrenia (Meijer et. al., 2003). In this study we were able to see that the summary scores of the SF-36 were lower in patients on antipsychotic medication compared to those that are not. It is not surprising that patients with psychotic disorders would have rated their physical and mental health as lower than that of control subjects regardless of antipsychotic treatment. There are a number of factors that are related to the disease pathology of schizophrenia and other psychotic disorders that may decrease the subjective quality of life. Such factors include its impact on of social relationships (Gupta et. al., 1998), depression (Siris, 2000), and adverse effects related to treatment may all contribute to lowering ones self described feelings of physical and mental health. Although the mental and physical health of people on antipsychotics were lower than that of the control group, improvements in subjective mental health were seen at the four month follow up in patients taking antipsychotics. This is not unexpected as the effects of antipsychotics may be improving symptoms in this group. Although mean PANSS scores did improve slightly by the second clinical interview, the improvements were not significantly different. This suggests that patients taking antipsychotics are feeling as if their mental health has improved after four months of treatment. This is consistent with the findings of Awad et. al. (2012) who found a general trend of SGAs to have a positive impact on quality of life of patients. We conclude that, by completion of the clinical trial or with longer duration of study, significant differences in PANNS scores may be seen. Lastly, we conclude that the lack of significant improvements in physical health of patients taking antipsychotics were related to the adverse events related to antipsychotic medication such as weight gain (Robson & Gray, 2007).

No significant differences were detected though analysis of the TFEQ. Trend differences were seen over time in factor one and two. Consistently patients taking antipsychotic medications scored higher than control participants in all three factors of the TFEQ however they did not reach statistical significance. Although no significant differences were detected in mean MARS, IPAQ, or PANSS scores, a significant improvement was seen in CDS scores at the second clinical interview in participants taking antipsychotic medication. Similar to the findings reported in Innamorati et. al. (2013) SGAs have been shown to decrease depressive symptoms in patients with schizophrenia, regardless of the type of SGA used. In this study we found that over the course of four months a significant improvement in depressive symptoms were seen in patients taking antipsychotic medications. In this study we reported no significant improvements in psychotic symptoms in light of significant improvements in depressive symptoms. We hypothesize that the CDS may be a more sensitive measure to test for initial improvements in symptomology in the early stages of antipsychotic treatment. This may prove a useful tool for clinicians wishing to assess the efficacy of antipsychotic treatment if a patient does not appear to be responding to treatment. Further research is needed to determine if the CDS could be used as a clinical tool to determine efficacy of SGAs in the early stages of treatment.

Lastly, a trend increase was observed in SOFAS scores at the second clinical interview. It is not unexpected that slight improvements in SOFAS scored would be seen after four months of antipsychotic treatment. By completion of the trial, significant improvements in SOFAS scored could be detected. Other hypotheses for why significant improvements in SOFAS scores could not be detected with the present

sample is that the population of participants taking antipsychotics is already at a relatively high level of functioning. In order to consent to the study and to participate in all aspects of the trial the individual was required to be at a higher level of functioning, as such, their baseline may be too high to detect differences. Moreover, in future studies it may be useful to utilize more sensitive questionnaires that are more sensitive at detecting improvements in global functioning.

4.2 Limitations

This study may have benefited though randomized method of participant recruitment. Method of recruitment for the treatment group was primarily though physician referral at a community based mental health treatment center in Vancouver, Canada. Although obtaining an adequate sample size would be difficult to achieve, It could be suggested that a degree of biases may have had impact on metabolic characteristics of the treatment group. Various, geographic, cultural, and socioeconomic factors may have played a roll in creating bias. Although significant differences in weight, WC, and CDS scores were reported, a high level of variance limits the strength. Longitudinal data was limited by participant retention. A number of participants in the antipsychotic group suffered relapses or exacerbation in psychotic symptoms and had to withdraw from the study or were unable to participate various assessments. Future studies may benefit though defining a set of criteria at the time of consent that will assess the likelihood of stability on ones chronic condition.

4.3 Future Directions

In this study we have performed an interim analysis of a four-month long clinical trial that has shown promising results. In future analysis, it will be beneficial to compare analysis of MRI data and waist circumferences. Given the findings in this study, it will be beneficial to perform analysis on high and low metabolic risk drugs over time. With large sample sizes it is likely that trend differences may reach statistical significance.

4.4 Conclusion

Consistent with previous studies, we have also found that patients with mental illness may benefit from health promotion and lifestyle coaching (Brown et. al., 1999). The results of this study are consistent with previous work (Mackin et. al., 2007) who found that patients with mental illness tend to have greater waist circumferences and higher BMIs than the general population. The results of this study suggest that individuals taking antipsychotics may benefit from regular monitoring of WC, weight and pulse measurements. SGAs may have a positive effect on mental health of patients with psychotic disorders. Given the results seen in this sample of drug naive patients, careful monitoring may be especially important in the initial phase of antipsychotic treatment.

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Appendix I: Mechanism of action of common SGAs

Appendix I has been adapted from a published manuscript by Whitney et. al. (2015).

Appendix II: Mechanism of action of common SGAs
Aripiprazole. The pharmacological mechanism of action of aripiprazole is somewhat different from all other SGAs in that it provides partial agonism at dopaminergic receptors. This partial agonistic effect decreases neuronal transmission in areas of hyperdopaminergic activity and increases neuronal transmission in areas of hypodopaminergic activity (Mailman, Murthy 2010). Aripiprazole has high affinity for the dopamine D2 and D3 receptors and moderate affinity for D4 receptors. Partial agonism occurs with the D2 receptors.
Clozapine. Clozapine was the first SGA to have been used widely in the clinic (Crilly 2007). It has moderate-to-low affinity for D1 receptors, low affinity for D2 and D3 receptors, but high affinity for D4 receptors (Ashby, Wang 1996). Clozapine has been shown to possess high affinity to both 5-HT2A and 5-HT2C receptors and moderate affinity to 5-HT3 receptors. Clozapine is unique among SGAs because it is known to be beneficial in patients with treatment resistant schizophrenia, and for persistent psychotic symptoms for which other antipsychotic agents have proven ineffective (Meltzer 2013).
Risperidone. Similar to other SGAs, it occupies more than 80% of cortical 5-

Appendix II: Mechanism of action of common SGAs
HT2A receptors and over 70% of D2 receptors at therapeutic dosages (Miyamoto, et al. 2005).
Quetiapine. The pharmacological mechanism of action of quetiapine is slightly different than other SGAs. Quetiapine exhibits weaker antagonistic effects at dopamine D2 and serotonin 5-HT2 receptors, stronger antagonistic effects at alpha-1 receptors, and modest histaminergic effects (Nasrallah 2008). This combination of receptor antagonism is thought to be responsible for its therapeutic effects and low risk of EPS.
Olanazpine. Like other SGAs, olanzapine produces antipsychotic effects through the antagonism of dopamine at D2 receptors and serotonin at 5-HT2A receptors (Kantrowitz, Citrome 2008). In addition, olanzapine also has antagonistic effects at 5HT-2C, 5HT3, 5HT6. D1-4, histamine H1, alpha1-adrenoreceptors, GABAa, beta-adrenoreceptors, and muscarinic M1-5 receptors (ibid). Olanzapine's effects at these other receptors have been hypothesized to be responsible for its adverse effects (ibid). Studies have indicated that olanzapine may be associated with significant pharmacokinetic inter-individual variability, due to induction and inhibition of its primary metabolizing enzyme CYP1A2. One study found that patients who smoked cleared olanzapine 55% faster than nonsmokers, men cleared olanzapine 38% faster than women, and black patients cleared olanzapine 26% faster than other ethnicities (Bigos, et al. 2008).
Ziprasidone. Ziprasidone is a newer SGA that has pharmacological properties distinct from other SGAs. Ziprasidone is understood to have high affinity for 5-

Appendix II: Mechanism of action of common SGAs
HT2A, 5-HT2C, 5-HT1A and 5-HT1B and 1D receptors (Schmidt et. al., 2001). Ziprasidone is also understood to possess high affinity for D2 receptors (Stahl, Shayegan 2003).

Appendix II: Consent form

If you are a parent or legal guardian of a child who may take part in this study, permission from you and the assent (agreement) of your child may be required. When we say "you" or "your" in this consent form, we mean you and/or your child; "we" means the doctors and other staff.

1. INVITATION

You are being invited to take part in this research study because you are being seen by one of the psychiatrists within the Mental Health Program in one of the Child and Adolescent Psychiatric Units at British Columbia's Children's Hospital, or in the Vancouver/Richmond EPI Early Psychosis Intervention Clinic on East Hastings Street in Vancouver (EPI Clinic).

We are asking male or female subjects who are at least 12 years old who are healthy or who have first-episode bipolar disorder, to take part in the study, as well as subjects who are at least 15 years old and who have first-episode psychosis. In addition, subjects with bipolar disorder or psychosis must be taking "aripiprazole" (ABILIFY®), "risperidone" (Risperdal®) or "quetiapine" (Seroquel®) for treatment.

2. YOUR PARTICIPATION IS VOLUNTARY

Your participation is voluntary. You have the right to refuse to participate in this study. If you decide to participate, you may still choose to withdraw from the study at any time without any negative consequences to the medical care, education, or other services to which you are entitled or are presently receiving.

Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts.

You also need to know that there are important differences between being in a research study and being cared for by your family doctor or psychiatrist. When you participate in a research study, the main goal is to learn things to help other patients in the future. Outside a research study, your doctor's sole goal is to care for your health. Nevertheless, the scientists have a duty of care to all subjects and will inform you of any information that may affect your willingness to remain in the study.

If you wish to participate in this study, you will be asked to sign this form. If you do decide to take part in this study, you are still free to withdraw from the study at any time and without giving any reasons for your decision.

If you do not wish participate, you do not have to provide any reason for your decision nor will you lose the benefit of any medical care to which you are entitled or are

presently receiving. Please take time to read the following information carefully and to discuss it with your family, friends, and psychiatrist before you decide.

3. WHO IS CONDUCTING THE STUDY?

This study is an investigator-driven study conducted by Drs. Barr and Kopala from the University of British Columbia (UBC). The Principal Investigators have received financial compensation from Bristol Myers Squibb (BMS) for the work required to do this clinical research. Bristol Myers Squibb is the company that produces ABILIFY® ("aripiprazole").

4. BACKGROUND

Fifteen percent of BC's youth suffer from psychiatric disorders; many of these individuals will be treated with atypical antipsychotics, such as "aripiprazole" (ABILIFY®), "risperidone" (Risperidal®) or "quetiapine" (Seroquel®). Over the past few years, prescription of atypical antipsychotics to youth has increased substantially with little evaluation of the potential side effects these medications may have on individuals who are still growing and developing. In adults, atypical antipsychotics have been shown to cause significant weight gain and other biological changes, leading to an increased risk of type 2 diabetes. Importantly, nothing is known about how atypical antipsychotics affect the storage of fat in the body: some fat ("subcutaneous", i.e. the fat just under the skin) is considered less harmful than other types of fat ("visceral", i.e. the fat that surrounds the internal organs). Also, it is uncertain whether all atypical antipsychotics affect fat storage in the same way. This will be the *first ever* study to use MRI to look at the levels and distribution of fat in subjects taking aripiprazole.

A total of 60 subjects with first-episode psychosis or first-episode bipolar disorder will be recruited for the study. In addition, another 30 healthy subjects will also be recruited as study controls. Recruitment will take place at BC Children's Hospital, as well as from the Vancouver/Richmond EPI Early Psychosis Intervention clinic on East Hastings Street in Vancouver, British Columbia (EPI Clinic).

5. WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to determine if treatment with the antipsychotic medications aripiprazole, risperidone or quetiapine causes an increase in both types of fat in the abdomen, or whether one type of fat or the other is more affected. We will also determine if these atypical (otherwise known as 'second generation') antipsychotics cause an increase in liver fat content, as this could increase the risk of developing type 2 diabetes in the future.

We are also interested in comparing the levels of glucose, cholesterol, fats, and hormones in our subjects' blood to see if there are any differences depending on what medication you are taking. Finally, we will be gathering information on mental health,

physical growth, eating behaviours and activity levels to see if we can observe between subjects taking aripiprazole, risperidone, or quetiapine, and subjects who are not taking any antipsychotics.

6. WHO CAN PARTICIPATE IN THIS STUDY?

You may be able to participate in this study if you:

- Are male or female
- Have bipolar disorder and you are at least 12 years old; or if you are healthy and you are at least 12 years old; or if you are at least 15 years old and have psychosis
- Have recently been admitted to the hospital or community care for first-episode psychosis or for first-episode bipolar, or if you are completely healthy
- Are taking aripiprazole, risperidone, quetiapine, olanzapine, or paliperidone principally for psychosis or bipolar.
- Have received no more than 6 months lifetime total of treatment with antipsychotic medication at the time of consent.

7. WHO SHOULD NOT PARTICIPATE IN THE STUDY?

You cannot participate in this study if you:

- Have diabetes mellitus, seizure disorders, mental retardation (IQ <70), or pregnancy (current or within 3 months postpartum). Because we do not know if or how an unborn baby/fetus could be harmed, you should avoid becoming pregnant. Talk to your study family doctor or psychiatrist about the risks to your unborn baby/fetus if you do get pregnant. Work with the study doctor to find the best solution to make sure you do not get pregnant, if you wish to be in the study.
- Received chemotherapy in the 4 weeks prior to baseline or 16-week follow-up interview.
- Are not able to fluently communicate in English.
- Have any of the criteria that exclude you from having an MRI scan (i.e., if you have had major surgery in the last 6 months, are morbidly obese, have claustrophobia, have metal in your body from a surgical intervention or from doing metalwork, are experiencing fever/dizziness/nausea/coughing/agitation, or have uncontrolled seizures).

8. WHAT DOES THE STUDY INVOLVE?

If you decide to take part in this study, you may be in one of three groups: the aripiprazole group, the risperidone/quetiapine/olanzapine/paliperidone group, or the control (healthy) group. Which group you belong to will depend on what type of medication your psychiatrist has prescribed for you.

Overview of the Study

If you are taking antipsychotics, you will need to come to 4 study visits. All of these appointments will take place at UBC Hospital. The first 2 visits will occur approximately 10 days apart, followed by a 3 month period where there will be no visits, and then you will have your third visit, and approximately 10 days after that, your fourth visit. During the 3 month period where there will be no visits, you will receive one telephone call each month and we will be asking you some questions about your eating habits, exercise level, and general health. For the first and third study visit, you will need to come to UBC Hospital in the morning to have your weight, height, blood pressure and heart rate measured, have an MRI scan, get some blood taken, and answer some questionnaires. These visits will take no more than 4 hours each to complete. One of the things you will be asked to do in preparation for these visits is to eat at least 150 grams of carbohydrates a day for the 3 days prior to your first and third visits **without increasing your total calorie intake** (this means you may have to cut back on the amount of fat in your food by an equivalent amount). This is approximately equal to one portion of pasta, plus a bowl of breakfast cereal, plus a sub sandwich every day for 3 days. We also ask that you maintain your regular level of activity, but refrain from heavy exercise, smoking or drinking alcohol. The reason we ask you to do this is to prepare you for one of the blood tests that we will be doing. **However, you do not have to do this if this is too challenging.** On the second and fourth visits, we will be evaluating your mental health by asking you some more questions. These visits may take place at UBC Hospital, but it is also possible to meet you in a private location of your choice (such as your home), and will take between 3 to 4 hours each.

If you are a healthy individual, we will ask you to come to UBC Hospital for the <u>first and third visit only</u>. At these two visits, we will take your weight, height, blood pressure and heart rate, give you an MRI scan, take some blood, and ask you some questionnaires. These two visits will take approximately 4 hours each to complete. You will not be required to come to the second and fourth visits because these assessments only apply to people with mental health conditions.

We also ask that you allow us to access your Pharmanet records. Pharmanet is a computer-based electronic record of all the prescriptions that you have filled through a pharmacy. The reason we ask for your permission to look at your Pharmanet records is so that we may gather accurate data on the medications that you have taken over the past year to see if any of these other medications affect weight gain.

Descriptions of Each Visit

<u>First Visit</u>:
Everyone comes to this first study visit. For the first study visit, you will start the day by receiving a magnetic resonance imaging (MRI) scan, which will last approximately 45

minutes. The MRI scan will help us to measure the effects of atypical antipsychotics on fat in your abdomen by obtaining a three dimensional image of the inside of your abdomen. MRI scans are completely non-invasive and work by use of powerful magnets, so they do not involve exposure to radiation or x-rays. **However**, if you have ever worked with metal (e.g., welding, metalworking) and/or you suspect the presence of metal in your eye, you will be required to complete an orbital x-ray (x-ray for your eyes). The x-ray will help us to determine whether or not it is safe for us to perform an MRI scan. If an orbital x-ray is required, it will be done in the same building as the MRI scan. The MRI scan itself occurs in a small space (approximately 1 metre in width) and the scanner generates a loud sound when it is active. You will be provided with ear protection during your scan. If you suffer from a fear of small spaces you may find the MRI scan uncomfortable, however you will not suffer any harm as a result of this scan.

After your scan, you will be taken to get your blood drawn for some blood tests. Please note that if you are female, we will also ask you to do a urine (pee) pregnancy test. We will take no more than 2 teaspoons (8 mL) of blood to measure for sugars, fats, cholesterol, and hormones. We will also perform a blood test on you called an oral glucose tolerance test. For this test, you will need to drink a sugary beverage that is made from sugar, water, and flavoring. We will be taking blood from your once before you drink the beverage, and once 2 hours later. This test will require 1 mL of blood. Thus, this means that in total, we will take no more than 2 teaspoons (9 mL) of blood for the first visit.

During the oral glucose tolerance test, while you are waiting for the 2 hours to pass, we will ask you to answer 4 or 5 questionnaires about your physical growth, your medications, your eating behaviour and your daily activity levels. One of these questionnaires will be 'self-reported' (meaning that you will read the questionnaire yourself and write in your answer); but the rest will be verbally asked to you by the Research Coordinator. You are not required to answer any question that you are uncomfortable answering.

The entire visit will last approximately 4 hours.

<u>Second Visit</u>:
People who are taking antipsychotic medications will be asked to come for a second study visit about 1 week after the first visit. This visit will also be at UBC Hospital, or it can be at a private location that is convenient for you (such as your home). For the second visit, we will ask you some questions to evaluate your mental health. The entire visit will last approximately 4 hours.

<u>Telephone Interviews (once a month for 3 months)</u>:
After these visits, there will be 3 months where you will not be required to come in for the study. However, for each of these months, you will receive a telephone call from the Research Coordinator, and she will be asking you the same questionnaires that you

answered at your first visit about your medications, your eating behaviour and your daily activity levels. In other words, you will be completing 3 telephone interviews between your visits (i.e., 1 month after first visit, 2 months after first visit, and 3 months after first visit; at 4 months after first visit, you will come in for your second visit). Each call will last no more than 30 minutes.

Third Visit:
A third visit will be scheduled 4 months (or 16 weeks) after the first visit. Again, everyone will come to UBC Hospital for this third visit. If you are a healthy volunteer, this will be the last visit you will have to make for the study. Everyone will repeat all of the same procedures that you were asked to do for the first visit (MRI scan, blood tests, questionnaires). The only difference is that for the third visit, we will take 1 additional teaspoon of blood (for a total of 3 teaspoons, or 16 mL) from people who are taking antipsychotic medications to measure for the levels of medication in your blood.

If you wish, there will also be an optional blood test that anyone may receive during your third visit that involves taking another 1 teaspoon of blood (6 mL) from your arm to look for potential genes that may play a role in antipsychotic-induced weight gain. There is a separate consent form for this part of the study if you wish to participate.

Fourth Visit:
For people who are taking antipsychotic medications, this is the last visit you will have to make to UBC Hospital (or this meeting can also occur at a private location of your choice). This visit will be scheduled 1 week after your third visit. Like the second visit, we will ask you some questions to evaluate your mental health. This visit will be shorter than the second visit and will last about 3 hours.

If You Decide to Join This Study: Specific Procedures

Study Visit	When?	Who Comes?	Preparing for the Visit	What We Do at This Visit…	Visit Location	Visit Length
First Visit	Week 0	• Subjects who are taking antipsychotics • Healthy subjects	Eat at least 150 grams of carbs for 3 days; fast for 12 hours before your visit	• Measure weight, height, blood pressure, heart rate • Take 2 teaspoons of blood (including glucose tolerance test) • Urine pregnancy test for females • Questionnaires ○ Three-Factor Eating Questionnaire(TFEQ) ○ Schematic Tanner Scale ○ Short-Form 36 (SF-36) ○ International Physical Activity Questionnaire (IPAQ) • MRI scan (45-60 min)	UBC Hospital	4 hours
Second Visit	< 10 days after First Visit	• Subjects taking antipsychotics	None	• Mental health assessments ○ Mini International Neuropsychiatric Interview for Children and Adolescents (MINI KID) ○ Positive and Negative Syndrome Scale (PANSS) for psychosis, or the Young Mania Rating Scale (Y-MRS) for bipolar ○ Social and Occupational Functioning Scale (SOFAS) ○ Calgary Depression Scale (CDS)	UBC Hospital, or a private location of your choice	4 hours
Telephone Interviews	Once a month after First Visit, for a total of 3 phone calls	• Subjects who are taking antipsychotics • Healthy subjects	None	• Questionnaires ○ TFEQ ○ SF-36 ○ IPAQ ○ MARS (for subjects taking antipsychotics)	Phone call	30 minutes each
Third Visit	4 months after first visit	• Subjects who are taking antipsychotics • Healthy subjects (*last visit*)	Eat at least 150 grams of carbs for 3 days; fast for 12 hours before your visit	• Measure weight, height, blood pressure, heart rate • Take 2 teaspoons of blood from healthy subjects; 3 teaspoons of blood from subjects who are taking antipsychotics (including glucose tolerance test) • Urine pregnancy test for females • Questionnaires ○ TFEQ ○ SF-36 ○ Schematic Tanner Scale ○ IPAQ ○ MARS (for subjects taking antipsychotics only) • MRI scan (approximately 45-60 min)	UBC Hospital	4 hours
Fourth Visit	< 10 days after Third Visit	• Subjects who are taking antipsychotics (*last visit*)	None	• Mental health assessments ○ PANSS/Y-MRS ○ SOFAS ○ CDS	UBC Hospital, or a private location of your choice	3 hours

Optional Blood Collection for Genetic Testing and Biobanking

There is an optional part of the study that will also be available to you. You do not have to do this optional part of the study in order to be a part of this main study. This optional part of the study involves taking some blood and storing it for genetic testing. You will be provided with a separate consent form for this optional study that describes the details to you. You will be required to sign this separate consent form if you wish to participate in the optional study. If you decide not to take part in the optional study your care will not be affected.

Please refer to the separate consent form for details regarding this part of the study.

9. WHAT ARE MY RESPONSIBILITIES?

We ask that all subjects who agree to participate try their best to make it to their study visits and complete the telephone interviews between visits. If you consent to the study and you take antipsychotic medications, you should take the medications prescribed to you by your psychiatrist(s).

In addition, we ask that you do your best to avoid pregnancy by taking the necessary birth control precautions or by abstaining for the duration of your participation in the study.

10. WHAT ARE THE POSSIBLE HARMS AND DISCOMFORTS?

Medications

The scientists will not be giving any subjects any experimental medications or drugs for you to take. If you have a mental health condition, the only medications you will be taking will be the ones that your psychiatrist has prescribed. The risks and side-effects of these usual treatments for first-episode psychosis or bipolar disorder will be explained to you by your psychiatrist as part of your standard care**.** If you experience any discomfort or side-effects from your medications, you should immediately contact your psychiatrist. The care that you receive from your psychiatrist will remain the same, regardless of whether or not you decide to do the study.

If your doctor has prescribed aripiprazole, and you experience an adverse event or *serious* adverse event which may or may not be related to taking aripiprazole, we are obligated to report this problem to our financial supporter, BMS Canada.

Blood Tests

The amount of blood that we will be taking in this study is well below the safe amount of blood loss for human beings. However, some people may be uncomfortable with needles and/or the sight of blood. The main risk of getting a blood test is pain or

bruising in the arm where the needle is inserted. This is usually minor, and the bruising goes away shortly after the procedure.

Urine Pregnancy Test

All female subjects will have a urine pregnancy test before performing the MRI scans. Because the effects of MRI scanning on an unborn child are not fully understood, we want to avoid performing an MRI scan on you if you are pregnant. If you find out that you are unexpectedly pregnant, it may potentially be psychologically or emotionally difficult for you to inform your partner or your family, and it may be difficult deciding what to do. Ask the study doctor or Research Coordinator about counselling and more information on pregnancy crises services if you require help, and we will provide you with the appropriate contact information. In addition, we will encourage you to contact your primary care physician. If you become pregnant while you are on this study, you should notify the study doctors.

Psychiatric Testing and Questionnaires

Some of the questionnaires that we will be doing with you will ask personal information that you may not feel like sharing with us. If you are not happy with sharing this information, you do not have to answer.

MRI Scan

The MRI scan is a well-established and safe procedure, with no major side-effects. The scan requires lying still for between 45-60 minutes. About 1 in 100 people will feel anxious or claustrophobic (a feeling of fear when in a closed or narrow space) during the scan. You will be asked questions prior to the scan regarding any metal you may have in your body. If you are unsure, you will have to be discontinued from the study. If you have metal in your body, the MRI scan is dangerous and cannot be done in this situation.

Orbital X-Ray

If you have done any metalworking in the past, you will require an x-ray for your eyes before going into the MRI scanner. This will be done using a very low level of radiation. You will be exposed to x-rays for only a few seconds. There is always a slight risk of damage to your cells/tissues from being exposed to radiation, even at the low levels required for this x-ray. The entire x-ray procedure will take no more than 10-15 minutes.

11. WHAT ARE THE POTENTIAL BENEFITS OF PARTICIPATING?

Benefits to You

No one knows whether or not you will benefit from this study. There may or may not be direct benefits to you from taking part in this study. One potential benefit is that you can receive a copy of your MRI scans on a CD at the end of the study. However, *a radiologist will not be reviewing your MRI scan*, which means that we will not be

diagnosing any new medical conditions, and we will not be telling you the 'results' of your MRI scan. The scans are for research purposes only.

Benefits to Others

We hope that the information learned from this study can be used in the future to benefit other people with a similar condition. The results of this study will help scientists understand how antipsychotics affect obesity, and if certain medications are worse than others. In the future, the results of this study may help psychiatrists to use antipsychotics to treat patients more effectively.

12. WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

Your participation in this research is entirely voluntary. You may withdraw from this study at any time without giving reasons – just let us know. If you decide to withdraw at any time in the future, there will be no penalty or loss of benefits to which you are otherwise entitled, and your future medical care will not be affected. **However, if you decide to drop out, we ask that you come in to complete all the procedures of the THIRD VISIT (i.e., blood tests, questionnaires, MRI scan) before you leave, if possible**.

If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during the study will be retained for analysis. By law, this data cannot be destroyed.

You will also be advised of any new information that becomes available that may affect your willingness to remain in this study.

13. CAN I BE ASKED TO LEAVE THE STUDY?

If you are not able to follow the requirements of the study or for any other reason, the scientists may take you out of the study and will arrange for your medical care to continue. You may also be withdrawn from the study at any time if your psychiatrist feels that it is in your best interests to do so, or if they feel that it would be better for your health.

14. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Your and your child's or your ward's confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of Health Canada, or the University of British Columbia's Research Ethics Board, for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a subject in this study. Only this number will be used on any research-related information collected about you during the course of this study, so that your identity (i.e. your name or any other information that could identify you) as a subject in this study will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

Primary Care Physican(s) /Specialist(s) Notification
Please indicate, by checking the applicable box, whether you want us to notify your primary care physician(s) or specialist(s) of your participation in this study. *This is not a consent to release medical information.*

___Yes, I want the study investigator to advise my primary care physician(s) or specialist(s) of my participation in this study. My primary care physician(s) and/or specialist(s) name(s) is/are: _____

The name of the medical clinic I attend is: _____

Subject Initials: _____

____No, I do not want the study investigator to advise my primary care physician(s) or specialist(s) of my participation in this study.
Subject Initials: _____

____I do not have a primary care physician or specialist.
Subject Initials: _____

I understand that if I choose not to advise my primary care physician(s) or specialist(s) of my participation in this study, there may be potential medical consequences which may affect my comprehensive medical care or treatment. I understand that the study investigator may not be responsible for these consequences.

You may wish to discuss the consequences of your decision with the study staff.

Disclosure of Race/Ethnicity

Studies involving humans now routinely collect information on race and ethnic origin as well as other characteristics of individuals because these characteristics may influence how people respond to different medications. Providing information on your race or ethnic origin is voluntary.

15. WHAT IF SOMETHING GOES WRONG?

Signing this consent form in no way limits your, or your child's, or your ward's, legal rights against the sponsor, investigators, or anyone else, and you do not release the study doctors or participating institutions from their legal and professional responsibilities.

16. AFTER THE STUDY IS FINISHED

The results of the study will be presented at medical conferences, and will be published in medical journals, but you will not be named in these presentations or publications.

Future Contact

We would like to be able to contact you in the future to let you know about our other studies that require participants. Please let us know below if you are interested in hearing about our future studies:

☐ Yes ☐ No

17. WHAT WILL THE STUDY COST ME?

Costs

You may need to cover the costs of commuting to UBC Hospital when you come in for your visits, which might include gas costs, or transit costs. However, if you drive to the hospital, we will reimburse your parking fees.

Honorariums

All subjects will receive an honorarium of $75 CAD at the end of the first visit, and at the end of your third visit. For subjects who are taking antipsychotics, you will also receive $50 CAD at the end of your second visit, and at the end of your fourth visit (healthy volunteers do not come to these visits; thus, they will not receive these honorariums). All subjects will also receive with an honorarium for each of the three

telephone interviews completed between visits ($10 CAD for first month, $10 CAD for the second month, and $15 CAD for the third month). These payments will be prorated if you withdraw from the study.

18. WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?

If you have any questions or desire further information about this study before or during participation, or if you experience any adverse effects, you can contact Dr. Alasdair Barr at any time at the numbers listed in the title page.

Or, you can speak to one of the Research Assistants, Delrae Fawcett or Heidi Boyda, at any time at the numbers listed in the title page.

19. WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A SUBJECT?

If you have any concerns or complaints about your rights as a research subject and/or your experiences while participating in this study, contact the Research Subject Information Line in the University of British Columbia Office of Research Services by e-mail at RSIL@ors.ubc.ca or by phone at 604-822-8598 (Toll Free: 1-877-822-8598).**A Longitudinal Comparison of Aripiprazole versus Higher Metabolic Risk Antipsychotic Drugs on Adiposity Using MRI (The CALM Study)**

Principal Investigators: Dr. Alasdair Barr, Assistant Professor; Dr. Lili Kopala, Psychiatrist

Subject Consent

- I have read and understood the subject information and consent form.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific objectives.
- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or withdraw from this study at any time without changing the quality of care that I receive.
- I authorize access to my medical record, Pharmanet record, and blood samples as described in this consent form.
- I understand that I am not waiving any of my legal rights by signing this consent form.
- I understand that there is no guarantee that this study will provide any benefits.
- I understand that I will be receiving MRI scans.

The parent(s)/guardian(s)/substitute decision-maker (legally authorized representative) and the investigator are satisfied that the information contained in this consent form was explained to the child/subject to the extent that he/she is able to understand it, that all questions have been answered, and that the child/subject assents to participating in the research.

I will receive a signed copy of this consent form for my own records.
I consent to participate in this study.

Participant/Parent/Guardian Signature Printed Name
Date

Signature of Person Obtaining Consent Printed name Study Role Date

---

Investigator Signature Printed name
Date

Investigator: My signature above signifies that the study has been reviewed with the study subject by me and/or by my delegated staff. My signature may have been added at a later date, as I may not have been present at the time the subject's signature was obtained.

Appendix III: Short Form 36 (SF-36)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

For each of the following questions, please mark an ✕ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very Good	Good	Fair	Poor
☐	☐	☐	☐	☐

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐	☐	☐	☐	☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports…	☐	☐	☐
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf…	☐	☐	☐
c. Lifting or carrying groceries…	☐	☐	☐
d. Climbing several flights of stairs…	☐	☐	☐
e. Climbing one flight of stairs…	☐	☐	☐
f. Bending, kneeling, or stooping…	☐	☐	☐
g. Walking more than a mile…	☐	☐	☐
h. Walking several hundred yards…	☐	☐	☐
i. Walking one hundred yards…	☐	☐	☐
j. Bathing or dressing yourself…	☐	☐	☐

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities…	☐	☐	☐	☐	☐
b. Accomplished less than you would like…	☐	☐	☐	☐	☐
c. Were limited in the kind or work or other activities…	☐	☐	☐	☐	☐
d. Had difficulty performing the work or other activities (for example, it took extra effort)…	☐	☐	☐	☐	☐

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities…	☐	☐	☐	☐	☐
b. Accomplished less than you would like…	☐	☐	☐	☐	☐
c. Did work or other activities less carefully than usual…	☐	☐	☐	☐	☐

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Did you feel full of life?	☐	☐	☐	☐	☐
Have you been very nervous?	☐	☐	☐	☐	☐
Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐
Have you felt calm and peaceful?	☐	☐	☐	☐	☐
Did you have a lot of energy?	☐	☐	☐	☐	☐
Have you felt downhearted and depressed?	☐	☐	☐	☐	☐
Did you feel worn out?	☐	☐	☐	☐	☐
Have you been happy?	☐	☐	☐	☐	☐
Did you feel tired?	☐	☐	☐	☐	☐

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most off the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false

I seem to get sick a little easier than other people.	☐	☐	☐	☐	☐
I am as healthy as anybody I know.	☐	☐	☐	☐	☐
I expect my health to get worse.	☐	☐	☐	☐	☐
My health is excellent.	☐	☐	☐	☐	☐

Comments:

_____
_____
_____
_____

Appendix IV: International Physical Activity Questionnaire (IPAQ)

READ: I am going to ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise, or sport.

READ: Now, think about all the *vigorous* activities which take *hard physical effort* that you did in the last 7 days. Vigorous activities make you breathe much harder than normal and may include heavy lifting, digging, aerobics, or fast bicycling. Think only about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities?
_____Days per week [range 0-7, 8, 9]
8. Don't know/Not sure
9. Refused

[**Interviewer clarification**: Think only about those physical activities that you do for at least 10 minutes at a time.]

[**Interviewer note**: If respondent answers zero, refuses, or does not know, skip to Question 3.]

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?
_____Hours per day [range 0-16]
_____Minutes per day [range 0-960, 998, 999]
998. Don't know/Not sure
999. Refused

[**Interviewer clarification**: Think only about those physical activities you do for at least 10 minutes at a time.]

[**Interviewer probe**: An average time for one of the days on which you do vigorous activity is being sought. If the respondent can't answer because the pattern of time spent varies widely from day to day, ask: "How much time in total would you spend over the last 7 days doing vigorous physical activities?"

_____Hours per week [range 0-112]
_____Minutes per week [range 0-6720, 9998, 9999]
9998. Don't know/Not sure
9999. Refused]

READ: Now think about activities which take *moderate physical effort* that you did in the last 7 days. Moderate physical activities make you breathe somewhat harder than normal and may include carrying light loads, bicycling at a regular pace, or doubles tennis. Do not include walking. Again, think about only those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities?
_____Days per week [range 0-7, 8, 9]

8. Don't know/Not sure
9. Refused

[**Interviewer clarification**: Think only about those physical activities that you do for at least 10 minutes at a time.]

[**Interviewer note:** *If respondent answers zero,* refuses, or does not know, skip to Question 5.]

How much time did you usually spend doing **moderate** physical activities on one of those days?
_____Hours per day [range 0-16]
_____Minutes per day [range 0-960, 998, 999]
998. Don't know/Not sure
999. Refused

[**Interviewer clarification**: Think only about those physical activities that you do for at least 10 minutes at a time.]

[**Interviewer probe**: An average time for one of the days on which you do moderate activity is being sought. If the respondent can't answer because the pattern of time spent varies widely from day to day, or time spent in multiple jobs, ask: "How much time in total would you spend over the last 7 days doing moderate physical activities?"

_____Hours per week [range 0-112]
_____Minutes per week [range 0-6720, 9998, 9999]
9998. Don't know/Not sure
9999. Refused]

READ: Now think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

During the last **7 days** how many days did you **walk** for at least 10 minutes at a time?
_____Days per week [range 0-7, 8, 9]
8. Don't know/Not sure
9. Refused

[**Interviewer clarification**: Think only about those physical activities that you do for at least 10 minutes at a time.]

[**Interviewer note**: If respondent answers zero, refuses, or does not know, skip to Question 7.]

How much time did you usually spend **walking** on one of those days?
_____Hours per day [range 0-16]
_____Minutes per day [range 0-960, 998, 999]
998. Don't know/Not sure
999. Refused

[**Interviewer probe**: An average time for one of the days on which you do moderate activity is being sought. If the respondent can't answer because the pattern of time spent

varies widely from day to day, ask: “What is the total amount of time you spent walking over the last 7 days?”

_____Hours per week [range 0-112]
_____Minutes per week [range 0-6720, 9998, 9999]
9998. Don’t know/Not sure
9999. Refused]

READ: Now think about the time you spent sitting on week days during the last 7 days. Include time spent at work, at home, while doing course work, and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television.

During the last **7 days** how many days did you spend **sitting** on a week day?
_____Hours per week day [range 0-16]
_____Minutes per week day [range 0-960, 998, 999]
998. Don’t know/Not sure
999. Refused

[**Interviewer clarification:** Include time spent lying down (awake) as well as sitting.]

[**Interviewer probe**: An average time per day spent sitting is being sought. If the respondent can’t answer because the pattern of time spent varies widely from day to day, ask: “What is the total amount of time you spent sitting last Wednesday?”

_____Hours on Wednesday [range 0-16]
_____Minutes on Wednesday [range 0-960, 998, 999]
998. Don’t know/Not sure
999. Refused]

Appendix V: Three Factor Eating Questionnaire (TFEQ)

One point may be given to each item in Parts I and II.

The response that scores a point is underlined in Part I (either true/false), and the corresponding Factor that is measured by each item in Part I is located beside the question.

For Part II, points are scored by splitting the responses down the middle. If the question is labeled '+', then responses above the middle (i.e., 3 or 4) are given a 0, and responses below the middle (i.e., 1 or 2) are given a 1. The corresponding Factor that is measured by each item is located beside the question.

Part I

				Factor Number
1.	When I smell a sizzling steak or see a juicy piece of meat, I find it very difficult to keep from eating, even if I have just finished a meal.	T	F	2
2.	I usually eat too much at social occasions, like parties and picnics.	T	F	2
3.	I am usually so hungry that I eat more than three times a day.	T	F	3
4.	When I have eaten my quota of calories, I am usually good about not eating any more.	T	F	1
5.	Dieting is so hard for me because I just get too hungry.	T	F	3
6.	I deliberately take small helpings as a means of controlling my weight.	T	F	1
7.	Sometimes things just taste so good that I keep on eating even when I am no longer hungry.	T	F	2
8.	Since I am often hungry, I sometimes wish that while I am eating, an expert would tell me that I have had enough or that I can have something more to eat.	T	F	3
9.	When I feel anxious, I find myself eating.	T	F	2
10.	Life is too short to worry about dieting.	T	F	1
11.	Since my weight goes up and down, I have gone on reducing diets more than once.	T	F	2
12.	I often feel so hungry that I just have to eat something.	T	F	2
13.	When I am with someone who is overeating, I usually overeat too.	T	F	3
14.	I have a pretty good idea of the number of calories in common food.	T	F	1
15.	Sometimes when I start eating, I just can't	T	F	2

seem to stop.			
16. It is not difficult for me to leave something on my plate.	T	F	2
17. At certain times of the day, I get hungry because I have gotten used to eating then.	T	F	3
18. While on a diet, if I eat food that is not allowed, I consciously eat less for a period of time to make up for it.	T	F	1
19. Being with someone who is eating often makes me hungry enough to eat also.	T	F	3
20. When I feel blue, I often overeat.	T	F	2
21. I enjoy eating too much to spoil it by counting calories or watching my weight.	T	F	1
22. When I see a real delicacy, I often get so hungry that I have to eat right away.	T	F	3
23. I often stop eating when I am not really full as a conscious means of limiting the amount that I eat.	T	F	1
24. I get so hungry that my stomach often seems like a bottomless pit.	T	F	3
25. My weight has hardly changed at all in the last ten years.	T	F	2
26. I am always hungry so it is hard for me to stop eating before I finish the food on my plate.	T	F	3
27. When I feel lonely, I console myself my eating.	T	F	2
28. I consciously hold back at meals in order not to gain weight.	T	F	1
29. I sometimes get very hungry late in the evening or at night.	T	F	3
30. I eat anything I want, any time I want.	T	F	1
31. Without even thinking about it, I take a long time to eat.	T	F	2
32. I count calories as a conscious means of controlling my weight.	T	F	1
33. I do not eat some foods because they make me fat.	T	F	1
34. I am always hungry enough to eat at any time.	T	F	3
35. I pay a great deal of attention to changes in my figure.	T	F	1
36. While on a diet, if I eat a food that is not allowed, I often then splurge and eat other high calorie foods.	T	F	2

Part II

Directions: Please answer the following questions by circling the number above the response that is appropriate to you.

Factor Number

37. How often are you dieting in a conscious effort to control your weight?

1	2	3	4	
Rarely	Sometimes	Usually	Always	+1

38. Would a weight fluctuation of 5 lbs affect the way you live your life?

1	2	3	4	
Not at all	Slightly	Moderately	Very much	+1

39. How often do you feel hungry?

1	2	3	4	
Only at mealtimes	Sometimes between meals	Often between meals	Almost always	+3

40. Do your feelings of guilt about overeating help you to control your food intake?

1	2	3	4	
Never	Rarely	Often	Always	+1

41. How difficult would it be for you to stop eating halfway through dinner and not eat for the next four hours?

1	2	3	4	
Easy	Slightly difficult	Moderately difficult	Very difficult	+3

42. How conscious are you of what you are eating?

1	2	3	4	
Not at all	Slightly	Moderately	Extremely	+1

43. How frequently do you avoid 'stocking up' on tempting foods?

1	2	3	4	
Almost never	Seldom	Usually	Almost always	+1

44. How likely are you to shop for low calorie foods?

1	2	3	4	
Unlikely	Slightly unlikely	Moderately likely	Very likely	+1

45. Do you eat sensibly in front of others and splurge alone?

1	2	3	4	
Never	Rarely	Often	Always	+2

46. How likely are you to consciously eat slowly in order to cut down on how much you eat?

1	2	3	4	
Unlikely	Slightly unlikely	Moderately likely	Very likely	+1

47. How frequently do you skip dessert because you are no longer hungry?

1	2	3	4	
Almost never	Seldom	At least once a week	Almost every day	-3

48. How likely are you to consciously eat less than you want?

1	2	3	4	
Unlikely	Slightly unlikely	Moderately likely	Very likely	+1

49. Do you go on eating binges though you are not hungry?

1	2	3	4	
Never	Rarely	Sometimes	At least once a week	+2

50. On a scale of 0 to 5, where 0 means no restraint in eating (eating whatever you want, whenever you want it) and 5 means total restraint (constantly limiting food intake and never 'giving in'), what number would you give yourself?

0 +1
Eat whatever you want, whenever you want it

1
Usually eat whatever you want, whenever you want it

2
Often eat whatever you want, whenever you want it

3
Often limit food intake, but often 'give in'

4
Usually limit food intake, rarely 'give in'

5
Constantly limiting food intake, never 'giving in'

51. To what extent does this statement describe your eating behaviour? 'I start dieting in the morning, but because of any number of things that happen during the day, by evening I have given up and eat what I want, promising myself to start dieting again tomorrow.'

1	2	3	4	
Not like me	Little like me	Pretty good description of me	Describes me perfectly	+2

Appendix VI: Medication Adherence rating Scale (MARS)

How closely you adhere to your medication plan affects the progression and outcome of your psychosis. The Medication Adherence Rating Scale (MARS) is a self-report measure of medication adherence in psychosis. Use the MARS tool to determine your willingness and ability to take oral medication every day.

For scoring purposes, answers that are assigned 1 point are filled in.

	Yes	No
1. Do you ever forget to take your medication?	☐	☐
2. Are you careless at times about taking your medicine?	☐	☐
3. When you feel better, do you sometimes stop taking your medicine?	☐	☐
4. Sometimes if you feel worse when you take the medicine, do you stop taking it?	☐	☐
5. I take my medication only when I am sick.	☐	☐
6. It is unnatural for my mind and body to be controlled by medication.	☐	☐
7. My thoughts are clearer on medication.	☐	☐
8. By staying on medication, I can prevent getting sick.	☐	☐
9. I feel weird, like a 'zombie', on medication.	☐	☐
10. Medication makes me feel tired and sluggish.	☐	☐

If subject scores…
0 – 5: They are not adhering to the prescribed medication schedule.
6 – 10: It is likely that they are adhering to their medication.

Appendix VII: Positive and Negative Syndromes Scale (PANSS)

Instructions for Rating:
1 = Absent 2 = Minimal 3 = Mild 4 = Moderate 5 = Moderate Severe 6 = Severe 7 = Extreme

POSITIVE SCALE (Circle one)

1	Delusions	1	2	3	4	5	6	7
2	Conceptual Disorganization	1	2	3	4	5	6	7
3	Hallucinatory Behavior	1	2	3	4	5	6	7
4	Excitement	1	2	3	4	5	6	7
5	Grandiosity	1	2	3	4	5	6	7
6	Suspiciousness / Persecution	1	2	3	4	5	6	7
7	Hostility	1	2	3	4	5	6	7

NEGATIVE SUBSCALE (Circle one)

1	Blunted Affect	1	2	3	4	5	6	7
2	Emotional Withdrawal	1	2	3	4	5	6	7
3	Poor Rapport	1	2	3	4	5	6	7
4	Passive Apathetic Withdrawal	1	2	3	4	5	6	7
5	Difficulty in Abstract Thinking	1	2	3	4	5	6	7
6	Lack of Spontaneity and Flow of Conversation	1	2	3	4	5	6	7
7	Stereotyped Thinking	1	2	3	4	5	6	7

GENERAL PSYCHOPATHOLOGY SUBSCALE (Circle one)

1	Somatic Concern	1	2	3	4	5	6	7
2	Anxiety	1	2	3	4	5	6	7
3	Guilt Feelings	1	2	3	4	5	6	7
4	Tension	1	2	3	4	5	6	7
5	Mannerism and Posturing	1	2	3	4	5	6	7
6	Depression	1	2	3	4	5	6	7
7	Motor Retardation	1	2	3	4	5	6	7
8	Uncooperative	1	2	3	4	5	6	7
9	Unusual Thought Content	1	2	3	4	5	6	7
10	Disorientation	1	2	3	4	5	6	7
11	Poor Attention	1	2	3	4	5	6	7
12	Lack of Judgment and Insight	1	2	3	4	5	6	7
13	Disturbance of Volition	1	2	3	4	5	6	7
14	Poor Impulse Control	1	2	3	4	5	6	7
15	Preoccupation	1	2	3	4	5	6	7
16	Active Social Avoidance	1	2	3	4	5	6	7

TOTAL SCORE:_____.

Appendix IX: Calgary Depression Scale (CDS)

INSTRUCTIONS: Ask the following questions as written. Use the follow up probes or qualifiers at your discretion. Time frame refers to the last two weeks unless stipulated. N.B. the last item, #9, is based on observation of the entire interview.

Circle the appropriate rating for each item following the clinical interview.

0 = None 1 = Mild 2 = Moderate 3 = Severe

• **Depression:** How would you describe your mood over the last two seeks? Do you keep reasonably cheerful of have you been very depressed or low spirited recently? In the last two weeks how often have you (own words) every day? All day?	0 = Absent 1 = Expresses some sadness or discouragement on questioning. 2 = Distinct depressed mood persisting up to half the time over the last two weeks: present daily. 3 = Marked depressed mood persisting daily over half the time interfering with normal motor and social functioning.
• **Hopelessness:** How do you see the future for yourself? Can you see any future? – or has life seemed quite hopelessness? Have you given up or does there still seem some reason for trying?	0 = Absent 1 = Has at times felt hopelessness over the past two weeks but still has some degree of hope for the future. 2 = Persistent, moderate sense of hopelessness over last week. Can be persuaded to acknowledge possibility of things being better. 3 = Persisting and distressing sense of hopelessness.
• **Self Depreciation:** What is your opinion of your self compared to other people? Do you feel better, not as good, or about the same as other people? Do you feel inferior or even worthless?	0 = Absent 1 = Some inferiority; not amounting to feeling of worthlessness. 2 = Subject feels worthless, but less the 50% of the time. 3 = subject feels worthless more than 50% of the time. May be challenged to acknowledge otherwise.
• **Guilt Ideas of Reference:** Do you have the feeling that you are being blamed for something or even wrongly accused? What about? (Do not include justifiable blame or accusation. Exclude delusions of guilt)	0 = Absent 1 = Subject feels blamed but not accused less than 50% of the time. 2 = Persisting sense of being blamed, and/or occasional sense of being accused. 3 = Persistent sense of being accused. When challenged, acknowledges that it is not so.
• **Pathological Guilt:** Do you tend to blame yourself for little things you may have done in the past? Do you think that you deserve to be so concerned about this?	0 = Absent 1 = Subject sometimes feels over guilty about some minor peccadillo, but less than 50% of the time. 2 = Subject usually (over 50% of time) feels guilty about past actions the significance of which he exaggerates. 3 = Subject usually feels s/he is to blame for everything that has gone wrong, even when not his/her fault.
• **Morning Depression:** When you have felt depressed over the last 2 weeks, have you noticed the depression being worse at any particular time of the day?	0 = Absent 1 = Depression present but no diumal variation. 2 = Depression spontaneously mentioned to be worse in a.m. 3 = Depression markedly worse in a.m., with impaired functioning which improves in p.m.
• **Early Wakening:** Do you awake earlier in the morning than is normal for you? How many times a week does this happen?	0 = Absent 1 = Occasionally wakes (up to twice weekly) 1 hour or more before normal time to wake or alarm time. 2 = Often wakes early (up to 5 times weekly) 1 hour or more before normal time to wake or alarm time. 3 = Daily wakes 1 hour or more before normal time.
• **Suicide:** have you felt that life wasn't worth living? Did you ever feel like ending it all? What did you think you might do? Did you actually try?	0 = Absent 1 = Frequent thoughts of being better off dead, or occasional thoughts of suicide. 2 = Deliberately considered suicide with a plan, but made no attempt. 3 = Suicidal attempt apparently designed to end in death (i.e., accidental discovery or inefficient means).
• **Observed Depression:** Based on interview's observations during the entire interview. The question "Do you feel like crying?" used at appropriate points in the interview, may elicit information useful to this observation.	0 = Absent 1 = Subject appears sad and mournful even during parts of the interview, involving affectively neutral discussion. 2 = Subject appears sad and mournful throughout the interview, with gloomy monotonous voice and is tearful or close to tears at times. 3 = Subject chokes on distressing topics, frequently sighs deeply and cries openly, or is persistently in a state of frozen misery if examiner is sure that this is present.

Appendix X: Social and Occupational Functioning Scale (SOFAS)

Consider social and occupational functioning on a continuum from excellent functioning to grossly impaired. Include impairments in functioning due to physical limitations, as well as those due to mental impairments. To be counted, impairment must be a direct consequence of mental and physical health problems; the effects of lack of opportunity and other environmental limitations are not to be considered.

100-91	Superior functioning in a wide range of activities.
90-81	Good functioning in all areas, occupationally and socially effective.
80-71	No more than slight impairment in social, occupational, or school functioning (e.g., infrequent interpersonal conflict, temporarily falling behind in schoolwork.
70-61	Some difficulty in social, occupational, or school functioning, but generally functioning well, has some meaningful interpersonal relationship.
60-51	Moderate difficulty in or school functioning (e.g., few friends, conflicts with peers or co-workers).
50-41	Serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep job).
40-31	Major impairment in several areas, such as work or school, family relations (e.g., depressed man avoids friends, neglects family, and is unable to work, child frequently beats up younger children, is defiant at home, and is failing in school).
30-21	Inability to function in almost all areas (e.g., stays in bed all day, no job, home or friends).
20-11	Occasionally fails to meet minimal personal hygiene; unable to function independently.
10-0	Persistent inability to maintain minimal personal hygiene. Unable to function without harming self or others or without considerable external support (e.g., nursing care and supervision).

Total SOFAS score: _____.