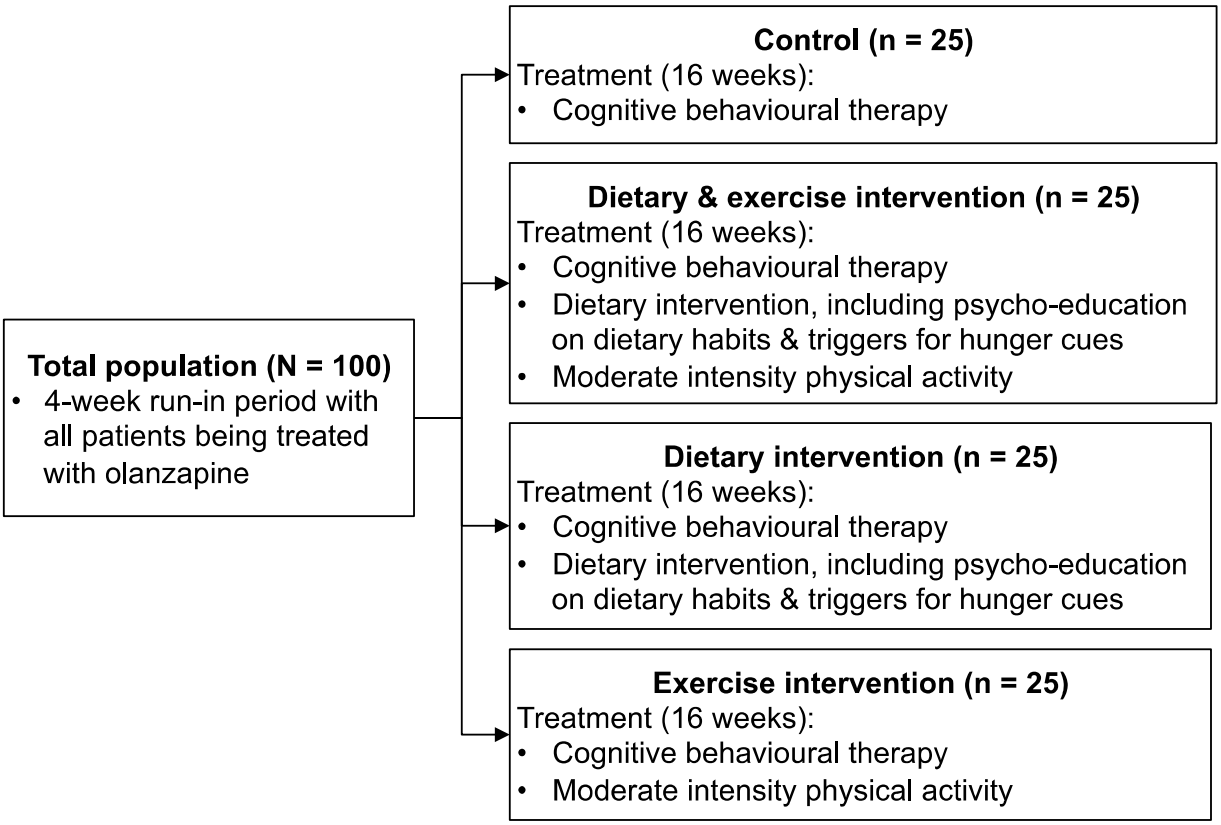

Assignment Submission Form

Student Name	**Mary Guiney**
Student Number	**4625561**
Assignment Title	Lifestyle intervention for the prevention of olanzapine-induced metabolic abnormalities, such as diabetes and obesity, in patients with schizophrenia who have a healthy BMI at baseline
Module Code	**FDSC40580**
Module Title	**Project Module**

Tutor	**Olga Grant**
Date Submitted	**08/05/17**

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Declaration of Authorship

I declare that all material in this assessment is my own work except where there is clear acknowledgement and appropriate reference to the work of others.

Signed: Mary Guiney

Date: 08/05/17

Lifestyle intervention for the prevention of olanzapine-induced metabolic abnormalities, such as diabetes and obesity, in patients with schizophrenia who have a healthy BMI at baseline

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ABSTRACT

Purpose: Newer atypical antipsychotics are commonly prescribed for individuals with schizophrenia because of their reduced risk of extrapyramidal side effects compared with first-generation antipsychotics. Atypical antipsychotics do carry other risk factors, such as metabolic dysfunction and possibly increased risk of diabetes. Indeed, olanzapine can induce increased fat mass, glucose intolerance, type-2 diabetes and elevations in low-density lipoproteins. Previous studies have shown that lifestyle interventions can be used to reduce the risk of metabolic syndrome and weight gain, in individuals undergoing drug therapy. These interventions, including dietary advice, exercise and cognitive behavioural therapy, can help reduce these side effects in individuals who are overweight or obese, but they have not been examined in those who are within a healthy body mass index (BMI).

Design: A randomised-controlled trial examining the use of lifestyle interventions on the prevention of weight gain and the potential to reduce risk factors associated with metabolic dysfunction in patients with schizophrenia, who are within a healthy BMI prior to commencing olanzapine treatment.

Methodology: Patients (n=100) will be recruited from psychiatric centres and be assigned to the following groups: control; dietary and exercise intervention; dietary intervention; and exercise intervention. All participants will undergo a 4-week run-in with olanzapine and remain on the drug for the duration of the study.

Word Count: 207

Key words: Atypical antipsychotic; body mass index; cognitive behavioural therapy; low-density lipoprotein; olanzapine; risperidone; second-generation anti-psychotic; type-2 diabetes mellitus

Introduction

Background

Obesity is more prevalent in individuals experiencing mental health issues, specifically schizophrenia, occurring at nearly double the rate relative to the general population (Aschbrenner, 2016). This is largely due to the complexity of their genotype, surrounding environment and the use of antipsychotic drugs in this population (Holt, 2009). It is believed that treatment with second-generation antipsychotics (SGAs) improves the dopamine reward response, while also heightening the hedonic impact of food (Elman, 2006), leading to over-eating and poor food choices based on increased perception of its palatability. Patients with schizophrenia are at a 2–4-fold increased risk of developing metabolic syndrome compared to the general population (Cordes, 2011). Around 1% of people worldwide will suffer from one or more episodes of schizophrenia in their lifetime (Dixon, 2000). For approximately half of these individuals, the illness will be life-long and will require long-term drug treatment.

Olanzapine has been reported to have a strong association with new-onset diabetes (Shah, 2016). While weight gain is a risk factor for diabetes, new-onset diabetes is also prevalent in those who are taking olanzapine and who do not experience any weight gain (Shah, 2016). Olanzapine is a newer anti-psychotic drug that acts by reducing extrapyramidal side effects and is prolactin sparing (Cordes, 2011); however, it is associated with side effects including weight gain, altered glucose metabolism and increased blood cholesterol and lipid levels (Buchanan, 2002). Numerous case reports have been published highlighting the incidence of diabetes or hyperglycaemia with olanzapine (Koro, 2002).

Antipsychotic-induced metabolic dysfunction

Atypical antipsychotics or SGAs, such as olanzapine, are as effective as older drugs, such as haloperidol, in treating schizophrenia and are less likely to cause extrapyramidal side effects and tardive dyskinesia; however, these newer drugs are associated with metabolic disturbances, weight gain and diabetes mellitus (Lambert, 2006). In a study by Ucok and colleagues, the average weight gain experienced over a 10-week period with olanzapine was 4.15 kg (Ucok, 2008). The prevalence of type-2 diabetes in people with schizophrenia is more than twice that of the general population (Dixon, 2000). Evidence suggests that drugs like olanzapine, which contribute to a greater increase in weight, are also associated with a greater increase in diabetes compared with those that cause less severe weight gain, such as risperidone (Ucok, 2008). The odds of developing type 2 diabetes within the first year of treatment with olanzapine are 3:1 compared with the risk of individuals with schizophrenia not receiving drug treatment (Lean, 2003). The risk of developing diabetes also contributes to a higher risk of developing cardiovascular complications and individuals with schizophrenia are two to three times more likely to die from cardiovascular disease than the general population (Lean, 2003).

In vitro studies have shown that olanzapine inhibits glucose transport at adrenal medulla pheochromocytoma PC12 cells and increases cellular levels of the glucose transporter isoforms GLUT1 and GLUT3 (Lean, 2003). This leads to an increase in insulin release, which could eventually lead to resistance due to the down-regulation of insulin receptors. In addition, leptin levels are usually elevated in individuals taking olanzapine (Teff, 2011). High leptin levels is linked to high blood pressure, obesity (Elman, 2006) and heart disease.

A previous study investigated whether there was an association between atypical antipsychotic occupancy of adrenergic, dopamine, histamine, muscarinic and serotonin receptors and weight gain and diabetes mellitus (Ohtani, 2005). The authors concluded that H1 receptor antagonism was the primary driving force for antipsychotic-induced weight gain and diabetes mellitus (Ohtani, 2005). It is thought that blocking hypothalamic H1 receptors with the use of atypical antipsychotics activates AMP-activated protein kinase (AMPK), which is a well-known regulator of food intake, resulting in a marked increase in caloric intake. It is also believed that H1 receptor antagonism decreases brown adipose tissue thermogenesis resulting in fat accumulation (Deng, 2013), which also occurs by decreasing lipolysis in white adipose tissue (Deng, 2013).

Atypical anti-psychotics induce weight gain due to the antagonism of hypothalamic histamine H1 receptors, serotonin 5-HT2C receptors and alpha-2 adrenergic receptors (Passani, 2011). Olanzapine and clozapine have the highest affinity of antipsychotics for H1 receptors and are associated with the greatest weight gain. One possible mechanism for the onset of diabetes mellitus involves alterations in pancreatic beta-cells, specifically antagonism of pancreatic alpha-2 adrenergic receptors, 5-HT1 alpha-receptors and M3 muscarinic receptors. When these receptors are inhibited, pancreatic beta-cells lose their ability to respond to changes in blood glucose levels (Berg, 2012). Additionally, the risk for metabolic disturbances is higher for antipsychotics with a tricyclic ring structure such as olanzapine; it is believed that their chemical structure may damage insulin secretion directly (Nagamine, 2014).

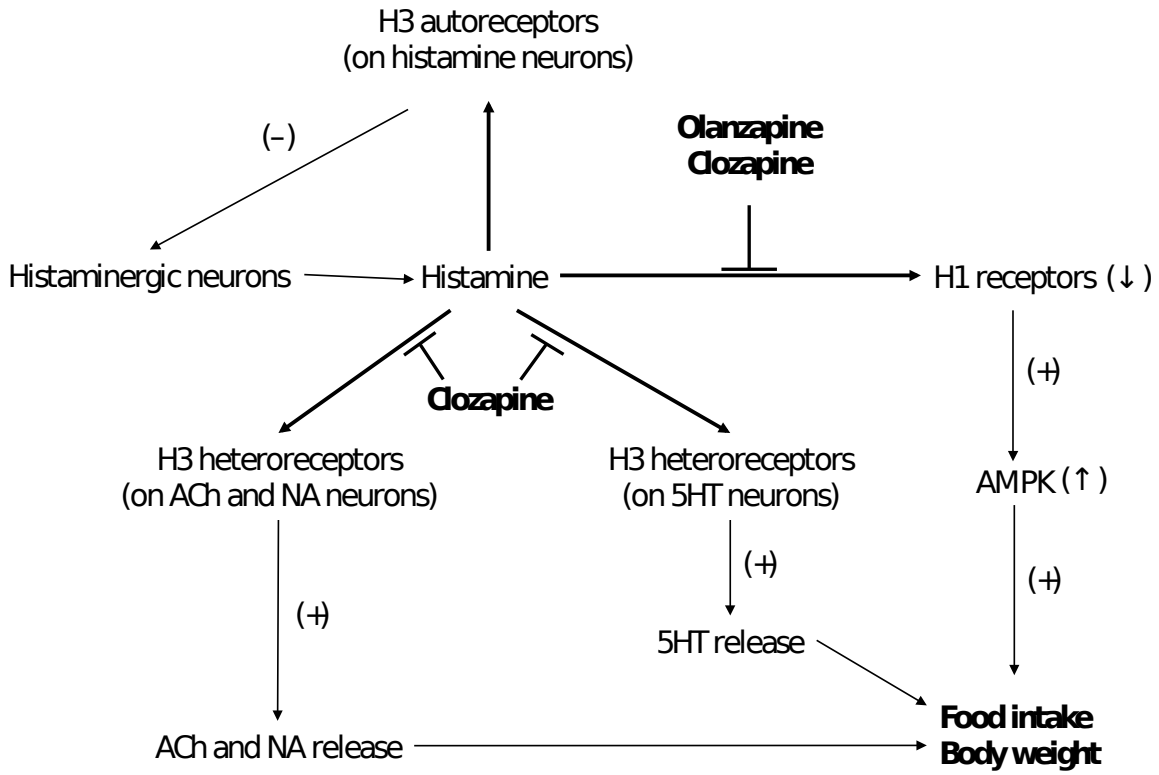

Figure 1. Olanzapine-induced receptor antagonism.

Current lifestyle interventions

Some studies have examined the use of health interventions to help individuals who are overweight or obese who are suffering from mental illness (Caemmerer, 2012). One such randomised controlled trial (RCT) involved six months of caloric restriction and exercise in individuals who were obese and who were taking SGAs. At the end of the six-month period, both body weight and body mass index (BMI) had decreased in the study group (Bai, 2007), while it did not decrease in those who did not receive lifestyle intervention. Lifestyle interventions are structured approaches that help individuals engage in physical activity, eat a balanced diet and participate in health promotion activities (Table 1). People with schizophrenia require baseline assessment and ongoing monitoring of physical health parameters. Treatment strategies should include encouraging a healthy lifestyle, smoking cessation, eating a balanced diet and undertaking physical activity (Annemans, 2011). Non-pharmacological interventions have achieved reductions in weight, waist circumference and body fat percentage, as well as decreases in plasma glucose, insulin and low density-lipoproteins compared with control individuals not receiving lifestyle intervention (Caemmerer, 2012).

Table 1: Different types of lifestyle interventions

Group	Description
CBT	Talking therapy to help control mental health issues by changing thinking and behaviour
Dietary intervention	Eating behavioural therapy to educate on the energy values and composition of different food groups, in addition to providing a recommended eating plan
Exercise intervention	To motivate individuals to participate in moderate intensity physical activity

An 18-month naturalistic study found that ongoing education and lifestyle intervention (with adherence rates of 85%), specifically with exercise, at the onset of drug therapy saw a 3.5% decrease in body weight compared with the control group with no intervention who experienced a 4.1% increase (Poulin, 2007). A lifestyle intervention study, involving both exercise and diet, in individuals who were obese or overweight saw a marked decrease in weight (5% or 10% depending on BMI) while receiving drug therapy (Aschbrenner, 2016).

A RCT investigating the effects of a six-month continuous caloric restriction and physical activity in individuals who were obese and who were taking an SGA similar to olanzapine (Bai, 2007). Anthropometric and biochemical parameters were assessed at three and six months. BMI and body fat did not differ significantly between the control and study groups at baseline. At the end of the six month period, BMI, body weight and waist circumference decreased significantly in the study group compared with the control population. Additionally, triglyceride levels significantly decreased in the study group, while they significantly increased in the control group.

Another trial examining psycho-educational or cognitive behavioural therapy (CBT) interventions aimed at weight loss or the prevention of weight gain (Berti, 2012). In the intervention group there was a reduction of 0.98 points in BMI or 3.1% loss of baseline weight. While this does not meet the 5–10% reduction in body weight recommended for reductions in risk factors such as diabetes or hypertension, it does provide evidence that lifestyle interventions are beneficial and, if continued long term, may contribute to further decreases in body weight and BMI.

Lifestyle intervention studies including both exercise and diet have been used successfully to promote weight loss while receiving drug therapy. The average weight loss recorded in these studies was between 2.9% and 5% of initial body weight; however, these studies were performed in individuals who were obese or overweight, in whom it is easier to lose some body weight if they adhere to the intervention. The aim of this study is to ensure that patients with mental disorders and who have a healthy BMI can control their weight while on antipsychotic drugs, thus preventing them from becoming overweight or obese and reducing the risk of associated risk factors.

Study objective

The aim of this study is to examine the effect of lifestyle interventions for patients with schizophrenia who are within a healthy BMI and are receiving an atypical antipsychotic, olanzapine versus control patients who are within a healthy BMI, who will receive olanzapine but no lifestyle intervention. To date, little has been done to intervene and improve the risk profiles of many individuals with schizophrenia (Faulkner, 2003). This study will be performed over the course of four months to investigate whether lifestyle intervention is an effective approach at preventing weight gain and metabolic disturbance in these individuals. Lifestyle interventions centred around a healthy diet and exercise may be an effective approach for addressing metabolic disturbance and in the prevention of anti-psychotic induced weight gain. The objectives of this study are:

- To examine whether dietary and exercise intervention can prevent anti-psychotic induced weight gain
- To examine whether dietary intervention alone can prevent anti-psychotic induced weight gain
- To examine whether exercise intervention alone can prevent anti-psychotic induced weight gain

While it is clear from the aforementioned studies that olanzapine causes a marked increase in weight, which can lead to metabolic disturbances, the optimal intervention to counteract these adverse effects while receiving drug therapy still needs to be determined. RCTs have shown that baseline screening and continued monitoring of secondary ailments associated with drug therapy are essential in risk reduction of obesity and metabolic disease (Citrome, 2011). Certain studies have also investigated the use of behavioural intervention in the treatment of weight gain and associated cardio-metabolic risk. One such study found that behavioural interventions can significantly improve insulin regulation and if administered at the start of drug therapy, some individuals may experience weight loss (Gabriele, 2009). Thus, we will employ these interventions in our study to examine whether they can help prevent anti-psychotic induced weight gain and metabolic risk.

Patient satisfaction while receiving antipsychotic drug treatment has been studied to some extent, with one cross-sectional study revealing that patients were not informed of the adverse effects of drug therapy and that practitioners could have communicated this better to these individuals (Gray, 2005). This study will aim to assess the well being of this group throughout a 16-week period in individuals who would not normally be categorised as being at risk for metabolic syndrome.

Study importance

This RCT will add value to current research in the investigation of weight gain and associated metabolic risk factors with the use of SGAs. Previous studies have reviewed altered neurobiology associated with the administration of SGAs and have discovered a link between their biochemical effects and the risk of increased adiposity and associated metabolic syndrome (Deng, 2013);

however, these studies emphasised groups of individuals who were at risk of complications and those who were overweight or obese. This study only investigates individuals who are within healthy BMI at baseline and thus aims to establish overall risk for this group.

Methodology

Study participants

A total of 100 participants suffering from first episode psychosis or schizophrenia will be recruited and included in the study. All participants will be aged between 18–65 years, of either gender and who have a healthy BMI at baseline (mean = 21.9 + 1.4/ - 2.2).

Study participants will be recruited via the psychiatrists who are treating patients. Psychiatrists are to ensure that individuals and guardians are made aware of the intervention study, what is involved, how long they will be assessed and any side effects which may be experienced. Once the individual agrees to be part of the study, they will provide written informed consent. Participants will be recruited from three different mental health clinics across Ireland and researchers require approval via the psychiatrist who is treating each individual. Below shows details of each of the services selected in Dublin, Cork and Limerick.

- Cluain Mhuire Community Mental Health Services, Newtown Park Avenue, Blackrock, Co. Dublin
- Dean Clinic Cork, Citygate, Mahon, Cork
- St. Joseph's Psychiatric Hospital, Mulgrave Street, Limerick

Table 2: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Aged 18-65 years	Aged <18 years or >65 years
BMI < 25 kg/m²	<2 kg body weight gain during the 4-week run-in olanzapine treatment period
≥2 kg body weight gain during the 4-week run-in olanzapine treatment period	Previous or current treatment with antipsychotic medications other than olanzapine

BMI, body mass index

Study Protocol

All participants will undergo a clinical examination and laboratory tests both pre and post-intervention. All patients will be monitored after four weeks of commencing olanzapine. Patients (N=100) will be randomised into four groups, as shown in Figure 1.

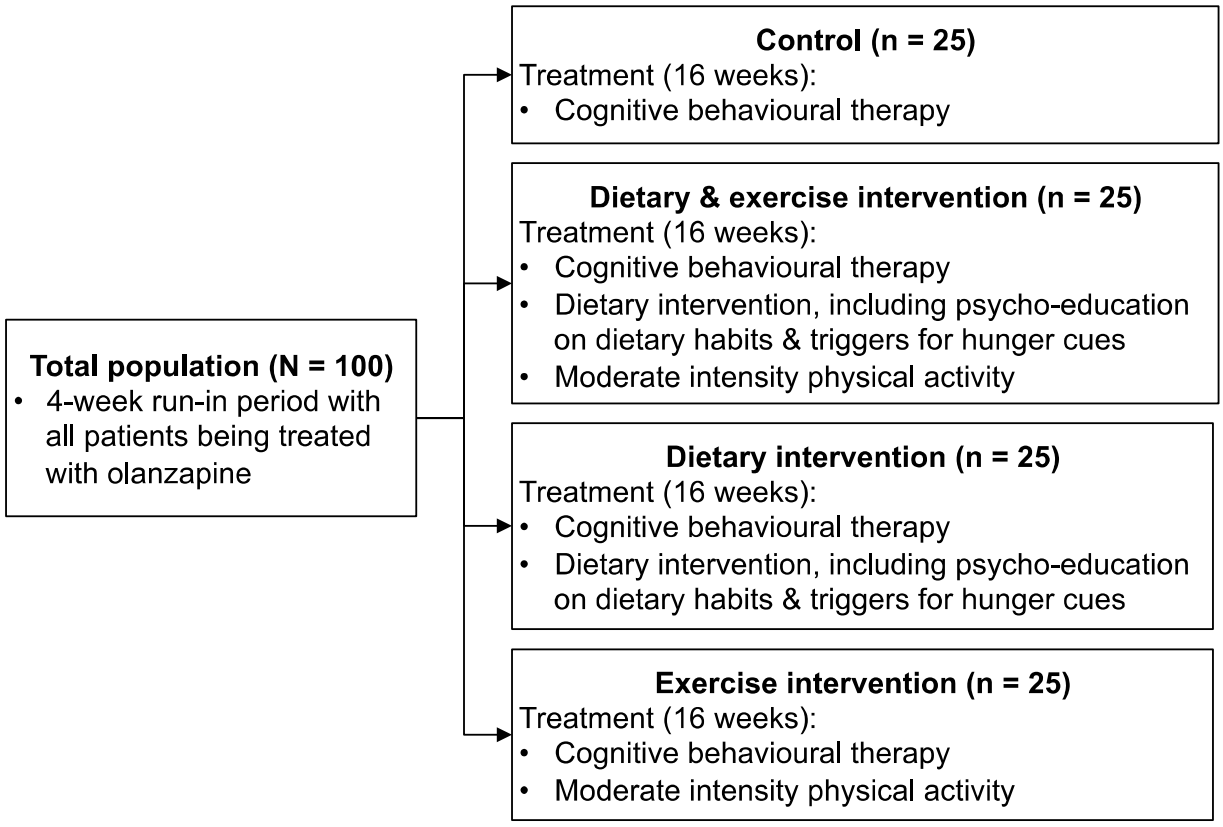

Figure 1. Randomisation of patients and details of group interventions.

Tables 3 and 4 show sample meal and exercise plans that will be used in the study in those being administered these types of interventions. Additional meal plans and exercise options, which can be personalised to the individual, will be available upon commencement of the study.

Table 3: Sample meal plans

Meal	Sample meal plan 1	Sample meal plan 2
Breakfast	Porridge and berries	Two eggs and whole-wheat toast
Lunch	Avocado and feta salad	Puy lentils and goats cheese
Dinner	Salmon and sweet potato	Chicken breast and rice
Snack	Handful of mixed nuts	Carrot sticks and hummus

Table 4: Sample exercise regime

New to exercise	More advanced
• 150 minutes/week of moderate intensity exercise, such as brisk walking or swimming	• 150 minutes/week of moderate intensity exercise such as brisk walking or swimming
• Encourage individuals to generally be more active, such as taking the stairs instead of the lift	• 60 minutes/week of high intensity exercise such as running or interval training

Food intake analysis

Photographic atlases will be used to give a more concrete estimation of food intake. As of late, these strategies are proving more useful than the standard weighted approach, which is associated with some error. Photographic atlases provide a memory aid for participants when involved in 24-hour recall of food intake (Lazarte, 2012).

Anthropometric measurements

Body fat: Callipers will be used to assess body composition and to record an accurate increase in adiposity in relation to lean mass. Callipers are not always accurate in their measurements; however, it will be maximised by instructing the health care nurse to obtain the measurements from the same area at baseline and at each study visit.

Waist circumference: A tape measure will be placed halfway between the hipbone and the lowest rib to measure waist circumference.

BMI: Weight and height will be measured to record BMI at the initiation of drug treatment and every 4 weeks thereafter. A gain of one BMI unit should indicate that the clinician should consider an intervention, which may include nutritional counselling, an exercise program or a change in antipsychotic medication, which has lower diabetogenic potential.

HbA1c levels: Since diabetes is not always associated with weight gain, monitoring weight alone is insufficient to measure for diabetes risk, thus HbA1c tests will also be performed. HbA1c, or glycated haemoglobin, is formed after

binding of haemoglobin to glucose, which subsequently becomes glycated. Tests are performed through blood analysis over the course of three months. HbA1c levels allow clinicians to get an overall picture of the average blood sugar levels over the course of three months as red blood cells survive for 8–12 weeks. The amount of glucose that combines with this protein is directly proportional to the total amount of sugar in the bloodstream. HbA1c provides a longer-term trend of how high your blood sugar levels have been over a period of time. The sample of blood will be taken from the arm.

Questionnaires

Each study participant will be required to complete a questionnaire at baseline (i.e. when the individual is taken into care initially and may still be in the midst of their mental illness (i.e. experiencing auditory hallucinations, delusions or else suffering from post-psychotic depression). These questionnaires will be repeated at monthly intervals. Pre- and post intervention questionnaires will be used to measure overall satisfaction, educational awareness, attitudes and overall behaviour modification.
While most questionnaires assess the individual's current life satisfaction, it can be quite intimidating to answer certain questions relating to their current mood. Of course these questions should be mandatory as they are imperative to ensure safety of the individual; however, questionnaires addressing life satisfaction (such as educational awareness on healthy eating and exercise), contentment with treatment plan and physician care are also needed.

Ethics approval

The study protocol will obtain approval by the Research Ethics Committee of the Medical Faculty of University College Dublin.
http://www.ucd.ie/researchethics/apply/applications/

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Word Count: 2,831References

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