ARIPIPRAZOLE AND WEIGHT GAIN: A META-ANALYSIS

By

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Abstract
This quantitative systematic review has focused on eight studies for a meta-analysis that has provided significant and positive evidence for the atypical antipsychotic, aripiprazole, on weight loss. Aripiprazole has been compared to other antipsychotics such as olanzapine, quetiapine, risperidone and haloperidol on weight loss (N=2,507). Although it has been argued that there is weight loss due to aripiprazole (Beebe, 2003), discussion of this treatment for mental illness has to be understood with respect to the psychological as well as the physical and adverse effects of taking antipsychotic medication. The significant factor that has emerged for a longer lasting solution for maintaining weight loss in the treatment of mental illness and psychoses is the integrative approach which has a psychological design (Citrome & Yeo+mans, 2005). This is most supportive for the sufferer, where clinicians respond to their issue armed with the knowledge from research and evidence-based practices for a long term treatment of weight management (Lean, 2003). The meta-analyses results was highly significant at -6.700 at p< or equal to 0.0001 that indicated that the hypothesis was supported with weight loss for aripiprazole compared to other antipsychotics in this review.

Declaration
I, Farah Hassan, acknowledge that this dissertation undertaken within the University of Bedfordshire is entirely original and written by me and within the University Regulations.

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Contents

Abstract ........................................................................................................... 1
Declaration ...................................................................................................... 1
Acknowledgements .................................................................................... 2
Glossary ......................................................................................................... 4
1. Introduction .............................................................................................. 5
2.0 Aim ......................................................................................................... 20
2.1 Objective ............................................................................................... 20
2.2 Hypothesis ............................................................................................. 20
3. Criteria for considering studies for this review ....................................... 20
4. Search methods for identification of studies ........................................... 21
5. Methods of the review ........................................................................... 22
6. Description of studies ........................................................................... 24
7. Methodological quality .......................................................................... 27
8. Results .................................................................................................... 31
9. Discussion ............................................................................................... 38
10. Conclusion ............................................................................................. 46
11. Dissemination ......................................................................................... 51
12. Limitation and potential conflict of interest ......................................... 51
13. Reflection ............................................................................................... 52
References .................................................................................................... 55
Bibliography .................................................................................................. 67
APPENDICES ................................................................................................ 68
Appendix 1. Aripiprazole ........................................................................... 69
Appendix 2. Characteristics of included studies ......................................... 70
Appendix 3. Characteristics of excluded studies ......................................... 76
Appendix 4. Adding weighted z's ................................................................. 81
Appendix 5. The Fisher's F-test ................................................................. 82
Appendix 6. Raw data (see floppy disc) ..................................................... 83

Tables
Table 1 Table of included studies ............................................................. 25
Table 2 Table of excluded studies ............................................................ 26
Table 3 Table of analyses ....................................................................... 36

Glossary
APA – American Diagnostic Association
BMI – body mass index
CBT – cognitive behavioural therapy
CVD – cardiovascular disease
DSM- diagnostic and statistical manual of mental disorders
EPS – extra pyramidal symptoms
LOCF – last observation carried forward
N- numbers
NICE – national institute of clinical excellence
NGA – new generation antipsychotics
RCT – randomised controlled trial
SGA – second generation antipsychotics
S.O.C. – standard of care
T- time
1. Introduction
This systematic review investigates if weight loss occurs by taking the atypical antipsychotic aripiprazole, for people who have been diagnosed with schizophrenia or bipolar I disorder. The rationale is based on research that has shown a positive new trend amongst the second and third generation of atypical antipsychotics that are counteracting some of the side effects better (Ehret et al., 2008). Since the introduction of the first generation of conventional antipsychotics from the 1950s of chlorpromazine and haloperidol (Comer, 2007, p.442) to the 1980s (McEnany, 2007) of second generation antipsychotics (SGAs) the significance of weight gain became important because there was weight gain with this latter group (Beebe, 2003). It is necessary to review this issue of weight management as advances in science support the psychological and emotional impact on self esteem and self management for not just the healthy population, but the mentally ill (Paton et al., 2004). If aripiprazole is an effective atypical antipsychotic agent with an impact on weight loss compared to other antipsychotics and some atypical antipsychotics, then this is truly an advantage (Ehret et al., 2008) and crucial to public health (Faulkner et al., 2003).

1.1 Atypical versus typical antipsychotic
The effects of antipsychotics have been seen frequently in the treatment of psychoses such as schizophrenia for which antipsychotics was pioneering work (Marder et al, 2003), as well as for depression, delusional disorders and dementia (Gardner et al., 2005, p.1703). Schizophrenia has been known to be best treated with antipsychotic medication and particularly when it is a long term illness (Naber & Lambert, 2004). These older antipsychotic drugs were also known as ‘neuroleptic drugs’ since they could cause movement disorders that mimicry ‘neurological disease’ (Comer, 2007, p.442), and these side effects were not treated because the drugs were not as sophisticated as they are now to improve these conditions (Gardner et al., 2005).
The neurologic side effects are less in the atypical antipsychotics (Schultz et al., 2007), which have adverse effects that are different from the first generation of antipsychotic medications (McEnany, 2007). These SGAs are different from the typical antipsychotics in their action because they do not create the movement disorders (known as the Extrapyramidal symptoms – EPS) when treating the mental illness (Gardner et al., 2005). But the atypical antipsychotics have the disadvantage of causing metabolic disturbances and weight gain as will be discussed later (Ehret et al., 2008; Schultz et al., 2007). Though, there has been extensive research on the new antipsychotics with enhanced knowledge of the biochemical effects, the scientists still cannot eliminate treatment effects for all the symptoms of psychoses (Miyamoto et al., 2005).

_Psychoses and mental illness_

There has been a rise in the numbers of people suffering mental illness since the last decade (Fox, 1999). This is disconcerting as it implies that together with this are the problems of 'suicide, drug and alcohol abuse and homelessness' (ibid, p.412) Other problems associated for people with psychoses are generally a greater risk of serious illnesses such as diabetes and cardiovascular disease (CVD) related to inactivity and medication more so than the general population (Paton et al., 2004). Connolly and Kelly (2005) address that there is inadequate physical health for those suffering mental health and more needs to be done in this area to develop better practices professionally to support them.

Psychosis has been defined as a 'loss of contact with reality' and is frequently associated with the illness schizophrenia (Comer, 2007, p.411). This explanation may be because it has been thought of as an illness with a lack of insight into the nature of the condition which has 'hallucinations' or 'delusions' (American Psychiatric Association, APA, 1994, p.273). It has also been linked to using 'LSD or abusing amphetamines or cocaine' (Comer, 2007, p.411).

_Schizophrenia_
The American Psychiatric Association (APA, 1994) has produced a diagnostic and statistical manual of mental disorders (DSM-IV) which Comer (2007) has recommended in the diagnosis of schizophrenia. Clinicians recognise this disease when symptoms of this disorder manifests as deterioration in 'work, social relations', and personal care (Comer, 2007, p.423). There are 'positive' and 'negative symptoms' in schizophrenia as well as 'psychomotor' ones (Comer, 2007, p.416). The positive symptoms are described as 'excesses or distortion of normal functions' whereas the negative symptoms are of 'diminution or loss of normal functions' (APA, 1994, p.274). The APA considers various researches and posits that there is a 'lifetime prevalence of schizophrenia between - 0.5% and 1%' (p.282).

In an explanation of the aetiology of the disease, the most popular theory is for the biological perspective, which is associated with genetic issues. This suggests that the onset of the disease is caused by stress in the early twenties or late teens, and this varies for both men and women with there being no gender difference in the precipitation of the disease (Comer, 2007).

**Bipolar I disorder**

DSM –IV-TR recognises two types of bipolar disorders – bipolar I and bipolar II disorder (Comer, 2007, p.243). Bipolar I disorder consists of 'full manic and major depressive episodes' with the 'full manic episode' lasting for a week or more of an unusually euphoric emotional state 'or irritable mood, along with at least three other symptoms of mania' (Comer, 2007, p.243). This stage could cause 'delusions or hallucinations' (ibid, p.243). There is an 'alternation' of the stages. The most recent theory explaining this disease has been one of the neurotransmitter activities with a 'low serotonin activity' together with 'high norepinephrine activity' that 'may lead to mania' (Comer, 2007, p.245). Genetics cannot be ruled out as a risk factor since family studies have provided evidence for development of the disorder as well (ibid). The 'lifetime prevalence..in community samples ...0.4% to 1.6%' (APA, 1994, p.353).

**Aripiprazole**
Aripiprazole was brought in to treat schizophrenia in the 1990s as an atypical agent and it is the most recent drug intervention (Beebe, 2003). Generally the atypical antipsychotics cause greater weight gain and cost more, but the action of aripiprazole has benefit because it has less weight gain (Beebe, 2003). It has a trade name known as ‘Abilify’ (Comer, 2007, p.445) and is seen in this meta-analysis to be consistently used in the treatment of schizophrenia, although it is also seen to be treating bipolar I disorder (Vieta et al., 2005; Keck et al., 2003).

The finding is that aripiprazole is more effective in the treatment of schizophrenia (Bandelow & Meier, 2003) and it is much less problematic in not just weight gain but diabetes (Ehret et al., 2008). As it is a recent drug for these treatments, there are only short-term published studies available (Beebe, 2003). Shajahan et al. (2008) consider aripiprazole to be of unique benefit compared to other atypsicals in the treatment of psychoses. Whereas, El Sayeh and Morganti (2007) did not believe that aripiprazole is of real uniqueness from other antipsychotics (and atypicals) for schizophrenia because clinical studies have been no different substantially from other drugs.

Aripiprazole was introduced as the new third generation of atypical antipsychotics, and it is similar in composition to the typical antipsychotics of the first generation (Bhattacharjee George & El-Sayeh, 2008) such as haloperidol. It is used in many countries including the UK (Bandelow & Meier, 2003).

1.2 Weight gain
In fact weight gain is known to be considerable in some of the atypical antipsychotics (Zipursky et al., 2005). The benefits of taking aripiprazole and not gaining much weight have been equated with the antipsychotics amisulpride and ziprasidone where each causes less than 2 kilograms of weight gain (Newcomer, 2004, p.1936). By contrast olanzapine has been found to cause ‘4-10’ kilogram of weight gain (ibid, p.1936) It is important to note that the increase in weight gain is varied amongst individuals (Connolly & Kelly, 2005).
People with psychoses have increased risks for the secondary complications of being overweight or obesity, that are related to the factors that this group have sedentary lifestyles and possible depression and sluggishness due to their medication (Marder et al., 2003; Paton et al., 2004). Together with smoking, a bad diet and little exercise the body's cardiovascular system is exacerbated for this group (Thomas, 2007, p. S119; Marder et al., 2003) more so than the general population (Paton et al., 2004).

It is necessary to consider the patients emotional feelings when there is weight gain because as secondary implications become a concern for people taking medication they may discontinue which could then be a contributory factor to relapse in mental illness (Naber & Lambert, 2004). The need to address the underlying emotional issues associated with weight gain is important, as seen in some studies in this review (De Souza & Ciclitira, 2005; Ascher-Svanum et al., 2005; Addington et al., 2003; Wadden et al. 2004; Carpenter et al., 2000; Connolly & Kelly, 2005; Weil et al., 2002). The issues of weight gain and the metabolic side effects have become salient features of importance when treatment with atypical antipsychotics are considered by clinicians and there is some choice for the patient that is in view of their concern for their image (Thomas, 2007).

The time span for incremental weight also differs considerably from patient to patient (Lean, 2003). Weight gain is a situation affected by environmental and genetic factors (Lean, 2003). There is a need for further research to advance the field of understanding the mechanisms of weight increase and its regulatory processes.

**Gender**

It is important to examine gender when looking at weight issues because weight and depression have been found to be different for men and women (Carpenter et al., 2000) which then requires differences in treatment. Women are more interested in weight loss than men (De Souza & Ciclitira, 2005).
De Souza and Ciclitira (2005) in association with overweight and obesity considered 'health and body image' for the U.K. and found that there was a gender context (p.793). This had created difficulties for intervention since weight management had been seen as an area for women and homosexuals. According to this article, this group are the ones who recognize dieting as an issue. A positive aspect of this study is that it has depth of experiences from the homosexual community in its constructions: this is in respect of masculine identities. It appears that heterosexual men report less mental stress because they do not 'diet' but the article highlights the neglect towards men's experience in this area. It confers an up-to-date account of how as semi-structured interviews, the discourse analysis and grounded theory with a small sample does not allow generalization and focuses on social culture. The outcome revealed issues of 'legitimacy' and 'support' (p.798; p.799). It was found that men were interested in losing weight for their health, whereas women had been known to desire weight loss for wanting to look good. This study also found that women were more caring towards men when men needed assistance in weight loss. Men do not acknowledge the issue of weight management with each other; therefore they find women understand better when they need to address this issue (De Souza & Ciclitira, 2005). This is important in terms of gender and identification.

Ascher-Svanum et al. (2005) have compared men and women in their susceptibility to the issues of weight gain and investigated weight increase for people with schizophrenia taking antipsychotic drugs. They found that women had become dissatisfied emotionally with their life when their weight increased. A vital point made was that although there was weight gain in the use of antipsychotic drugs, the mental illness had improved, which is of significance but bear in mind also that the impact of how much weight was gained needs to be ascertained. These researchers proffer logically that this significant improvement happened because these people are 'medication adherent' (Ascher-Svanum et al., 2005, p. 10). This is an important point to the argument of taking antipsychotics.
Addington et al. (2003) similarly, found that there were sex differences in weight gain with the medications they examined and they emphasized the significance of recording weight and Body Mass Index (BMI) of all patients on SGAs. They pointed out that they need to know the 'plateau of weight gain' and when this starts, as this is not known. Another good point that Addington et al (2003) make for reducing weight is that when implementing 'lifestyle' changes, it should be done relating to the needs of the group concerned (p.275), thus the significance of background for the population being studied is of value.

**Obesity**

It is recognized by the public that obesity, is 'stigmatized' and by contrast more so than other 'eating disorders' and there is 'discrimination' (Russell, 2005, p.182). This creates dissatisfaction with one's body and feelings of shame for the sufferer (ibid). Indeed, the public health model advocates change for 'the population's environmental circumstances so that the susceptible individual members of the population are less liable to become obese' (World Health Organization – W.H.O., 1991, p.69). Since, it has been found that obesity leads to 'the same complications' regardless of culture the 'definitions' in this context may be applied 'universally' (WHO, 1991, p.69-70).

If obesity occurs there are serious clinical implications (Zipursky et al., 2005) of Type 2 Diabetes Mellitus (T2DM), hypertension, Cardiovascular diseases (CVDs) and respiratory diseases, and a number of cancers (Marder et al. 2003; Connolly & Kelly, 2005). Thus it is crucial that the issue of antipsychotic –induced weight gain should not be neglected from the outset of treatment for each individual.

There have been great numbers of people who have become overweight in the western societies and in the industrialized centres of the third world during this past decade (Lean, 2003). The World Health Organization (W.H.O.) guidelines defines what is overweight on the 'basis of body mass index (BMI)' which is 'BMI = weight (Kilogram- kg) /height^2 (metre^2)'. (W.H.O., 1997, cited in Lean, 2003, p.5). The components of BMI are generally adipose tissue or
muscle mass and the average weight range is '18-25 kg/metre²' (Lean, 2003, p.5), and this range will help in most populations to maintain good health. Epidemiologically, a BMI of greater than or equal to 30 kilogram per metre squared has been stated as an obese range (ibid). It is not unusual to observe that there are BMIs of greater than 30 depending on gender, ethnicity and age issues (Cooke & Wardle, 2007). How cultural views impact on the individual is important; indeed the western view links excessive obesity with depression for women (Cooke & Wardle, 2007). Historically, women were desired to be fuller figured because this suggested 'fertility' (Dolan & Gitzinger, 1995, p.2). By contrast, the 1960's brought slimmer images, and the 1920s and 1930s also presented this image as fashionable.

Even though there are genetic factors that predispose individuals to suffer the diseases associated with excess adipose tissue (Lean, 2003), it is in fact those who are overweight with the greatest fat distribution focussed around the abdominal area that are the most susceptible to diabetes and CVDs (Lean, 2003). Indeed, it does not help if there is a build up of adipose tissue but physical activity, dieting, excess weight, smoking and too much alcohol are contributory factors (Lean, 2003, p.13). There will be the drawback of costs associated with treating these problems for the health sector in future years if nothing is done now to prevent this crisis (Harvey et al., 2001).

The metabolic syndrome

This era has seen a revival to investigate the association between antipsychotics and psychoses, with relation to the endocrine system (McIntyre et al., 2005). Although research beginning in the 1970s had recommended that antipsychotics should be investigated further for its effects on the metabolism, such as for raised lipids (Bushe & Paton, 2005), it still appears that the interaction of antipsychotics on raised lipids needs further research (Bushe & Paton, 2005). The impact of weight gain associated with metabolic disorders related generally to issues faced by those who experience schizophrenia (Bushe & Paton, 2005) and this has yet to be wholly determined for this group. In fact, there is only current, reliable data on the atypical antipsychotics 'olanzapine, risperidone and aripiprazole' which are
known to have a better cholesterol profile (p.81). Whilst the results for other antipsychotics should be treated with caution because their methodologies have been seen to have omitted ‘fasting data’ and are not over long durations (ibid, p.81).

1.3 The meta-analytic studies

This review has found schizophrenia and bipolar I disorder (Vieta et al., 2005) being treated by aripiprazole. The literature review found publications no earlier than 2002 on aripiprazole (Kane et al., 2002) and no later than 2008 (Kolotkin et al, 2008; Newcomer et al., 2008). The countries of interest in this review were the U.K., European countries, U.S.A. and Asia and all the studies were randomised.

Chan et al. (2007) was an abstract of a Taiwanese population of patients, which examined aripiprazole and risperidone at the stage of acute schizophrenia. This study did not support the hypothesis for aripiprazole and weight loss in its result since there was ‘mild’ weight increase for the two groups, with no significant difference finding. It was fortunate that this data was found on aripiprazole for the asian population, as studies are rare on aripiprazole for this group, and this study highlighted no differences between the asian group with the white patients (Chan et al., 2007, p.29).

Chrzanowski et al. (2006) examined aripiprazole and olanzapine at the stage of ‘acute relapsing or chronic, stable schizophrenia’ with results that indicated olanzapine had significantly greater weight gain compared to aripiprazole at all time points (p.259). This was a significant difference.

Kane et al. (2002) was an abstract that examined aripiprazole and haloperidol and placebo, without mentioning the stage for schizophrenia and schizoaffective disorder, and found no significant differences between weights for the groups.

Kolotkin et al. (2008, p.1) is a secondary analysis of Kerwin et al. (2007) examining aripiprazole with standard of care (S.O.C. – olanzapine, quetiapine
and risperidone) with the hypothesis that 'patients treated with aripiprazole would experience fewer negative Health Related Quality of Life (HRQOL) consequences associated with weight change than patients treated with other atypical antipsychotic medications' (p.2). There was a significant reduction in weight with aripiprazole. The results from this study may be more reliable in use with 'community patients with schizophrenia' (p.5). The outcome, in terms of weight related and general quality of life issues, was much better for the aripiprazole group and for weight loss over the duration of 26 weeks.

McQuade et al. (2004) compared aripiprazole and olanzapine with the result that there was a significant difference for more weight gain with olanzapine than aripiprazole, at the 'acute relapse' stage for schizophrenia when hospitalization was necessary.

Newcomer et al. (2008) aripiprazole and olanzapine found that there was significant difference with weight loss for aripiprazole compared to olanzapine. The stage of treatment involved switching to aripiprazole after weight had been gained on olanzapine. There was observed to be decreases in lipid profile.

Potkin et al. (2003) examined aripiprazole and risperidone and placebo found no significant difference with minimum increase across the groups of weight, during acute schizophrenia and schizoaffective disorders. The purpose of this study was to measure effectiveness of dosage and to assess the negative symptoms.

Vieta et al. (2005) examined aripiprazole and haloperidol with no significant difference between these two groups at the stage of patients 'experiencing acute manic or mixed episodes' (p.235).

1.4 Policies
It has been identified that a lack of an adequate diet can lead to early death and disease such as cardiovascular disease especially in the Western world, with estimates that it has resulted in 'over four million deaths per year'
The importance of policies is crucial to make the changes for people to have better resources in 'food production, availability, and access' (ibid). This is necessary in the poorer countries and in regions where people suffer deprivation (Robertson et al., 2006, p.172). The positive bearing on the community for economy is also important when considering policy making (WHO, 1991).

In implementing change the government and 'nongovernmental organizations, health care workers, and the community at large' should be included (WHO, 1991, p.13). This is to communicate knowledge of food issues in relation to health (ibid). Informed choices are necessary when buying food and so labelling would also be criteria for policy making to make it easier for the mentally ill.

In the past, studies that have focussed on public policy for the wellbeing of people's health have been in relation to 'diet, nutrition, and health'; but these areas were not understood satisfactorily therefore the outcome was dissatisfaction with the policies (WHO, 1991, p.14). It has been recognized that there are 'vulnerable groups' such as 'children, pregnant women, and the elderly' (WHO, '1991, p. 122), but the mentally ill also are left out in this description for 'deficiency diseases' and issues around nutrition and health. The issues associated with mental illness and weight management appears to have not been attended adequately (Connolly & Kelly, 2005).

It is important to give choices and this need to be understood for the person's circumstances and the issue of weight management is one such area where the mentally ill should be supported. It is apparent that the mentally ill are stigmatised in society and neglected because they do not voice their concerns (Crisp, 2005). It would be ideal to guide people in these circumstances with the appropriate counselling on nutrition and physical activity (Connolly & Kelly, 2005).

*Practice issues*
The National Institute of Clinical Excellence (N.I.C.E.) (2007):46 have instructed that for depression, implementation of guidelines for grade A classification should be from randomised controlled trials. NICE (2007):6 have suggested that those with a chronic condition should receive a combined treatment of medication and personalised Cognitive Behavioural Therapy (CBT) in order to minimise the long term costs of care. They also emphasise the significance of definitions because of difficulties that arise for effective treatment plans when the theories of explanations have been so diverse. The NICE (2007) guidelines support practices through an evidence-base in relation to the varied organizational levels that support those suffering mental illnesses.

Anti-discriminatory practice
In the use of antipsychotics the National Service Framework (NSF) for mental health has set out policies to address inequalities from the White Paper ‘Modernising Mental Health’ (Department of Health, D.O.H., 1999, p.1). This supports the National Health Service to implement NSF and National institute for Clinical Excellence (N.I.C.E.) recommendations on this issue to consider various assessments such as by the ‘National Survey of patients’ (p.2) and to incorporate the use of ‘psychological therapies’ as well as ‘decreasing suicide’ (D.O.H., 1999, p.12; 8).

The antipsychotic drugs which the patient takes should allow choice based by a balanced knowledge of adverse effects and the merits of taking the medication that involves both the patient and the doctor together (N.I.C.E. date). Also, the switching of antipsychotics is a possible option that the patient needs to know about (Schmidt, 2006). These ‘choices’ along with the financial outlay should be made clear from the outset for the patient (Gardner et al., 2005, p.1703). This is in consideration of giving the best treatment possible (DoH, 1999).

Prevention
A preventative approach ideally for patients beginning treatment with atypical antipsychotics would be to have a package of treatment (Littrell et al., 2003)
that involves a baseline medical assessment involving BMI and blood tests for risks of the metabolic syndrome (Newcomer, 2004; Lindenmayer et al., 2003) and this should be continually assessed. Weight should be monitored frequently in respect of these health issues (Lindenmayer et al., 2003).

The best outcome is achieved when support is given to patients to advise and change their eating habits and encourage exercise, such as in institutional and residential environments (Faulkner et al., 2003). A suggestion by Malhi (2003) is that a regime to control weight which involves regular exercise could be designed to suit the patient's requirements from the initial consultation in therapy and then consistently regulated (p.3). This is ideal for long term health benefits.

**Exercise**

There are numerous slimming campaigns which are prominent, in the media, which impart negativity for the general public because of the images of so-called perfection being portrayed, but the positive benefits of slimming are self-esteem and well-being (Wadden et al., 2004). Alongside nutritional requirements, it is recommended that exercise is crucial to manage body weight as well as develop a healthy condition and impart well-being (Pietrobelli et al., 2005). There are psychological boosts for low self-esteem and isolation through exercise (Richardson et al., 2005). In the mentally ill population what has been found is that structured group programs such as walking can be supportive (ibid). Evidence suggests that exercise is evaluated as one of the best gains from treatment (Richardson et al., 2005). This value of exercise has been similar to that in the general population (ibid). Thus health professionals in this field should also incorporate exercise interventions for people experiencing episodes of psychoses (Richardson et al., 2005).

Connolly and Kelly (2005) examine alternative therapy when medications have exacerbated the eating habits of people, by side effects that increase appetite, cause sluggishness and create a lack of motivation to exercise. The outcome of various studies concerning these metabolic diseases reflects that lifestyle modification is a needed feature (Paton et al., 2004), and health
progress has been positively reported across numerous studies (Wadden et al., 2004;) psychological advantages for this population from studies which review benefits of exercise and diet alongside counselling for long-term weight maintenance (Faulkner et al., 2003)

Suicide
Carpenter et al's (2000) work on gender differences found that suicidal tendencies were more likely amongst the normal weight men, because of body image dissatisfaction, compared to obese men; and even more intense depression and suicide issues were found when men were underweight. Women on the other hand behaved suicidal when obese and were more balanced emotionally when they were underweight and normal weight. Thus weight gain is a problem as research has identified in that the negative psychological impact of neglecting overweight issues may lead to loss of image, isolation, and even suicide (Carpenter, et al., 2000). The interventions for the mentally ill group are even more difficult (Paton et al., 2004) not just because of their negative lifestyles but because of the prevalence of comorbid illnesses and diagnosis such as those known for schizophrenia (Connolly & Kelly, 2005).

Self-esteem
Self-esteem is pivotal in every individual's mental framework for coping healthily and it appears that a low self-esteem indicates a dysfunctional mindset (Fox, 1999). Low self-esteem is one of the problems that can arise from obesity. Wadden et al (2004) found that obese patients with a BMI of over or equal to 40 kg per metre square, had significantly greater depressive symptoms and significantly lower self-esteem than those with a BMI less than 40 kg per metre square. Research seems to imply that as a result of ensuing health issues and suffering prejudice and discrimination, people who are obese become depressed (Fabricatore & Wadden, 2003) and obesity may occur over a period of time as food is consistently sought for as source of comfort to replace human contact (Fabricatore & Wadden, 2003).
Fabricatore and Wadden (2003) have examined prejudice and discrimination as causes of depression and other emotional problems in obesity, even though the relationship between depression disorders and obesity is unclear (Cooke & Wardle, 2007); it appears that the societal impressions of slimness is so portrayed that it undermines healthy behaviours psychologically.

Although there is known to be weight gain with most antipsychotics (Newcomer, 2004), the effects of weight gain is important to acknowledge because of the profound implications for self-management when suffering mental illness (Richardson et al., 2005). Wadden et al. (2004) compared ‘self-esteem, and body image’ for women, in weight management amongst the mentally healthy population (p.561). They gave counselling for lifestyle change surrounding the issues such as ‘control’ and found that the participants were better in their ‘body image and self-esteem’ even when they did not lose weight.

The importance of body image is also vital to the mentally ill population as researched by Weil et al. (2002) who found that people with a mental illness were interested in losing weight ‘more frequently than the general population’ (p.1267). This research done in the United States, found that obesity was higher in this group than for the mentally healthy groups. A high proportion of people with disabilities desired to lose weight and embarked on ‘exercise counselling’ (p.1267). Weil et al. (2002) pointed out that their outcomes were similar to previous studies which revealed ‘an association between obesity and disability’ issues (p.1267). This population is susceptible to increases in weight because of the use of medications, and this should not be ignored, likewise for the mentally healthy groups.

The purpose of this review is to explore whether there is weight loss in patients taking the atypical antipsychotic, aripiprazole. There is also the underlying aim to give support to those suffering mental illness in regard to treatment and identify the ways in which further exploration of these findings could improve their health and well-being psychologically. The impact of weight management within this population is also being examined because it
is known to facilitate improvements in long-term health, through support that relates to self-esteem. There was less literature on the issues of weight gain and aripiprazole, since as recent drug for mental illness it has not yet had extensive research and there have been good expectations (Naber & Lambert, 2004).

2.0 Aim
To conduct a meta-analysis on eight primary studies to investigate the atypical antipsychotic, aripiprazole, compared with a few other antipsychotics in the treatment of mental illness for weight loss.

2.1 Objective
Primary objective: to explore the effects of aripiprazole and weight loss compared with other antipsychotics for people with a mental illness both psychologically and with regard to a benefit in weight management.

2.2 Hypothesis
To determine whether aripiprazole, as an atypical antipsychotic, has an effect on weight loss compared to other antipsychotics.

3. Criteria for considering studies for this review

3.1 Types of studies
Initially only relevant randomised controlled trials were selected. Then after narrowing down the field, only studies where criteria for meta-analysis was possible were collated, for all types of designs, due to limitations of the number of studies available because this area of interest involves a relatively new medication (aripiprazole), on the market and there is less research on it at the moment.

3.2 Types of participants
People with schizophrenia and schizophrenia spectrum disorders, were accepted to start with, and then it became all psychoses and mental illness, defined with a respectable well known diagnostic criteria. This population consisted of all people between the ages 18-65, not excluding race or gender. Illness was over any length of time and treatment in any setting.

3.3 Types of intervention

The comparison of all antipsychotics for weight gain or weight loss across all single and groups of meta-analytic reviews were found. Next, further searches focused on the atypical antipsychotic aripiprazole, because as a newer drug it was purported to be more effective in producing less weight gain than other antipsychotics. Thus the primary outcome had to be weight loss in the included studies for the support of the hypothesis and then only single reviews were sought.

a) Aripiprazole: oral doses ranged from 10 – 30 mg/day.

b) Standard of Care (S.O.C.): olanzapine (5-20 mg/day) risperidone (2-8 mg/day), quetiapine (100-800mg/day). Other antipsychotics: Haloperidol (10mg/day). Atypical antipsychotics: Risperidone (6mg/day). Olanzapine (10-20mg/day).

3.4 Types of outcome measures

3.4.1 Adverse effects of weight gain. The weight was measured in kilograms (mean change in body weight from baseline), mean BMI (Kolotkin et al., 2008) or seen as a probability p value (Kane et al., 2002). The period of outcome measures for weight gain was defined as 12 weeks or less for short term, medium term was 12-52 weeks and long term was over 52 weeks (or over one year) (Duggan et al., 2005, p.3).

4. Search methods for identification of studies

4.1 The search strategy involved the electronic databases of the Cochrane Collaboration/Library. The searches were done for any year by using the keywords schizophrenia, weight gain, and random controlled trials. Then, the
keywords antipsychotics and weight gain were tried, alongside aripiprazole and weight loss and also for the health care databases of the digital library of AMED (alternative medicine), Medline via Ebscohost Research Databases, Medline through PubMed, Ebscohost EJS (Electronic Journals Service), Ebscohost RD (Research database), CINAHL Plus with full text, SocINDEX with full text, Psych Info, Scirus for scientific information, Intute, Sage premier, Biological and biomedical sciences databases that led to Biomed central and the National library for health.

Searches were also done using the keywords: aripiprazole and weight gain or weight loss, aripiprazole and atypical antipsychotics and weight loss, with any of my search terms to be found with full text or abstracts. The other keywords also tried were psychological impact, weight management, metabolic disturbances, and metabolic syndrome.

4.2 The literature search included conference papers, journals, electronic journals, research report reference lists, research bibliographies, alongside reference databases (such as Psych Info).

5. Methods of the review

5.1 Methods.
All the designs were randomised; duration of the studies ranged between 4 weeks to 52 weeks; therefore average duration was 18 weeks. The double-blind reflects current practices of evidence-based medicine that is preferred to avoid 'bias' (Steptoe, 2007, p.355). Double-blind is a strategy that aims to avoid knowledge of the treatment conditions for both the experimenter and the participant so that the outcome is not affected by their personal influences (ibid).

5.2 Participants and setting.
All studies included people diagnosed with schizophrenia or schizoaffective disorders and Bipolar I disorder. The majority stated the DSM-IV criteria for
diagnoses, and in only one study the diagnostic criteria was not reported (Chrzanowski et al., 2006) but appropriate measures were applied for mental and 'Clinical Global Impression Improvement scale (CGI-I)' and scales of 'Positive and Negative Syndrome Scale (PANSS)' for schizophrenia (Chrzanowski et al., 2006, p.260).

The studies were examining the participants at the stages of 'acute, relapsing or chronic, stable schizophrenia' (Chrzanowski et al., 2006, p.259); 'acute schizophrenia' (Chan et al., 2007, p.29); 'acute relapse' for 'hospitalization' for schizophrenia (McQuade et al., 2004, p.47); 'acute exacerbation or schizophrenia or schizoaffective disorder' (Potkin et al., 2003, p.681) or at a stage of switching medication for schizophrenia (Newcomer et al., 2008); and for 'acute manic or mixed episodes' of Bipolar I disorder (Vieta et al., 2005, p.235). There were slightly more male than female participants in Kolotkin et al. (2008) and Chrzanowski et al. (2006) whereas in the other studies the percentage was not stated either in the full article or the abstract. The participants were aged between 18 – 65 (Potkin et al., 2003; Vieta et al., 2005) with a mean age of 38.5 years in Kolotkin et al., (2008) and data for the other studies were not provided (Kane et al., 2002; Chan et al., 2007; McQuade et al., 2004; Newcomer et al., 2008; Chrzanowski et al., 2006). The mean BMI of the participants at baseline was provided in Kolotkin et al. (2008); the mean weight of the participants at baseline was approximately 74.6 kg with a standard error of 1.1 for aripiprazole (Vieta et al., 2005, p.247).

5.3 Setting.
Four studies included only outpatients (Chrzanowski et al., 2006; Chan et al., 2007; Kolotkin et al., 2008; Newcomer et al., 2008), three studies included only inpatients (Kane et al., 2002; McQuade et al., 2004; Potkin et al., 2003) and one involved both (Vieta et al., 2005).

5.4 Study size.
Most studies were large and ranged between 83 – 555 participants at the start of the study (mean number randomized 313). The total number of participants from the eight studies were N = 2, 507.
5.5 Interventions.
The studies were comparisons for aripiprazole, with a control group for S.O.C. (Kolotkin et al., 2008), risperidone (Chan et al., 2007; Potkin et al., 2003), olanzapine (Chrzanowski et al., 2006; McQuade et al., 2004; Newcomer et al., 2008) and haloperidol (Kane et al., 2002; Vieta et al, 2005).

5.6. Selection of trials
This was done by careful examination of all research articles, with titles and abstracts being read first before accessing the full article for further investigation. Then the decision to accept the studies was considered if the criteria for inclusion were met for the review in the methods section.

5.7 Data collection.
The data from the selected studies were extracted with regard to use of the statistical method of meta-analysis.

5.8. Data synthesis.
Calculations were done using the formulae from Rosenthal (1978). The $p$ value and $z$ scores on the Gaussian curve have a normal distribution of data here, and this method was applied for all the included primary studies.

5.9 Incomplete data.
There are high rates of discontinuation in this area, but studies were not excluded on the basis of the percentage of participants completing them.

6. Description of studies
The following tables summarise the information for the studies that were suitable for the meta-analyses and those that were rejected.
## 6.1 Included studies

### Table 1 Table of included studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Method</th>
<th>Condition</th>
<th>No. of participants</th>
<th>Weight findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan, Lin, Lin, Hwang, Su, Chiang &amp; Hwu (2007)</td>
<td>Randomised Double blind</td>
<td>Schizophrenia or schizoaffective disorder</td>
<td>83</td>
<td>No significant difference with mild weight gain for both aripiprazole and risperidone.</td>
</tr>
<tr>
<td>Chrzanowski, Marcus, Torbeys, Nyilas &amp; McQuade (2006)</td>
<td>Randomised Double blind</td>
<td>schizophrenia</td>
<td>214</td>
<td>Olanzapine had significantly greater weight gain compared to aripiprazole at all time points. At week 52 [LOCF]: +2.54 vs. + 0.04 kg; p &lt; 0.001</td>
</tr>
<tr>
<td>Kane, Carson, Saha, McQuade, Ingenito, Zimbrow &amp; Ali (2002)</td>
<td>Randomised Double blind</td>
<td>Schizophrenia or schizoaffective disorder</td>
<td>414</td>
<td>No significant differences with weight. P &lt; or = .05</td>
</tr>
<tr>
<td>Kiolotkin, Corey-Lisle, Kan &amp; McQuade (2008)</td>
<td>Randomised</td>
<td>Schizophrenia</td>
<td>555</td>
<td>Significant reduction with aripiprazole P &lt; .05</td>
</tr>
<tr>
<td>McQuade, Stock, Marcus, Jody, Gharbia, Vanveggel, Archibald &amp; Carson (2004)</td>
<td>Randomised Double blind</td>
<td>Schizophrenia</td>
<td>317</td>
<td>More significant weight gain for olanzapine (37%) compared with aripiprazole (14%). p &lt; .001</td>
</tr>
<tr>
<td>Newcomer, Campos, Marcus, Breder, Berman, Kerselaers, L'italien, Nys, Carson &amp; McQuade (2008)</td>
<td>Randomised Double blind</td>
<td>Schizophrenia or schizoaffective disorder</td>
<td>173</td>
<td>Significant weight loss for aripiprazole (&gt; 0r = 7%) compared to olanzapine (11.1% vs. 9.1%; p = .082)</td>
</tr>
<tr>
<td>Potkin, Anutosh, Saha, Kujiwa, Carson, Ali, Stock, Stringfellow, Ingenito &amp; Marder (2003)</td>
<td>Randomised Double blind</td>
<td>Schizophrenia or Schizoaffective disorders</td>
<td>404</td>
<td>Not sure if there is a significant increase in weight for aripiprazole. Minimum increase across (not significant) -1.2kg, 0.8kg, 1.5kg. But significant difference to placebo. t-tests for placebo vs aripiprazole or chi square.</td>
</tr>
<tr>
<td>Vieta, Bourin, Sanchez, Marcus, Stock, McQuade, Carson, Abou-Gharbia, Swanink &amp; Iwamoto (2005)</td>
<td>Double blind Controlled comparison of Aripiprazole and Haloperidol Fixed 1:1 Ratio</td>
<td>Bipolar I disorder with acute or mixed episode</td>
<td>347</td>
<td>No significant difference between aripiprazole and haloperidol. No significant difference in Aripiprazole (+0.27Kg)</td>
</tr>
</tbody>
</table>
6.2 Excluded studies.

**Table 2 Table of excluded studies.**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Method</th>
<th>Condition</th>
<th>No. of participants</th>
<th>Weight findings and reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karunakaran, Tungaraza &amp; Harbome (2007)</td>
<td>Randomised</td>
<td>Schizophrenia</td>
<td>26</td>
<td>Significant weight loss 95.3 kg to 90.2 kg, p=.002, z= -2.58 N=20. Excluded because this is a review of case notes.</td>
</tr>
<tr>
<td>Keck Jr., Marcus, Tourkodimittris, Ali, Liebeskind, Sah &amp; ingenito (2003)</td>
<td>Randomised Double blind</td>
<td>Bipolar I disorder</td>
<td>262</td>
<td>Non significant weight gain. -0.3 kg small weight loss for aripiprazole, N= 130, z=130, z=0 p&lt;.5. slight decrease in both -.8 for placebo. Non significant. Excluded because it is a placebo controlled study.</td>
</tr>
<tr>
<td>McElroy, Suppes, Frye, Altshuler, Stanford, Martens, Leverich, Post &amp; Keck Jr (2007)</td>
<td>Prospective</td>
<td>Bipolar I disorder</td>
<td>31</td>
<td>Weight gain is for aripiprazole only. t= 1.95 df 26 p=.06, z=1.6?, p=.9 p&gt;.5 cohen d=.76. Very non significant. Excluded because it is a placebo controlled study.</td>
</tr>
<tr>
<td>Sachs, Sanchez, Marcus, Stock, McQuade, Carson, Abou-Gharbia, Impellizzeri, Kaplita, Rollin &amp; Iwamoto (2006)</td>
<td>Aripiprazole vs. Placebo</td>
<td>Bipolar I disorder</td>
<td>272</td>
<td>Non significant weight gain. Small weight gain .53kg. Decreased (&lt;.6kg) n=137 (aripiprazole), n=135 (placebo), non significant reduction p&lt;.5, p=.5, z=0. No specific significant test. Excluded because it is a placebo controlled study.</td>
</tr>
</tbody>
</table>
7. Methodological quality

7.1 Randomisation
The eight studies chosen for meta-analysis used random allocation.

7.2 Blinding
There were seven studies that were double-blinded (Chan et al., 2007; Chrzanowski et al., 2006; Kane et al., 2002; Potkin et al., 2003; McQuade et al., 2004; Newcomer et al., 2008; Vieta et al., 2005) and one study that did not state method of blinding (Kolotkin et al., 2008).

7.3 Discontinuation
There were people leaving the study early in Kolotkin et al. (2008) due to side effects (20.1% for aripiprazole and 15.9% for S.O.C.) and at the end of the study at week 26 the figure for those still participating was 60% (p.5). There were 162 out of the original 404 participants who discontinued in Potkin et al. (2003) with main reasons such as inadequate clinical treatment or becoming psychotic (not related to study regime). Chrzanowski et al. (2006) had least number of participants leaving the study early (69% remained) because of 'withdrawal of consent' (p. 261). It is not reported in Chan et al. (2007) or Kane et al. (2002) of any numbers leaving the study early (they are abstracts only included studies). There were large numbers of dropouts in Vieta et al. (2005) as well, with 59.9% and the reason given was for side effects again such as EPS (p.238). Other reasons were listed as 'patient withdrawal of consent (6.1%) and lack of efficacy (5.2%)' also liver damage 'related to study medication' (p. 239; p.238). The numbers of people leaving for all the remaining studies were unclear as in the abstracts only included studies (McQuade et al., 2004, Newcomer et al., 2008).

7.4. Data reporting
Potkin et al. (2003) presented data in graph form as a boxplot which indicated that there were also ‘p’ values. Vieta et al. (2005) gave graphs to depict changes and tables of demographic information; and various measures for
assessments such as 'efficacy' and 'depression ratings' (p.237; 238); also analyses that used the Last Observation Carried Forward (LOCF) analysis which are 'observed cases, defined as those completing the trial' (ref.) and observed cases data- sets for results (p.236). Percentages were given and body weight in kilograms and means with standard error from baseline in Vieta et al. (2005; Newcomer et al., 2008; Kolotkin et al., 2008; Chrzanowski et al., 2006; McQuade et al. (2004) reported data in kilograms, pounds and percentages with 'p' values. Chan et al. (2007) and Kane et al. (2002) gave significant levels with 'p' values.

7.5 Overall quality
The methodological quality of included trials in this review was done by following guidelines described in the Cochrane Handbook (2008). The hypothesis was important in choosing the studies and then to understand the bias in the methods for reliability (Hunter & Schmidt, 2004). In the assessment of quality there may be limitations encountered that does not accept the studies, and may lead to reject a study. There were five studies (Karunakaran et al., 2006; Keck et al., 2003; Kerwin et al., 2007; McElroy et al., 2007; Sachs et al., 2006) that were rejected. There was similarity seen across the studies with similar researchers, because they were involved in second studies as members of a group such the ‘S.T.A.R.’ (Schizophrenia Trial of Aripiprazole) (Kolotkin et al., 2008).

The included studies were good because the methodology provided results for them that were different from the excluded studies which had been judged as bad choices, with differences between them that allowed rejected (Hunter & Schmidt, 2004). The issue of limitations in the method is important in evaluating the quality for the overall results of the meta-analysis (Hunter & Schmidt, 2004). It is stated that meta-analysis may "mix apples and oranges" (for example atypicals and typicals such as aripiprazole with haloperidol ) in the outcomes, though this may mean seem to complicate matters, if each case is presented with its outcomes separately then the regardless of the strangeness of this concept this issue can be interpreted (Hunter & Schmidt, 2004, p.469).
The possibility of bias in the included studies

1. Randomisation.
All the studies were reported as randomised.
However half of the included studies did explicitly describe the methods section with inclusion and exclusion criteria. Although, for the other half of the included studies this was difficult to know because they were abstracts only.

2. Blindness.
There was only one study that did not state blinding and this was a secondary study (Kolotkin et al., 2008). The participants are blinded to prevent losing them from the study and to avoid influencing the results by giving away any knowledge of the areas being investigated (Christensen, 2004).

3. Loss to follow up
None of the included studies mention a follow-up over their losses except Potkin et al. (2003) which comments on a follow up being done that needs to be longer, because of taking weight measurements that represent consistent findings (p.690):

4. Data reporting
The data was fairly well reported in the included studies; and those that could not be used were outcomes that were often presented as graphs, or just reported as inexact p-values (Keck at al., 2003).

This systematic review sought general information from the title, authors (such as those in a group studying the same issues), publication date — generally recent in this case, type of intervention which needed to include aripiprazole, and the presence of a meta-analysis. The title and abstracts were first read to assess whether the study was relevant for meta-analysis. Then the introduction led the approach for the systematic literature review, with the results next for the p values to conduct a meta-analysis. Then an evaluation of what the authors reported in the methods section of their review was done for
quality assessment. This included whether the authors revealed that they had made quality assessments and by what methods this was done, such as a scale or checklist as in the criteria for exclusions, for instance (Kolotkin et al., 2008). It is not known if each study carried out a quality assessment but DSM criteria for assessment of disorders was present and this indicated good quality.

Random Controlled Trials's (RCTs) are observed as the most objective method of removing bias by choosing a sample by chance and it takes account of the variability of the participants (McQueen & Knussen, 2002). Random sampling does not require in depth details of the population under investigation to make a generalisation (McQueen & Knussen, 2002). RCTs randomly allocate participants into a control group and an intervention group, with the two groups being identical for any significant variables (Christensen, 2004). They should be followed up for their specific outcomes (ibid). Public health is less well suited to RCTs because it believes in evidence based practices and RCTs are slow and expensive producing results that can be difficult to apply to real situations (McQueen & Knussen, 2002). In fact RCTs may limit generalisations to geographical demographics, known as 'area sampling' (McQueen & Knussen, 2002, p.73). Thus this could be an issue of selection bias.

This review gives threats to internal validity. Internal validity is the understanding that 'only' the independent variable impacted on the dependent variable in a 'cause and effect' design (Christensen, 2004, p.198). This requirement is not possible in this case since it is possible that there are 'extraneous variables' acting on the weight outcome other than the medication (ibid. p.199). Therefore a causal inference cannot be made in this review. Internal validity is the 'extent to which systematic error (bias) is minimised in clinical trials' and this is affected by 'selection bias, performance bias, detection bias, and attrition bias' (Juni et al., 2001, p.1) Attrition bias is 'biased occurrence and handling of deviations from protocol and loss to follow up' (ibid, p.1).
The scales had been cleared every time for a weighing and the same scales were used every time thus there was a standardised procedure (Kolotkin et al., 2008). In this case the weighing of the participants should all be of the same procedure as well as the definitions for the scales of measurements for their mental health and weights. The qualifications of the researchers is important in the treatment interventions being given because of the serious clinical nature of the issues being dealt with, and their ability to give an objective and reliable method of measure is also referred to as standardisation (Coolican, 1990). This is important because it makes the trials the same for everyone by adjusting it using reliability and validity tests (Clegg, 1990, p.42). This is of 'scientific and ethical importance' (Coolican, 1990, p.113). It is important to consider other variables in order to reduce bias. Validity and reliability are affected by researcher bias (Christensen, 2004). In evaluating the quality of the review, risks of bias may be found.

8. Results

8.1. Included studies.
There were eight studies that were included, which reflected the hypothesis well. The studies had included the S.O.C. drugs of olanzapine, risperidone, quetiapine, as well as the antipsychotic, haloperidol and the atypical antipsychotic, aripiprazole. The psychoses were included along with all mental illnesses that were being treated by the drug aripiprazole effectively, such as bipolar 1 depression (Vieta et al., 2005), schizophrenia and schizophrenia spectrum disorders. The focus was weight management for this population and included weight loss or weight gain. The designs were all Randomised Controlled Trials (RCT's), and the articles were published from 2002 to 2008, which highlights that this drug is new and it is an effective agent in the treatment of psychoses and mental illness. The characteristics of these eight included studies are seen in appendix 2.

8.2 Excluded studies
The characteristics of excluded studies are seen in the appendix 3. Studies were excluded on basis of age - over 65s, placebo, comorbidity, under 18, learning disability, single case history studies, and the addition of chemical compounds such as sibutramine and fluoxetine for weight loss (Faulkner et al., 2007, p.12). Five studies were excluded from the meta-analyses (Kerwin et al., 2007, McElroy et al., 2007, Karunakaran et al., 2007, Keck Jr. et al., 2003, Sachs et al. 2006). Kerwin et al. (2007) was rejected because it replicated the findings of Kolotkin et al. (2008) and it was an earlier study. McElroy et al. (2007) was rejected because it was examining aripiprazole only for weight gain and there were no other comparators. Sach et al (2006) was a non-significant reduction at p > .5 value but it was comparing with a placebo which was an exclusion factor and there was no specific significant test. Whereas Keck et al. (2003) indicated small a weight loss over three weeks with aripiprazole being at -.3 kg and this was not significant at p< .5 value, but it was comparing with a placebo as well. Finally, Karunakaran et al. (2006) had a significant weight loss at p = .002 with a z = -2.58, but this was a review of cases and thus excluded.

8.3 The meta-analysis found that most of the eight studies were between 4 and 52 weeks (short term and medium term), and indicated that weight loss is achieved and it seems that aripiprazole has beneficial and less problematic side effects (Naber & Lambert, 2004). Similar to other atypical agents it causes less extrapyramidal effects symptoms, and in contrast it seems to prevent some of ‘the metabolic and cardiac side effects’ (Naber & Lambert, 2004, p.1217).

There was not enough information to test issues of race and gender as well because only the abstracts were available in some cases. In testing the one-tailed hypothesis for aripiprazole with other antipsychotics, the meta-analysis was calculated with Rosenthal’s formulae. There are various methods in meta-analysis but in this review the method used is of cumulative values of $p$ seen through similar studies with the same question in mind (Hunter & Schmidt, 2004). The statistical significance of the hypothesis is being tested. The null hypothesis needs to be known for being true or false in this case and
the error rate can be defined (Hunter & Schmidt, 2004). Generally the 5% rate is the ideal for significance testing with sample sizes, but this applies specifically when the null hypothesis is true (Hunter & Schmidt, 2004) thus values of $p$ are termed significant or not for the hypothesis. The overall statistical significance level ($p$ value) for the eight studies have cumulating $p$ values across these studies, and for an assumed null hypothesis finding $z=0$ was assigned in some instances. Fisher (1932, in Hunter & Schmidt, 2004, p. 453) in significance testing of the null hypothesis has provided the $F$-test for small numbers in a population, as seen in some of the studies, with a parametric, Gaussian curve for $p$ values and $z$ values for significance.

Rosenthal (1978a) has been interested in the significance level with $p$ value in one-tailed tests where this has to be 'converted to a standardized normal deviate, denoted $z$' (cited in Hunter & Schmidt, 2004, p.447). The $z$ values have been 'either summed directly or used to compute a weighted sum of the $z$s' (ibid, p.447). 'Then the average of these $z$s is computed and the significance level ($p$ value) of the average $z$ value is determined. This is the $p$ value for the set of studies as a whole' (ibid, p.447). This is a fixed-effects model and applies the method of a 'partially hierarchical breakdown' (Hunter & Schmidt, 2004; 447, 424). Fisher (1932) too has recommended this method (in Hunter & Schmidt, 2004, p.453).

The data was of continuous type and normally distributed, though data on clinical and social outcomes are not normally distributed (ref.). The change data (endpoint minus baseline) and endpoint data were recorded. It was expected that aripiprazole would be lower at time 2 ($T_2$) for weight than other drugs to support the hypothesis, by showing a difference between the comparison drug and aripiprazole for effect. The studies showed body weight in kilograms or a change from baseline to endpoint also BMI was given in some cases and means. In some instances the study lacks specific data for the statistical calculation so assumptions have been made for a valid meta-analysis.
Effects of interventions

Only abstracts were available for 4 studies (Chan et al., 2007, Kane et al., 2002, McQuade et al., 2004 & Newcomer et al., 2008). The search strategy identified 15 studies. Of these 13 potentially relevant trials were selected. Included were eight studies and seven studies were excluded.

8.3.1 Chrzanowski et al. (2006) aripiprazole versus olanzapine, at 28 weeks duration (medium term)
Weight: Olanzapine had increased weight at all points in time than aripiprazole (week 52 [LOCF]: +2.54 vs +0.04 kg; \( p < 0.001 \)).
The statistics were calculated using tables, \( N_1 = 71, N_2 = 89 \) (Total \( N=160 \)), \( p< .01 \), to produce the value of \( z = -2.33 \).

8.3.2 McQuade et al. (2004) aripiprazole versus olanzapine, at 26 weeks duration (medium term)
Weight: 37% of olanzapine had significant weight gain versus 14% of aripiprazole.
This was statistically calculated by \( p< .001 \) and total \( N=317 \), with \( z=-3.00 \).

8.3.3 Newcomer et al. (2008) aripiprazole versus olanzapine, at 16 weeks duration (medium term)
Weight: Greater proportion of participants on aripiprazole had weight loss (> or = 7%) versus olanzapine (11.1% vs. 2.6%; \( p=.038 \)).
Total \( N= 173 \), Aripiprazole \( N = 88 \), olanzapine \( N = 85 \), at 16 weeks weight decreased significantly with aripiprazole versus olanzapine \( p< .001 \), \( z= - 3.00 \)

8.3.4 Chan et al. (2007), aripiprazole versus risperidone, at 4 weeks duration (short term)
Weight: There was a minimal weight gain for both aripiprazole and risperidone.
Total \( N= 83 \), aripiprazole \( n = 49 \), Risperidone \( n = 34 \), \( z \) was given a value \( z=0.00 \) and there was no significant difference and both would gain. An assumed null finding of \( z=0 \).
8.3.5 Kane et al. (2002) aripiprazole versus haloperidol (against placebo), at 4 weeks duration (short term)
Weight: There was found to be 'no statistically significant differences in mean changes in body weight across the treatment groups versus placebo' (Kane, 2002, p.1)
Assumed N=276, aripiprazole n= 138, haloperidol n= 138, placebo n= 138, z is given value z=0.00. An assumed null finding of z=0. No significant difference (assumed n is 414/3 for each group).
\[ z = 0.000 \]

Weight: Over the entire 26 weeks duration there was decreased weight for aripiprazole treated patients compared to S.O. C.
\[ N=555, z = -7.5, p< .000000 \]
\[ t= - 7.5. \text{Interaction F} = 25.98 \]
\[ (3, 1146) p<. 0001 \]
\[ N=278, -1.45\%. \text{P}=0.05, z=-1.65. \text{Significant reduction p}<. 05 \]
A t-test of difference was done for this at 0.05 and the t value was square root of 56 t=7.5. A complex interaction was reported – Aripiprazole versus. S.O.C a three time follow up. Also reported contingency table chi significant weight gain/loss z= -4.6 p<. 001.

8.3.7 Potkin et al. (2003) Aripiprazole versus resperidone.
Weight: Not sure if there is a significant increase in weight for aripiprazole. Minimum increase across (not significant) – 1.2kg, .8kg, 1.5kg but significant difference to placebo.
\[ t –\text{tests for placebo versus aripiprazole or chi square.} \]
\[ N=100 \]
\[ Z=0 \]
N=300, aripiprazole n= 101 + 100, resperidone n= 99, N = 300, n = 404/3, no significant difference z=0.00, this was an assumed null hypothesis finding of z=0.

8.3.8 Vieta et al. (2005) aripiprazole versus haloperidol, at 12 weeks duration (short term)

Weight: No significant difference between aripiprazole versus haloperidol.

No significant difference in aripiprazole +.27kg z=0, N=174

N= 347, z= +0.50

n = 175 versus n= 172, therefore total N = 347

8.4 Table of analyses.

The following table summarises the analysis of the results.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Results</th>
<th>Sample size</th>
<th>Estimated z value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al. (2007)</td>
<td>Aripiprazole vs. risperidone</td>
<td>No significant difference</td>
<td>N= 83</td>
<td>Z = 0 assumed null</td>
</tr>
<tr>
<td>Chrzanowski et al. (2006)</td>
<td>Aripiprazole vs. olanzapine</td>
<td>P &lt; .01 significance difference</td>
<td>N= 214</td>
<td>Z =-2.33</td>
</tr>
<tr>
<td>Kane et al. (2002)</td>
<td>Aripiprazole vs. Haloperidol vs. placebo</td>
<td>No significant difference P&lt; or = .05</td>
<td>N=414</td>
<td>Z = 0.000 assumed null</td>
</tr>
</tbody>
</table>
| Kiolotkin et al. (2008) | Aripiprazole vs. S.O.C. | t =-7.5  
F= 25.98  
p = 0.05  
p < .0001  
Significant difference | N=555       | Z = -7.5 -1.45% result from Kerwin et al. (2007) – an earlier study Z= -1.65 |
| McQuade et al. (2004) | Aripiprazole vs. olanzapine | P< .001 Significant difference    | N= 317      | Z = -3.00         |
| Newcomer et al. (2008) | Aripiprazole vs. olanzapine | P < .001 Significant difference  | N= 173      | Z = -3.00         |
| Potkin et al. (2008) | Aripiprazole vs. risperidone vs. placebo | No significant difference | N= 404     | Z = 0 assumed null |
| Vieta et al. (2005) | Aripiprazole vs. haloperidol | No significant difference     | N= 347      | Z = + 0.50        |

8.4 Rosenthal (1978) formula was applied for a statistical method for data analysis in meta-analysis for the included eight studies. It was important to
assess the baseline values and time as common in all to show any differences in weight.

\[ Z = \frac{T}{\sigma T} \]

\[ = \frac{(N_1 \times Z_1) + (N_2 \times Z_2) + (N_3 \times Z_3) + (N_4 \times Z_4) + (N_5 \times Z_5) + (N_6 \times Z_6) + (N_7 \times Z_7) + (N_8 \times Z_8)}{\sqrt{(N_1^2 + N_2^2 + N_3^2 + N_4^2 + N_5^2 + N_6^2 + N_7^2 + N_8^2)}} \]

The meta-analysis involved combining z's and adding weighted z's

Formula:
\[ Z = \frac{T}{\sigma T} = \frac{df_1Z_1 + df_2Z_2 + ... + df_nZ_n}{(df_1^2 + df_2^2 + ... + df_n^2)^{\frac{1}{2}}} \]

(Rosenthal, 1978, p.187)

Or
\[ Z = \frac{T}{\sigma T} = \frac{(N_1 \times Z_1) + (N_2 \times Z_2) + ...}{(N_1^2 + N_2^2 + N_3^2 ...)^{\frac{1}{2}}} \]

Therefore sum of z's = (160 x -2.33) + (317 x -3.00) + (173 x -3.00) + (83 x 0) + (276 x 0) + (555 x -7.5) + (300 x 0) + (347 x 0) / [(160)^2 + (317)^2 + (173)^2 + (83)^2 + (276)^2 + (555)^2 + (300)^2 + (347)^2] = -5831.8 / (757517) square root

= - 5831.8 / 870.35

Sum of z = -6.700
p < .0001

Thus the value of -6.700 indicates that the result is highly significant at p < or equal to .0001 and the hypothesis is supported.

8.5 File drawer calculation is not always necessary, but it clarifies the influence of sampling bias (Rosenthal, 1978).

\[ X = \frac{(k)}{2.706} \frac{(k)}{(Z_k)^2 - 2.706} \]
(Rosenthal, 1979, p.639)

\[ z = -1.645 \]
\[ X = \frac{8}{2.706} \]
\[ X = \frac{(-.6.7)^2}{2.706} - 8 \]
\[ X = \frac{-6.7 \times -6.7}{2.700} - 8 \]

This means that it would take studies averaging 9, \( z = 0.000 \) to overturn the overall \( z \) combined from -6.7 to -1.64 and therefore no longer significant.

This calculation of the unseen studies has potential impact on the conclusion and is called the file drawer problem (Rosenthal, 1979).

**9. Discussion**

The meta-analysis showed significant differences between the conditions to support the hypothesis that there is weight loss for aripiprazole, compared to a few other antipsychotics in this review. Unfortunately, not all the studies support that aripiprazole is best for weight loss (Chan et al., 2007). Therefore there are a few inconsistencies, although the overall result is a strongly significant one allowing a generalisation to be made of this population sample. The pooling of data found that the included studies showed little variation and this is a homogenous sample. There was homogeneity of information from the studies, which suggest that there are only a few reliability issues. It is thought that ‘many study characteristics may affect study results’ but this study does not have much variation (Hunter & Schmidt, 2004, p.471). An advantage of this review was that the search strategy was flexible.

Aripiprazole, as an atypical antipsychotic, has a strong positive outcome from four of the included studies with significant differences of having weight loss with its comparator (Chrzanowski et al., 2006; Kolotkin et al., 2008; McQuade et al., 2004; Newcomer et al., 2008) whereas the other four studies are such that they showed less strength and consistency, with three of them having unclear direction and no significant difference between its groups (Kane et al., 2002; Potkin et al., 2003; Vieta et al., 2005) and one study with ‘mild weight gain’ for its groups (Chan et al., 2007, p.29). So these other antipsychotics
need to be investigated separately for interventions in weight loss and their effectiveness.

The causal mechanisms were not investigated in this study for weight gain and antipsychotics and this would be another area for investigation. It is important to point out that previous studies have involved participants who have normally been on medication for their illness over a long period of time, before they embarked as participants in these trials, which could indicate an exaggerated or imprecise weight gain (Reynolds, 2007). The meta-analysis has provided evidence for aripiprazole to be seen as a promising new drug as for weight loss as well as treatment of mental illness; and in relating to weight and self-esteem psychologically, there needs to be understanding of the depth of these issues, that include what is a healthy diet, weight, exercise and management issues (Faulkner et al., 2003). Weil et al. (2002) found that people were conscious of their weight and keen to take measures to reduce excess weight in the mentally ill population, even more so than the general population.

Aripiprazole is one of the NGAs, which are extremely popular in the 'industrialized' economies (Kommossa et al., 2007, p.1) with minimal loss in weight that is hoped will mean that aripiprazole will allow treatment to be continued for a length of time where 'adherence' to the medication, and with a dosage that will benefit the patient, to encourage maintenance to occur during their mental illness, for long term benefits (Thomas, 2007, p. S115). Although the studies that support aripiprazole have claimed that a more positive picture for mental illness is emerging for side effects such as weight gain, there is a need to balance the impact of weight gain with the benefits of treatment to recovery (Ascher-Svanum et al., 2005). The wider impact of understanding these issues with the treatment of mental illness should allow for the prevention of secondary complications which are associated with weight gain (Lean, 2003).

There should be monitoring and regular screening while people are on medications (Kolotkin et al., 2008). Weight gain is a major issue now for all
those practicing in the health professions and the use of antipsychotics are being investigated more closely for their benefits and limitations for weight in individuals, since it has been found that the side effects vary from individual to individual and may not even occur in any depth for a few individuals (Malhi, 2003). The problems of weight gain and metabolic disorders have become a clinical issue (Thomas, 2007).

**Ethical Issues**

The authors of the studies used for the review, defined the ethical procedures they undertook such as the Declaration of Helsinki and Good Clinical Reporting Practice, as well as an ethics committee for approval with participants consent in Chrzanowski *et al.* (2006); Vieta *et al.* (2005) pointed out that they had ethical approval and participant consent; Potkin *et al.* (2003) similarly received approval from an ethics committee, followed the Good Clinical Practice guide, Food and drug Administration regulations, the Declaration of Helsinki and consent of participants; and Kolotkin *et al.* (2008) followed the Declaration of Helsinki, received approval by Institutional Review Boards and participants gave consent. Whereas for the other four of the studies which were abstracts this information was not obtained. The studies seem to assess the patients' conditions during their research by their own experts which indicate concerns of anonymity, confidentiality and protection from harm issues in the knowledge of these participants illness and although consent was given (not known for the abstract only studies) the impact of a follow up and debrief is crucial in these studies because of the psychological issues to respect and reassure participants. There is concern for the cases where one patient died (Chrzanowski *et al.*, 2006), and another where there was worsening psychosis (Potkin *et al.*, 2003) but in both these studies the incidences are clearly stated as unrelated to study treatments. In Vieta *et al.* (2005) one patient had liver damage 'related to study medication' (haloperidol) (p.238) which could have been due to dosage.

A debrief is very important as an ethical issue and a follow-up (Coolican, 1990), both of which is not mentioned in nearly all of the studies. There was only one follow-up mentioned (Potkin *et al.*, 2003). The significance of
'psychological harm' from the study could have repercussions or worsen mental health if ethics is not dealt with properly for this group (ibid. p.254). The ethical issues incorporate the ideals such as of anonymity, confidentiality, allowing withdrawal, consent, debriefing, and protection for participants from physical and emotional harm (Coolican, 1990). Also on ethical issues the side effects of weight gain should be informed so there is prevention of complications (Lean, 2003).

The consequence with taking antipsychotics for the 'blood glucose' such as diabetes (McIntyre et al., 2005, p.118) should be understood with respect that people with schizophrenia as well as bipolar disorder and depression could suffer diabetes regardless of taking these drugs and weight gain, because of other factors such as the relevance of lifestyle and genetics (Guthrie, 2002). Aripiprazole has better reviews in metabolic disturbances alongside risperidone, quetiapine, and ziprasidone – though there has not been enough research on the long-term impact of these drugs to verify this adequately and there may be bias (McIntyre et al., 2005) since they are relatively new. Similarly for the association between antipsychotic weight gain and diabetes there has not been enough research to provide conclusive evidence (McIntyre et al., 2005); and diabetes and obesity are often related and people with these complaints are more likely to have depression (Fabricatore & Wadden, 2003).

The themes identified here require further exploration with participants from other populations so generalisation may occur. There are few RCT's that have tested this association between weight gain and antipsychotics (Faulkner et al., 2007). The number of studies for meta-analyses in this review was adequate and the study sizes were large (this study provided a sample size that was reliable N= 2, 507). A negative point is that the lengths of studies were variable - of short duration to medium length (Chrzanowski et al., 2006; Kolotkin et al., 2008; Vieta et al., 2005; McQuade et al., 2004; Newcomer et al., 2008). Kane et al. (2002) and Potkin et al. (2003) stated fixed doses while there was variability in Vieta et al. (2005) which could affect generalisability for results. There were a large proportion of participants leaving studies early which could again be a weakness in the design which is a problem for
generalisability (Vieta et al., 2005). These issues made it difficult to draw a robust conclusion about the meta-analyses. A good point is that there was no variability in study methodology since all studies described adequate randomisation with blinding procedures except one (Kolotkin et al., 2008). The descriptions of the methods were good with inclusion and exclusion criteria explained in the included studies (not possible to know from abstracts only studies). A comparison between the studies was not possible, as weight change was not given in all eight studies. The scales of measurement were BMI (Kolotkin et al., 2008) and weight in kilograms and means (Vieta et al., 2005). Some of the studies give percentage changes in weight (Chrzanowski et al., 2006).

Faulkner et al (2003) recommend BMI measurement, although this does not consider the ‘central fat distribution’ or ‘intra-abdominal’ adipose tissue, which is detrimental to health (Lean, 2003, p.13). Lean (2003) point out that this measurement should be done with a ‘waist circumference’ measurement, which would indicate the depth of this fat distribution (p.14). A weakness in this review is there were no long-term studies, so an exploration of the longer-term benefits of this drug use is difficult to ascertain. Another point is that inaccuracy may happen in the results because patients do not take their medication.

This issue of disability and mental illness has been classified according to cultural perception and society’s stigmatization of it; this is similar for weight gain (Lean, 2003). There have been interrelationships between the issues with inequalities in societal attitudes and clinical understanding that does seem to be changing with health promotions (Douglas et al., 2007). Faulkner et al. (2003) propose that clinicians should advocate exercise and diet counselling alongside antipsychotic therapy, even though changes brought about by these modifications may be short term (ibid), and the group may arrive with co morbid conditions that exacerbate weight management, that make treatment difficult.
The issues associated with mental illness and weight management appears to have not been attended adequately (Connolly & Kelly, 2005). Connolly and Kelly (2005) point out that the 'psychological state' is a 'risk factor' and that people with schizophrenia may need support because of the drugs used for treatment. They recommend that 'monitoring' with 'exercise and lifestyle' advice should be routinely given and switching medication to one that has less chances of weight increase should be given if possible. They suggest that listening to people with schizophrenia especially when they are suffering symptoms of the disease should be vital (ibid). Whereas for the bipolar I disorder the issues of weight management require similar judgement and CBT has been recommended as well as an appropriate method of treatment (NICE, 2007) that would equally well apply for adaptation for people with schizophrenia (Rector & Beck, 2001) with an integrated approach to treatment (Schultz et al., 2007).

Race differences could be examined for weight gain or loss and this ideology should be included in an education program that aims to advice on improving health and fitness (Littrell et al., 2003) because empathy of cultural issues would maximise greatest capacity for weight management. All issues need to be considered in the context of diet and activity with the significance of age, body weight adiposity, and ethnicity as background details that are important (Lean, 2003). The sample population could also be considered in view of their education and employment as well for extraneous variables).

9.1 Interventions
9.1.1 Weight
There were minimal differences between the groups of endpoint weight from baseline but they were significant; with mean baseline weight for aripiprazole being 73.6 kg (and 72.1 kg for olanzapine) in Chrzanowski et al. (2006, p.266) and this was similar across the studies. Most participants lost weight with aripiprazole compared to the control group (Chrzanowski et al., 2006; Kolotkin et al., 2008; Newcomer et al., 2008). In Chan et al. (2007) there was weight gain.
9.1.2 Discontinuation
There was discontinuation across the included studies, though the abstracts of Kane et al. (2002) and Chan et al. (2007) do not specify this loss.

9.2 All the eight studies are clear in their allocation of randomisation; community/hospital base and the short term and medium term gain of weight, but not for age and gender in control of other variables. The inclusion and exclusion criteria were compared and differed slightly from each other with Kolotkin et al. (2008) allowing comcomitant medication, while generally this was not allowed (Chrzanowski et al., 2006; Potkin et al., 2003). This use of concomitant medication is also an issue for worsening disease and needs to be known in the studies being conducted (Bushe & Paton, 2005). When patients take concomitant medications the results may become confounded.

9.2.1 Chan et al. (2007) was a study of asian patients from Taiwan receiving aripiprazole as treatment for schizophrenia with risperidone as a control; with findings that were not significant with a little weight gain for both groups. This showed no difference in the result compared to the ‘white patients’ (p.29).

9.2.2 Chrzanowski et al. (2006) were comparing ‘the efficacy and safety of aripiprazole with olanzapine’ and they had a sample from a predominantly ‘white 96%’ background (p.261). Unfortunately they also recorded that one 57 year old woman died due to heart failure which was deemed unrelated to the study’s medication; she had been ‘in the olanzapine group’ (p.262). Indeed past research had identified that olanzapine and clozapine cause more weight than some other atypicals (Newcomer, 2004; Reynolds, 2007). Also, in this study, there was more weight gain with olanzapine (2.54 kg) compared to aripiprazole (0.04 kg) (p.263). Aripiprazole also fared better in lipid profile overall to olanzapine, which is beneficial in adherence, and long term health concerns on the medications (p.265).

9.2.3 Kane et al. (2002) was a short-term study and seen as an abstract only with a large number of participants (N= 414) conducted in the U.S.A of in patients that were investigated for ‘EPS, serum prolactin level, and QTc
interval - 'as well as' weight gain' (p.763). Aripiprazole was not implicated in high levels of these other side effects or for significant weight differences (ibid, p.763).

9.2.4. Kolotkin et al. (2008) provided results from time taken at 8 weeks as time 1. The stages were a three-time stage of 8, 18 and 26 weeks in this study. Overall, S.O.C. had greater weight gain by (27.9%) 'at least 5% of their baseline weight, compared to only 11.7% for aripiprazole ($z = -4.62$, $p < 0.001$)' (p.4). This may be explained by controlling for confounding variables. The aripiprazole group 'lost approximately 1.5% of their baseline weight by week 8, and maintained that loss throughout the remainder of the study' (p.4). This was a significant result but it did not take account for smoking as a confounding factor in weight gain/loss or whether they were 'equally distributed after randomization' (p.6). Although the S.O.C. group are also atypical antipsychotics their mechanism of working is not as effective to counteract the side effects that aripiprazole has advantages over, because it is a partial agonist at $D_2$ receptors and at $5HT_{1A}$ receptors and antagonist activity at $5HT_{2A}$ receptors (Potkin et al., 2003, p. 690). This was examined by Beebe (2003) on treatment of schizophrenia with the atypical and typical medications with the latter in respect of their effectiveness due to their blockage of dopamine receptors and encouraging 'dopamine destruction' for positive symptoms and the former as preferable in terms of being better for the negative symptoms (p.116). Thus aripiprazole is called 'a dopamine system stabiliser' which is effective in treatment of both positive and negative symptoms of schizophrenia (Bandelow & Meier, 2003). Thus if side effects are controlled then empowerment to living independently may be achieved with 'a good health-related quality of life' (Thomas, 2007, p. S116). This is a benefit to public health issues.

9.2.5 McQuade et al. (2004) the weight gain was defined by a 'greater than or equal to 7% increase in body weight from baseline' (p. 47). In this study olanzapine had greater increases in weight compared to aripiprazole. Aripiprazole had improved 'lipids profile' and weight that indicates that it has a
'potentially lower metabolic and cardiovascular risk in patients treated with aripiprazole compared with those treated with to olanzapine' (p. 48).

9.2.6 Newcomer et al. (2008) found that when switching to aripiprazole from olanzapine there was improved 'weight and lipids' with benefits psychologically. At the end of the study there was weight loss for aripiprazole against olanzapine (-1.8 vs. 1.41 kg; p < .001) (p.1046).

9.2.7 Potkin et al (2003) had aripiprazole and risperidone, an atypical antipsychotic as a control group, to determine the effectiveness of doses of aripiprazole at 20 mg and 30 mg. The weight gain level was set at 'greater than or equal to 7% increase from baseline' and found that there was no significant difference between the groups (p.688).

9.2.8 Vieta et al. (2005) was interested in compliance to improve bipolar I disorder and compared aripiprazole with haloperidol, a first generation antipsychotic. There were more people leaving the study because of side effects with haloperidol than aripiprazole (p< 0.001). There was no significant difference in weight between the two groups.

The implications of issues such as these mentioned for the 'sampling, measurement, analyses, and findings' validate the study to be repeated (Hunter & Schmidt, 2004, p.471). Considering that this drug aripiprazole is fairly new on the market then it would be a feasible assumption to make that there would be more research as interest and use in this as treatment proceeds, so that the limitations seen will be addressed. These are good results with good quality data and a few well-conducted studies comparing aripiprazole with other antipsychotics.

10. Conclusion
The issue of choices for both the patients and clinicians should be presented with the atypical antipsychotics in mental illness with appropriate consideration of the patient's needs as well as of ideas of what they
understand for improving their lifestyle (Thomas, 2007). The amount of dosage of the drugs and time span of treatment is crucial for the best treatment (Vieta et al., 2005). The meta-analysis has shown that the results are significant with little variability so that there is a consensus to advocating drug therapy. It is apparent that there are risks of weight gain with some antipsychotics and atypical antipsychotics (Schultz et al., 2007). The atypical antipsychotic, aripiprazole could be given as a treatment that has a benefit of weight loss or minimal weight gain with the hope that long-term weight maintenance is successful where it is warranted.

It is necessary to explore this area because the negative impact of not managing overweight can lead to obesity and serious illnesses (Newcomer, 2004) and this is also important to public health practitioners. Therefore when antipsychotic use has produced weight gain this is of significance to health. Aripiprazole is just as effective as the past drugs and produces weight loss so this is an asset to the individual's self-esteem and body image. Even though the effect of antipsychotics is vital for these illnesses, an overall impact of side effects should assess the impact on self image when there is weight gain. It is with a tentativeness that the health professionals are awaiting to observe whether the good results from the clinical environment will extrapolate to the real world for aripiprazole (Naber & Lambert, 2004). This review adds to the encouraging evidence that through research a new generation of antipsychotics have emerged to bring an optimistic outlook in mental illness (Thomas, 2007).

10.1 The implications for practice
10.1.1 for mental illness.
Psychoses and mental illness are both debilitating and concerns issues of self-management; schizophrenia and bipolar I disorder are conditions that require treatment with antipsychotics that can cause weight gain due to environmental, genetic or medication (Comer, 2007). It is well known that people with schizophrenia may become overweight Faulkner et al., 2007). It seems that a minimum weight loss can be achieved but it is not known over what time span with the atypical antipsychotic aripiprazole (Beebe, 2003). The
number of studies chosen was important and it was enough to carry out a meta-analysis. There were not much variation of interventions and their dosage was acceptable, but the time period for studies was all short term and medium term. It is better if sufferers of these mental illnesses could turn to their clinician and forge a strong rapport for weight management and a long term treatment plan (Faulkner et al., 2007). N.I.C.E. (2007) and Rector and Beck (2001) advocate an integrated approach for treatment with combined therapy such as CBT. This should be considered for both bipolar I disorder and schizophrenia. The impact of self image in mental illness is highlighted by Weil et al. (2002) since this can lead to suicide if it is not managed adequately (Carpenter et al., 2000).

10.1.2 for clinicians
There is not much evidence from research with RCTs because they are so few to build a strong argument for evidence that treatments do impact on weight gain (Faulkner et al., 2007). The current data in this review comes from single studies and suggests that short-term to medium term modest weight loss is possible. The priority should be to ameliorate the severity of the condition but weight gain or metabolic disturbance should also be an issue because of the various serious complications associated with this. Psychoeducation of patients, family, and caregivers should be about the metabolic risks and lifestyle advice regarding diet and physical activity (Merinder, 2000) and on any ‘adjunctive psychosocial treatments on antipsychotic effectiveness’ (Bagnall et al. 2003, p. 8). The significance of screening and monitoring at the beginning of antipsychotic treatment should be administered to reduce the risks of the metabolic disturbances (Smith et al., 2008). Drugs such as Orlistat for this population is an ‘anti-obesity’ treatment (Connolly & Kelly, 2005) which is suitable for patients who cannot adapt to ‘lifestyle interventions alone’ (Faulkner et al., 2007, p.38).

10.2 For managers and policy makers
An awareness of the health issues related to weight gain is important; and the prognosis of this population should be a concern because if the situation of obesity is ignored, it will incur financial liabilities (Harvey et al., 2001).
10.3 Implications for research

10.3.1 General
Definitions are important and the standardisation of reporting data for meta-analysis should be also consistent. This was seen in the included studies. The clarity of methods of randomisation gives confidence in the studies that selection bias had been minimised and controlled, and that the double blinding has enabled better conduction of performance and detection bias (Juni et al., 2001). The reporting of outcomes with means and standard deviations would provide usable data and facilitated synthesis of findings. It is preferred to have the exact numbers and standard deviations when a graph is depicted, as this was unclear in Potkin et al. (2003) (Gillies et al., 2005, p.14).

10.3.2 Specific
In treatment with antipsychotic medications further randomized controlled studies with longer treatment duration are needed to explore the effectiveness and safety of both atypical antipsychotics and antipsychotics of the first generation for preventing weight gain and or bringing about weight loss in mental illness (Bagnall et al., 2003). Studies should state initial and endpoint values including means difference and binary outcomes that are descriptions such as the number of patients losing ‘> or = 7%’ initial body weight’ for interpretation information and clarity (McQuade et al., 2004, p.47). The methods section for the sample population and interventions should be precisely described and the results should encompass the participants who had left early to be followed –up.

These eight studies represented large studies that seem to be well designed and logically reported for the full accessed articles. These studies mainly used weight in kilograms and means or BMI as the outcome measure. Other measures such as waist-to-hip ratio and waist circumference should also be included because BMI does not recognise fat distribution (Lean, 2003). The distribution of weight gain needs to be examined (Littrell et al., 2003) and there needs to be further research for the initial period of antipsychotic
treatment when there appears to be the most increases in weight (Faulkner et al., 2007).

The quality of evidence was good on the effectiveness of treatment with aripiprazole for weight loss on short to medium term duration, but generalisations are not acceptable to the rest of the mentally ill population as definitions vary and they tend to be based on limited evidence and should be treated with caution. Further research is needed. There are financial implications with introducing the medications, along with the methodology, and ‘new innovative approaches to achieve long term weigh loss are necessary’ (Addington et al., 2003, p.275).

10.4 Recommendations

RCTs comparing other atypical antipsychotics with one another would be beneficial (Bagnall et al. 2003). It is important to specify research comparisons and interventions for either antipsychotic versus antipsychotic or of atypical antipsychotic versus atypical antipsychotic clearly so that it is known what their working mechanisms for effective treatment are. This is done, for instance, to investigate if the NGAs work similarly or differently to one another (Kommossa et al., 2007), to offer better patient choice (Gardner et al., 2005). Research into combined therapies compared with the atypicals is also a good idea (Bagnall et al., 2003).

Further research using RCTs could be done on the young and the elderly (Bagnall et al. 2003) and first episode and long term cases as well to observe for other side effects such as for ‘prolactin’ and ‘sexual’ problems which had been ‘poorly reported’ (Bagnall et al. 2003, p. 7). The impact of gender and ethnicity should also be determined in relation to antipsychotic drugs (ibid). This review has provided evidence that aripiprazole is beneficial in treatment with weight loss and that aripiprazole may prevent relapse (McQuade et al., 2004).
11. Dissemination
The review will improve awareness for the general public, develop and improve the accessibility of services for sufferers and educate for better lifestyle for family as well; and to keep those in the health professions up to date. This study has objectives to disseminate through the media, community involvement, and influence health care professionals (WHO, 1991, p.154).

There is a need to inform various professional organizations of the academic production of this review because influence is needed to fund and provide resources for further research. The issues of this review could be particularly well suited to dissemination at conferences with ‘posters sessions’ (Polit & Hungler, 1993, p.51), which could be supported by academic or professional organizations with a presentation in the form of verbal or ‘visual displays’ (ibid, p. 51).

12. Limitation and potential conflict of interest
There is none known.
13. Reflection

I feel that my attitude to learning has expanded, by learning about these issues. I have worked very hard to grapple with the terminology and realise that there are a number of concepts that are a part of this area, but a few major ideas are enough at this stage for me to deal with, so what I have presented in this review of a complex issue is one that is hopefully interesting and succinct.

This dissertation has provided the learning experience for me where my outlook of meta-analysis has developed with an appreciation of the methodical approach that it provides. The idea that it is a methodological approach to searching information has had various issues for me in producing this work – some personal and some academic, but the challenge has been rewarding (Greenhalgh, 2002). Basically, since I am very chaotic in my organization mentally of approaching work, and it is not unusual for me to dip in and out of various sections as and when ideas occur - I set strict targets and goals so that this ideology would not pass me by. The definitions needed to be understood and I knew that I should aim to review between 8-20 studies with starting the literature review. Structure became very crucial to achievement and the methodological issues were pertinently at the fore so the inclusion and exclusion issues were considered for the review.

There was a lot of collating facts together and ideas on the topic, and printing off but I knew that nothing should be thrown away. This was time-consuming and an on going process to the end. Next, came the reading and assimilating of information and to start the search for the meta-analysis. I thought about the inclusion and exclusion criteria first. All this had to be an objective approach with preparation being the key; and adherence to targets. I had produced a Gantt chart in my proposal with timelines and this time span I found was limited, considering the vast quantity of work required. There was more work involved than met the eye initially because it was all very detailed. I soon realised that I was missing the Gantt chart deadlines first, then my own
deadlines, and by the stage of the write up I was far behind because of the confusion with the information and literature.

Focussing was very important as there was a huge amount of information all very much similar. The subject proved to be more complex than appeared at first sight and a direction was important. Thus meeting up with Andy and Sandra helped clarify the areas of concern such as the structuring of the systematic review and basic knowledge of what a systematic review is and a meta-analysis. Every meeting was beneficial in building up a picture for the review and its development. This allowed a positive aim for me to work at the sections because I could take in work for meta-analysis and ask questions. The Professional Academic Development team also helped me to understand the synthesis of work and in improving my planning skills. Definitions are very important and finding out about global measures as a concern with mental health was a definition amongst many that I came across.

I felt that people suffering mental illness need more support because information is not as accessible. This was an assumption that I had from the beginning and that awareness of concepts such as discrimination is an important issue to raise with the public, alongside the fact that dietary issues should be taken more seriously in mental health. The reading has provided an in depth account of relevant history and I was surprised that there were so many drugs that produced weight gain.

If this had been a study that was going to be published then time permitting, I would have tried to access the full journal articles that were only obtained in this review as abstracts (four of them). This would have been done by requesting authors of relevant studies. I would also contact them to find out about those leaving the study early since a follow-up or debrief was not particularly well proffered; I would like to examine this further. I had to balance my introduction and this took much longer than I expected to finish, in fact right to the end! Schizophrenia is a psychosis whereas bipolar I disorder is not, so I needed to balance my perspective of mental illness and psychoses
when writing my dissertation, without getting my personal interests involved in one more than the other.

The hypothesis was formed when ideas were still growing; and there were changes being made to the criteria for including studies when it seemed apparent that time was a limitation - so antipsychotics as a comparison was decided on for the atypical antipsychotic, aripiprazole - and haloperidol was chosen, which was a conventional antipsychotic. This was instead of comparing atypical antipsychotics with atypical antipsychotics. The areas that I could have covered with the participants in the research studies I reviewed may have been gender, socioeconomic status, race and culture if there were full articles available.

It is important to appreciate that this piece of research should advance human understanding of the topic because the issues in this have been very profound since it revolves around our health and affects are mortality and susceptibility to illness. Since there are few randomised studies in this area this may provide a contribution to encourage more research and dissemination would further create awareness and support, bearing in mind that it is the economic and political climates that dictate the funding possible for this population and others in generating the changes for improvements (Darnton-hill et al., 2004).

The reflection is a part of the experience of modern day understanding for working and allows us to consider what one is capable of with a view to further development. It enables effective reasoning and acceptance of limitations in working. I found that I wanted to pore through all the literature that I had printed out only to realise that I do not have the time to utilise them all. Thus I needed to feel confident in what I have produced to the best of my knowledge and believe that I am part of a learning process at this level where there are going to be limitations. The dissertation has provided an insight into my learning where I feel that I have been a part of generating a provocative contribution to an issue that has been revolutionary.
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[Accessed: 30.8.08]


[Accessed: 1.9.08]


[Accessed: 15.5.08]

[Accessed: 4.9.08]

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APPENDICES

1. Abilify / aripiprazole  
   appendix 1.

2. Characteristics of included studies  
   appendix 2.

3. Characteristics of excluded studies  
   appendix 3.

4. Adding weighted zs  
   appendix 4.

5. The Fisher's F -test  
   appendix 5.

6. Raw data  
   appendix 6
Appendix 1. Aripiprazole.

Brand:

Abilify® (Dynamic Medical, 2008, p. 1)

Chemical Name:

3, 4-dihydro-7-[4-[4-(2, 3-dichlorophenyl)-1-piperazinyl]butoxy]-2(1H)-quinolinone (Dynamic Medical, 2008, p. 1)

Treatment:

Schizophrenia (Miyamoto et al., 2005)
Bipolar I Disorder with acute manic and mixed episodes (Vieta et al., 2005; Keck et al., 2003)

General adverse Effects:
Headache, insomnia, and anxiety (Beebe, 2003).

Dosage:
The preferred doses for aripiprazole are 10-30 mg/day (Bandelow & Meier, 2003, p. 14).
Appendix 2. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Kolotkin et al. (2008)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td></td>
</tr>
<tr>
<td>Allocation</td>
<td>randomized</td>
</tr>
<tr>
<td>Blindness</td>
<td>not stated</td>
</tr>
<tr>
<td>Duration</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Design</td>
<td>Aripiprazole (ARI) vs. standard of care (SOC, consisting of olanzapine, quetiapine, and risperidone).</td>
</tr>
<tr>
<td>Participants</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Schizophrenia (DSM-IV-TR criteria)</td>
</tr>
<tr>
<td>N</td>
<td>555</td>
</tr>
<tr>
<td>Age</td>
<td>mean 38.5 years (SD 10.9)</td>
</tr>
<tr>
<td>Sex</td>
<td>59.7% M</td>
</tr>
<tr>
<td>History</td>
<td>Signed informed consent.</td>
</tr>
<tr>
<td>Setting</td>
<td>Naturalistic (community treated or hospital-based outpatient centre), multicentre (98), open label study. 12 European countries</td>
</tr>
<tr>
<td>Interventions</td>
<td></td>
</tr>
<tr>
<td>1. Aripiprazole, dose: 10-30mg/day or</td>
<td></td>
</tr>
<tr>
<td>2. Standard of Care</td>
<td></td>
</tr>
<tr>
<td>- Olanzapine, dose: 5-20 mg/day, or according to the approved local medication label, or</td>
<td></td>
</tr>
<tr>
<td>- Quetiapine, dose: 100-800mg/day, or according to the approved local medication label, or</td>
<td></td>
</tr>
<tr>
<td>- Risperidone, dose: 2-8 mg/day, or according to the approved local medication label</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>Mean baseline body mass index of 27.2 (SD 5.1). ARI participants lost an average of 1.7% of baseline weight in comparison to a gain of 2.1% by SOC participants (p&lt; 0.0001) at 26 weeks (p. 1)</td>
</tr>
</tbody>
</table>
### Study Potkin et al. (2003)

| Methods | Allocation: randomised  
| Blindness: double  
| Duration: 4 week  
| Design: Aripiprazole, and risperidone vs placebo. |

| Participants | Diagnosis: Schizophrenia or schizoaffective disorders (DSM -IV)  
| N= 404  
| Age: 18-65 years  
| Sex: both  
| History: Written informed consent.  
| Setting: Multicentre (40 Medical centres). U.S. Hospitalized |

| Interventions | 1. Aripiprazole, dose: 20 mg/day or  
| 2. Aripiprazole 30 mg/day. N= 101 or  
| 3. Placebo N= 103, or  
| 4. Risperidone 6mg/day |

| Outcomes | The percentage of patients with significant weight gain was evaluated by the Cochran-Mantel- Haenszel test (p.4); both groups showed a 'low incidence of clinically significant weight gain' (p.1) |

### Study Vieta et al. (2005)

| Methods | Allocation: randomised  
| Blindness: double  
| Duration: 12 weeks  
| Design: Aripiprazole versus haloperidol |
| Participants              | Diagnosis: Bipolar I disorder with acute or mixed episode (DSM-IV).  
|                          | N = 347  
| Age:                     | 18-65 years  
| Sex:                     | both  
| History:                 | Written informed consent or legally acceptable representative.  
| Setting:                 | Multicentre (76 internationally). Inpatient or outpatient treatment.  
|                          |  
| Interventions            | 1. Aripiprazole 15 mg/day N = 175, or  
|                          | 2. Haloperidol 10 mg/day N = 172.  
| Outcomes                 | Minimal mean changes in body weight' with both groups (p. 241)  

| Study                     | Kane et al. (2002)  
| Allocation:               | randomised  
| Blindness:                | double  
| Duration:                 | 4 weeks  
| Design:                   | Aripiprazole versus haloperidol versus placebo  

| Participants              | Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV).  
|                          | N = 414  
| Age:                     | not stated in abstract  
| Sex:                     | not stated in abstract  
| History:                 | not stated in abstract  
| Setting:                 | 36 U.S. centres  

| Interventions            | 1. Aripiprazole 15 mg/day, 30 mg/day  
|                          | 2. Haloperidol 10 mg/day  
|                          | 3. placebo  

72
<table>
<thead>
<tr>
<th>Study</th>
<th>Chan et al. (2007)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Allocation: randomised</td>
</tr>
<tr>
<td>Blindness:</td>
<td>double</td>
</tr>
<tr>
<td>Duration:</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Design:</td>
<td>Aripiprazole versus risperidone</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV).</td>
</tr>
<tr>
<td></td>
<td>$N=83$</td>
</tr>
<tr>
<td></td>
<td>Age: not stated in abstract</td>
</tr>
<tr>
<td></td>
<td>Sex: not stated in abstract</td>
</tr>
<tr>
<td></td>
<td>History: not stated in abstract</td>
</tr>
<tr>
<td></td>
<td>Setting: 5 medical centres, Taiwan</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>1. Aripiprazole 15 mg/day, $n=49$</td>
</tr>
<tr>
<td></td>
<td>2. Risperidone 6mg/day, $n=34$</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>'Both groups showed mild weight gain' (p.29).</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Study</th>
<th>McQuade et al. (2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Allocation: randomised</td>
</tr>
<tr>
<td>Blindness:</td>
<td>double</td>
</tr>
<tr>
<td>Duration:</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Design:</td>
<td>Aripiprazole versus olanzapine</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Diagnosis: schizophrenia (DSM-IV).</td>
</tr>
<tr>
<td></td>
<td>$N=317$</td>
</tr>
<tr>
<td></td>
<td>Age: not stated in abstract</td>
</tr>
<tr>
<td>Study</td>
<td>Newcomer et al. (2008)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td></td>
</tr>
<tr>
<td>Allocation</td>
<td>randomised</td>
</tr>
<tr>
<td>Blindness</td>
<td>double</td>
</tr>
<tr>
<td>Duration</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Design</td>
<td>Aripiprazole versus olanzapine</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>schizophrenia or schizoaffective disorder (DSM - IV-TR) N= 173</td>
</tr>
<tr>
<td>Age</td>
<td>not stated in abstract</td>
</tr>
<tr>
<td>Sex</td>
<td>not stated in abstract</td>
</tr>
<tr>
<td>History</td>
<td>not stated in abstract</td>
</tr>
<tr>
<td>Setting</td>
<td>Multicentre</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole n= 88 or olanzapine n= 85 dosage not stated in abstract.</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>‘At week 16, weight decreased significantly with aripiprazole'</td>
<td></td>
</tr>
</tbody>
</table>
vesus olanzapine (-1.8 vs. +1.41 kg; \( p < .001 \))' (Newcomer et al. 2008, p.1) 'Significantly more subjects receiving aripiprazole had clinically relevant (> or = 7%) weight loss versus olanzapine (11.1% vs. 2.6%; \( p = .038 \)), and a lower percentage of subjects receiving aripiprazole had clinically relevant weight gain (2.5% vs. 9.1%; \( p = .082 \))' (ibid, p.1).

<table>
<thead>
<tr>
<th>Study</th>
<th>Chrzanowski et al. (2006)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td></td>
</tr>
<tr>
<td>Allocation</td>
<td>randomised</td>
</tr>
<tr>
<td>Blindness</td>
<td>double</td>
</tr>
<tr>
<td>Duration</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Design</td>
<td>Aripiprazole versus olanzapine</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>schizophrenia</td>
</tr>
<tr>
<td>N</td>
<td>214</td>
</tr>
<tr>
<td>Age</td>
<td>not stated in abstract</td>
</tr>
<tr>
<td>Sex</td>
<td>54% M; 46% F</td>
</tr>
<tr>
<td>History</td>
<td>informed written consent</td>
</tr>
<tr>
<td>Setting</td>
<td>Multicentre, open label.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole dose 15-30mg/day, n=104, or</td>
<td></td>
</tr>
<tr>
<td>olanzapine dose 10-20 mg/day, n=110</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>'At study end, mean weight gain with olanzapine was 2.54 vs. 0.04 kg with aripiprazole (( p&lt;0.001; ) LOCF)' (p. 263).</td>
</tr>
</tbody>
</table>
## Appendix 3. Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Kerwin et al. (2007)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td></td>
</tr>
<tr>
<td>Allocation:</td>
<td>randomised</td>
</tr>
<tr>
<td>Blindness:</td>
<td></td>
</tr>
<tr>
<td>Duration:</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Design:</td>
<td>Aripiprazole (ARI) vs. standard of care (SOC, consisting of olanzapine, quetiapine, and risperidone).</td>
</tr>
</tbody>
</table>

| **Participants** | |
| Diagnosis: | Schizophrenia (DSM-1V-TR) |
| N= | |
| Age: | 18-65 years |
| Sex: | M; F |
| History: | Written informed consent obtained. |
| Setting: | Naturalistic (community practice or hospital-based outpatient (98) multicentre, open-label. 12 European countries) |

| **Interventions** | |
| 1. Aripiprazole, N = 268, dose: 10-30mg/day or | |
| 2. Standard of Care – Olanzapine, dose: 5-20 mg/day, or according to the approved local medication label, or Quetiapine, dose: 100-800mg/day, or according to the approved local medication label, or Risperidone, dose: 2-16mg/day, or according to the approved local medication label. | |

| **Outcomes** | |
| Weight: SOC –treated group had clinically significant weight gain (21.2 % vs. 7.3% for aripiprazole) | |

**Reason for exclusion** | replica data of Kolotkin et al. (2008) |
<table>
<thead>
<tr>
<th>Study</th>
<th>McElroy et al. (2007)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Allocation: Prospective, nonrandomized</td>
</tr>
<tr>
<td></td>
<td>Blindness: None</td>
</tr>
<tr>
<td></td>
<td>Duration: 8 weeks</td>
</tr>
<tr>
<td></td>
<td>Design: Aripiprazole as monotherapy</td>
</tr>
<tr>
<td></td>
<td>Participants: 31</td>
</tr>
</tbody>
</table>

| Participants       | Diagnosis: Bipolar depression I N= 17, bipolar II N=13, bipolar NOS N= 1 (DSM-IV) |
|                    | N=                                                        |
|                    | Age: 18 and over                                         |
|                    | Sex: both                                                |
|                    | History: Written informed consent.                       |
|                    | Setting: Open-label 3 sites, out-patient                 |

| Interventions      | 1. Aripiprazole, dose: 15mg/day or 5-10 mg/day and increased to 30mg/day. |
|                    | N=13 (42%) Aripiprazole as monotherapy                    |
|                    | N= 18 (58%) aripiprazole adjunctively.                    |

| Outcomes           | T-tests were used to assess changes in weight.            |
|                    | Weight: Insignificant weight gain statistically (0.8 +/-2.5 kg) (p. ) |

| Reason for exclusion | The design is the reason for exclusion, since it is only aripiprazole being investigated as monotherapy |

<table>
<thead>
<tr>
<th>Study</th>
<th>Sachs et al. (2006)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Allocation: randomized</td>
</tr>
<tr>
<td></td>
<td>Blindness: double</td>
</tr>
<tr>
<td></td>
<td>Duration: 3 weeks</td>
</tr>
</tbody>
</table>
Design: Aripiprazole vs placebo. Placebo controlled trial

Participants
- Diagnosis: Bipolar I disorder experiencing an acute manic or mixed
  N=272
- Age: 18 years and over
- Sex: Not stated
- History: written consent.
- Setting: Hospitalized. U.S. 29 centres

Interventions
1. Aripiprazole, dose: 30mg/day (could be reduced to 15mg/day) N=137, or
2. Placebo N=135

Outcomes
'Aripiprazole treatment resulted in no significant difference from placebo in change in mean body weight' (p.)

Reason for exclusion
The design is the reason for exclusion, since aripiprazole is being investigated with a placebo and a placebo in the design is an exclusion criteria

Study

Methods
- Allocation: randomized
- Blindness: double
- Duration: 3 weeks
- Design: Placebo-controlled trial of aripiprazole

Participants
- Diagnosis: Bipolar with acute manic or mixed episode (DSM-IV)
  N=262
- Age: 18 years and over
<table>
<thead>
<tr>
<th>Sex:</th>
<th>both</th>
</tr>
</thead>
<tbody>
<tr>
<td>History:</td>
<td>written informed consent.</td>
</tr>
<tr>
<td>Setting:</td>
<td>Multicentre (38). U.S. Hospitalized at least 2 weeks.</td>
</tr>
</tbody>
</table>

**Interventions**

1. Aripiprazole, dose: 30 mg/day (reduced to 15mg/day for tolerability). N= 130, or Placebo N=132.

**Outcomes**

'Both treatment groups experienced a small decrease in body weight during the study, and there was no significant difference between groups in the incidence of clinically significant weight gain' (ref.).

**Reason for exclusion**

The design is the reason for exclusion since it is a placebo-controlled trial.

---

<table>
<thead>
<tr>
<th>Study</th>
<th>Karunakaran <em>et al.</em> (2006)</th>
</tr>
</thead>
</table>

**Methods**

Allocation: randomized
Blindness:  
Duration:  
Design: case notes

**Participants**

Diagnosis: schizophrenia
N=26
Age: mean 39.04 (+ or – 9.95) years
Sex: 19 M; 17 F
History:  
Setting:  

**Interventions**
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mean level: weight 95.2 kg 18 out of 24 (75%) lost a mean weight of 5.05kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason for exclusion</td>
<td>The design is the reason for exclusion because this is a review of case notes.</td>
</tr>
</tbody>
</table>
Appendix 4. Adding weighted z’s.

This was done firstly as a meta-analysis value for the following studies by Keck et al. (2003), Sachs et al. (2006), McElroy et al. (2007), Kolotkin et al. (2008), Karunakarun et al., (2006).

Adding weighted z’s

\[ Z = \frac{T}{\sigma T} = \frac{(N_1 \times Z_1 + N_2 \times Z_2)}{(N_1)^2 + (N_2)^2} \]

\[ = \frac{(278 \times -1.65) + (31 \times 1.6) + (137 \times 0) + (20 \times -2.58)}{(278)^2 + (31)^2 + (137)^2 + (20)^2} \]

\[ = \frac{460.7}{154590} \] sq. root.

\[ = -460.7/393.2 \]

\[ p = .50 \]

\[ z = -1.17 \ (p = .12) \]
Appendix 5. The Fisher's F-test.

The illustration below shows the p-value as alpha for a one-tailed Fisher F-test (Soper, 2008, p.1)
Appendix 6. Raw data (see floppy disc)

1. Chan et al. (2007)
Aripiprazole vs. Risperidone
Total N= 83
At 4 weeks no significant difference z=0.00

2. Chrzanowski et al. (2006)
Aripiprazole vs. olanzapine
‘olanzapine was associated with significantly greater weight gain than aripiprazole at all time points’ (p. 259 )
Time points were at weeks 8/16/28/52
Week 52 [last observation carried forward – LOCF]: +2.54 vs. +0.04 kg; p< 0.001
At week 28 n1 = 71, n2 = 89, total N= 160.
p< .01 z= -2.33
N= 156, 161

Weight for aripiprazole 73.9 kg and (1.7) S.E. (standard error). Weight for olanzapine 72.1 kg and (1.78) S.E. (p. 262)

Aripiprazole vs. haloperidol (against placebo) at 4 weeks
N = 414/3 for each group
n= 138 for aripiprazole, n= 138 for haloperidol and n = 138 for placebo.
Assume N = 276 for aripiprazole and haloperidol total.
p < or = .05 z= 0.00
No significant difference.

Aripiprazole vs. S.O.C.
The meta- analysis for aripiprazole vs. standard of care (S.O.C.) to see if aripiprazole is lower at Time 2 (T2) than S.O.C.
N = 555 total
Weight loss for aripiprazole participants on average of 1.7 % of baseline in comparison to a gain of 2.1% by S.O.C. participants (p< 0.0001) at 26 weeks. (p.1)

Fisher’s exact and chi square used for weight gain/loss z= -4.6 p<0.001 at 8 weeks aripiprazole vs S.O.C.

BMI is 27.2 for aripiprazole (n=278)
and mean, SD is 5.2. } significance
BMI is 27.3 for S.O.C. (n=266) } t (536) = -0.13,
and SD is 5.1 } p=0.893

p< .000000
z=-7.5
t=7.5
intervention at week 8 n=222 for aripiprazole at time 1.
n =219 for S.O.C.
F (3, 1146) = 25.98 p<0.0001

The result taken from research by Kerwin et al. (2007), which was done first,
is -1.45
p< .05 significant reduction
n=278
p=.05 z= -1.65

5. McQuade et al. (2004)
Aripiprazole vs. olanzapine
At week 26 37% of olanzapine had significant weight gain vs. 14% of aripiprazole.
p< .001 z= -3.00
Total N= 317
At week 26, ‘mean weight loss of 1.37 kg (3.04 lb) with aripiprazole compared
with a mean increase of 4.23 kg (9.40 lb) with olanzapine among patients who
remained on therapy’ (p. 47)

6. Newcomer et al. (2008)
Aripiprazole vs. olanzapine
N= 173
At 16 weeks weight decreased significantly for aripiprazole versus olanzapine
(-1.8kg vs. + 1.41kg; p< .001)
n=88 for aripiprazole, n = 85 for olanzapine.
p< .001 z= -3.00
‘Significantly more subjects receiving aripiprazole had clinically relevant (> or
= 7%) weight loss vs. olanzapine (11.1% vs. 2.60%; p= .038 and a lower
percentage of subjects receiving aripiprazole had clinically relevant weight
gain (2.5% vs. 9.1%; p= .082) (p. 1046).

Aripiprazole vs. risperidone + placebo
N= 404/3
n= 101 for aripiprazole, n= 100 for risperidone, n= 99 for placebo.
N= 300 z=0.00 z=0
Non significant minimum increase across 1.2 kg, .8kg, 1.5kg but significant difference to placebo (p. 688). 
t-tests or chi square for placebo vs. aripiprazole 
No significant difference.

8. Vieta et al. (2005)

Aripiprazole vs. haloperidol
N= 174 at week 12 (L.O.C.F.)
There was no significant difference for aripiprazole (0.27 kg) in weight change.
N=347 z=+0.50
Answer the following question by ringing/deleting \textit{yes} or \textit{no} as appropriate:

1. Does the study involve vulnerable participants or those unable to give informed consent (e.g. children, people with learning disabilities, your own students)? \textbf{Yes}\n
2. Will the study require permission of a gatekeeper for access to participants (e.g. schools, self-help groups, residential homes)? \textbf{Yes (No)}\n
3. Will it be necessary for participants to be involved without consent (e.g. covert observation in non-public places)? \textbf{Yes (No)}\n
4. Will the study involve sensitive topics (e.g. sexual activity, substance abuse)? \textbf{Yes (No)}\n
5. Will blood or tissue samples be taken from participants? \textbf{Yes (No)}\n
6. Will the research involve intrusive interventions (e.g. drugs, hypnosis, physical exercise)? \textbf{Yes (No)}\n
7. Will financial or other inducements be offered to participants (except reasonable expenses)? \textbf{Yes (No)}\n
8. Will the research investigate any aspect of illegal activity? \textbf{Yes (No)}\n
9. Will participants be stressed beyond what is normal for them? \textbf{Yes (No)}\n
10. Will the study involve participants from the NHS (e.g. patients or staff)? \textbf{Yes (No)}\n
Signature of Applicant \hfill \textit{[Signature]}

Date \hfill \textit{12/12/08}\n
Signature of Director of Studies \hfill \textit{[Signature]}

Date \hfill \textit{[Date]}\n
\section*{SECTION B Consideration by Research Institute}

\textbf{B(i)}

If the answers to Questions 1 to 8 are no and the Director of the Research Institute considers that:

\textbf{There are no significant ethical issues}\n
Signature of Director of Research Institute \hfill \textit{[Signature]}

Date \hfill \textit{[Date]}\n
This form should then be filed with the RS1 form

\textbf{B(ii)}

If the answer to any of the questions 1 to 8 is yes or if there are other significant ethical issues then further ethical consideration is required. This further ethical consideration will involve scrutiny by local ethics research committees as appropriate. Once this has been undertaken this form, together with the research proposal and the recommendations from the further ethical consideration should be submitted to the University Research Ethics Committee for approval.

Please note if the answer to Question 6 is yes then the proposal should be submitted through NHS procedures to the appropriate COREC. The University Research Ethics Committee should be informed of the outcome.)
There are significant ethical issues see recommendation attached

Director of Research Institute ......................... Date..............

This form together with the recommendation and a copy of the research proposal should then be submitted to the University Research Ethics Committee

SECTION C  Consideration by University Research Ethics Committee

The University Research Ethics Committee has

Approved / not approved

This application for ethical approval

Chair University Research Ethics Committee ................ Date..............

If successful a copy of this approval should be included with the RS1 Form in the student's file. If the application is unsuccessful formal feedback will be provided.