Comparative incidence of metabolic syndrome in patients with schizophrenia being treated with second generation antipsychotics vs. first generation antipsychotics: A Systematic Review of Literature

By

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Acknowledgements

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Abstract

Background: Schizophrenia is a chronic condition negatively influencing quality of life of affected people. Evidence exists that there is increased prevalence of metabolic syndrome in people with schizophrenia. Current medications used in treating schizophrenia have been implicated in further exacerbating this already increased baseline prevalence of metabolic syndrome in schizophrenia patients, specifically second generation antipsychotic agents more than first generation antipsychotic agents. This connection between developing metabolic syndrome and use of second generation antipsychotic agents is still being clarified.

Objective: To systematically review available evidence on the incidence of developing metabolic syndrome in patients with schizophrenia being treated with second generation antipsychotic agents versus those treated with first generation antipsychotic agents.

Methods: In order to review available evidence, this author searched MEDLINE, CINAHL, The Cochrane Library, and BIOSIS (January 1990 to May 2011) using MeSH terms such as “antipsychotic agents” and “metabolic syndrome.” Additional articles were identified through a hand search of reference lists of selected articles.

Results: The initial literature search identified 326 articles. After abstract review, 9 articles underwent full text review, and finally 2 studies were included into the review after applying inclusion and exclusion criteria. The results of these 2 studies indicate fair to poor quality evidence of increased incidence of developing metabolic syndrome in patients with schizophrenia being treated with second generation antipsychotic agents when compared to patients with schizophrenia treated with first generation antipsychotics.

Conclusion: This review identified that there is an overall lack of adequate studies to properly answer the question posed. The studies included in this review suffered from several limitations lessening the utility of their findings. Therefore, future research is needed to determine the effect of second generation antipsychotic agents on developing metabolic syndrome when compared to first generation antipsychotic agents.
Introduction

A. Purpose
Schizophrenia and metabolic syndrome are chronic conditions that have a significant effect on the quality of life of those affected. There is evidence of increased prevalence of metabolic syndrome in those with schizophrenia. More recently, researchers and clinicians have questioned whether the pharmacotherapies used to treat persons with schizophrenia play a role in the development of metabolic syndrome. Additionally, researchers, and clinicians need to know if there are differential contributions to the risk for metabolic syndrome induced by different classes of medications. This paper will attempt to evaluate the research thus far to determine whether there is a differential contribution of second generation antipsychotics versus first generation antipsychotics.

B. Background

Metabolic syndrome
Metabolic syndrome as it is known today consists of a constellation of risk factors including central obesity, hyperglycemia, hypertension, and dyslipidemia. These components of metabolic syndrome lead to end organ damage resulting in cardiovascular disease, retinopathy, neuropathy, renal disease and amputations. This causes significant morbidity that can greatly reduce quality of life.

There are several definitions of metabolic syndrome which all share similar characteristics however; there is some variance in the relative importance given to certain diagnostic criteria. Two commonly used definitions for metabolic syndrome are the adapted National
Cholesterol Education Program Adult Treatment Panel III criteria by the American Heart Association (NCEP ATP IIIa) and the International Diabetes Federation (IDF) \(^3,^4\).

Utilizing the NCEP ATP IIIa criteria, metabolic syndrome is diagnosed when 3 or more of five criteria are met: elevated waist circumference (≥40 inches in men and ≥ 35 inches in women), elevated fasting triglycerides (≥150mg/dL), reduced HDL (<40 mg/dL in men and <50 mg/dL in women), elevated blood pressure (≥130/85 mm Hg) or taking antihypertensive medication, and elevated fasting glucose (≥100 mg/dL) or taking insulin or hypoglycemic medication. The only difference between original NCEP ATP III criteria and the adapted version (NCEP ATP IIIa) was that the original criteria used the older threshold of elevated fasting glucose at ≥110 mg/dL and the adapted version changed this criterion based on the American Diabetes Association lowering the criteria for elevated fasting glucose to ≥100 mg/dL.

The IDF criteria require the presence of central adiposity (elevated waist circumference) which is defined using ethnicity specific values \(^4\). In addition, two of four other criteria also need to be present for diagnosis of metabolic syndrome. These four criteria (elevated fasting triglycerides, reduced HDL, elevated blood pressure, and elevated fasting glucose) are defined in the same way as the NCEP ATP IIIa definition. As these definitions are very similar, I will use both definitions in this review in order to be more inclusive of results.
Schizophrenia

Schizophrenia is a chronic and debilitating mental illness affecting 1% of the world’s population. Symptoms of schizophrenia include positive symptoms (delusions, hallucinations, disorganized speech, negative symptoms (flattened affect, alogia, and avolition), and neurocognitive deficits (attention impairment, memory deficits, executive dysfunction).

Patients with schizophrenia when compared to the general population have a shorter life span. The reasons for this are currently under study. Although persons with schizophrenia have a higher prevalence of suicide attempts as well as successful suicides, a majority of persons with schizophrenia die of coronary heart disease, an endpoint of metabolic syndrome. Furthermore, the prevalence of coronary heart disease is also higher in patients with schizophrenia than in the general population.

De Hert, Schreurs, Vancampfort et al. conducted a review of thirty-eight studies on the association of metabolic syndrome in people with schizophrenia. They found that the increased prevalence and incidence of metabolic syndrome in people with schizophrenia is approximately 2 to 3 times greater than in the general population. This increased risk is theorized to be due to several causes including aspects of schizophrenia itself, lifestyle issues, genetics, and finally, antipsychotic medications.

Those with schizophrenia tend to have a sedentary lifestyle without much physical activity, improper nutrition, and substance abuse especially tobacco abuse. Aspects of schizophrenia
such as the negative symptoms and increased stress levels further contribute to these lifestyle issues \(^1\). In combination, these lifestyle factors can easily result in weight gain and obesity, hypertension, and dyslipidemia, all of which are components of metabolic syndrome.

The involvement of genetics in the association between schizophrenia and metabolic syndrome has been purported as studies have shown that there is an increased risk of metabolic dysregulation, specifically diabetes and glucose intolerance, in first degree relatives of people with schizophrenia \(^1,6\).

**Schizophrenia treatment**

Treatment for schizophrenia involves the use of antipsychotic medications. These medications can be divided into two groups: first generation or typical antipsychotics, and second generation or atypical antipsychotics.

First generation antipsychotics are older, and mainly target positive symptoms. They are distinguished by their high affinity for blocking D2 dopamine receptors in the brain which is directly related to their ability to target and treat positive symptoms. However, they have a significant side effect profile involving movement related side effects such as: parkinsonism (rigidity or difficulty initiating movements), dystonia (strong involuntary muscle contractions), akithisia (inner motor restlessness resulting in the inability to sit still and causing patients to feel they need to move to be comfortable), and tardive dyskinesia (abnormal involuntary movements that persist and can be stigmatizing or, in more severe cases, can cause functional difficulties). Furthermore, some first generation antipsychotics
have been noted to cause weight gain. Due to these side effects, there is concern that first generation antipsychotics are not well tolerated when used for long periods of time.

Second generation antipsychotics are newer, target positive symptoms and may result in fewer secondary negative symptoms. Several of these drugs entered the market in the 1990s and quickly gained popularity. They have a different side effect profile than the first generation antipsychotics as they have a reduced incidence of movement related side effects. In some of the second generation antipsychotic medications, this has been attributed to their decreased affinity for D2 dopamine receptors and utilization of other neurotransmitter systems, such as the serotonin system. They are currently the first-line therapeutic agents used in those presenting with symptoms of schizophrenia.

It has been discovered, however, that these second generation antipsychotics can contribute to metabolic side effects including weight gain, dyslipidemia, and impaired glucose regulation. Pramyothin and Khaodhia conducted a review of current literature evaluating the effect of various second generation antipsychotic medications on individual metabolic criteria. They found that of the seven commonly prescribed second generation antipsychotics (clozapine, olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, amisulpride), two (olanzapine and clozapine) were most associated with increased weight gain, increased risk for diabetes and a worsening lipid profile. Of these factors, the two medications had the most effect on weight gain. These results suggest that different second generation antipsychotics have differential effects on weight and metabolic regulation.
Schizophrenia, in some cases, can be a truly devastating illness on its own and, when compounded with potential adverse effects of antipsychotic medications can further diminish the quality of life of those affected.

C. Rationale for systematic review

Persons with schizophrenia have a higher risk of developing coronary heart disease and metabolic syndrome when compared to the general population. It is important to determine whether using second generation antipsychotics increases the risk of metabolic syndrome beyond the already elevated baseline risk in schizophrenia patients, and how this risk compares to the risk conferred by first generation antipsychotic agents.

The inclusion of metabolic syndrome in the psychiatric literature is recent. The first study detailing metabolic syndrome in patients with schizophrenia was published in 2003. The connection between second generation antipsychotics and metabolic syndrome is even more contemporary as their general use has been popular only for the past two decades. As such, the long term complications of these medications are just now being realized and the question of their implication in increasing the risk of metabolic syndrome is concerning.

Several prevalence studies have been conducted comparing metabolic syndrome in people treated with first versus those treated with second generation antipsychotics. Most of these studies are cross sectional with very few randomized controlled trials and prospective cohort trials. In one study, Saddichha, Manjunatha, Ameen et al. conducted a short term randomized controlled trial on consecutively admitted patients with a first episode of
schizophrenia. These patients were randomized to treatment with olanzapine, risperidone, or haloperidol. Baseline measures were completed prior to the start of treatment with antipsychotic medication and follow up measures were completed at 6 weeks which was the end of the study period.

The authors calculated prevalence of metabolic syndrome using NCEP ATP III and IDF for each of the treatment groups. Prevalence of metabolic syndrome in those treated with olanzapine was 20.0% (NCEP ATP III) and 25.7% (IDF) at the end of the trial. Prevalence of metabolic syndrome in those treated with risperidone was 9.1% (NCEP ATP III) and 24.2% (IDF) at the end of the trial. Prevalence of metabolic syndrome in those treated with haloperidol was 0% (NCEP ATP III) and 3.2% (IDF) at the end of the trial.

In one cross sectional study conducted in outpatient clinics in northern England, Mackin, Watkinson, and Young found that 11.6% of subjects on second generation antipsychotics had metabolic syndrome but 0% of those on first generation antipsychotic medication had metabolic syndrome.

In another cross sectional study in long term patients at psychiatric rehabilitation facilities in Australia, Tirupati and Chua found that the prevalence of metabolic syndrome in those taking only one first generation antipsychotic and second generation antipsychotic was 66% and 60.3% respectively. The prevalence of metabolic syndrome is high in both first and second generation antipsychotic treated groups; however this study was conducted in people with long standing psychiatric disease as well as long term treatment with antipsychotic
medications. Furthermore, patients who were treated with first generation antipsychotics may have previously been treated with second generation antipsychotics which may confound the study and lead to a decreased sensitivity of the study to find differences in the influence of first- and second generation antipsychotics on the prevalence of metabolic syndrome.

The results of these prevalence studies are concerning. However, these studies are not able to causally indicate whether second generation antipsychotics confer an increased risk in developing metabolic syndrome in comparison to first generation antipsychotics.

This emerging problem within the population of those with schizophrenia needs to be understood. Therefore, a systematic review of available literature is needed to determine whether treatment with second generation antipsychotics in patients with schizophrenia results in an increased incidence of metabolic syndrome in comparison to first generation antipsychotics.
Methods

A. Focused Question

This systematic review seeks to answer the question: “Do patients with schizophrenia treated with second-generation antipsychotics have an increased incidence of developing metabolic syndrome when compared to patients with schizophrenia treated with first-generation antipsychotics?”

Past studies have focused on the difference in prevalence of metabolic syndrome between those treated with first generation antipsychotics and those treated with second generation antipsychotics. Although, prevalence is an important measure, incidence gives us more information about the development of metabolic syndrome itself and provides a way to measure the attributable burden of antipsychotic agents.

B. Eligibility Criteria (Table 1)

For the purposes of this review, the included articles had to describe a study comparing the development of metabolic syndrome of at least one first and one second generation antipsychotic agent in people with schizophrenia. There is data indicating that some of the most commonly used second generation antipsychotic medications, specifically olanzapine and clozapine, seem to have the greatest effect on individual metabolic parameters (weight gain, impaired fasting glucose)\(^6\). Furthermore, some of the remaining commonly used second generation antipsychotic medications (risperidone, quetiapine) also have a moderately increased effect on individual metabolic parameters as well\(^6\). Therefore, since many of the commonly prescribed second generation
antipsychotics have been implicated in causing metabolic abnormalities, this paper will focus on examining second generation antipsychotic medications as a group instead of specifying a few drugs from the first- and second-generation groups to compare.

The second generation antipsychotics were introduced in the United States starting with Clozapine, in 1990. Therefore, to meet inclusion criteria, articles must have been published between January 1990 and May 2011. Case reports and cross-sectional studies were ineligible for this review as they would not be able to measure incidence. Study types eligible for inclusion were randomized controlled trials (RCTs) and cohort studies (retrospective and prospective) as these study types could potentially measure incidence.

Studies that only evaluated specific metabolic effects of antipsychotic medications were excluded from the review. These studies generally concentrate on changes in individual metabolic parameters such as weight gain, lipid level changes, or insulin resistance which would not be appropriate for answering the question proposed in this systematic review. Furthermore, studies had to define metabolic syndrome using criteria set forth by the American Heart Association adapted National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP IIIa) or the International Diabetes Federation (IDF) (Table 2).

The study population in the included studies had to include people with schizophrenia. If the study population included people with schizophrenia as well as others with psychotic disorders, the study was eligible for review if the investigators elucidated the proportion
of people in the study with schizophrenia. Current recommendations by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity recommend monitoring of lipids after 12 weeks of treatment by second generation antipsychotic medications, therefore treatment duration of at least three months was required for inclusion into this review \(^1\).
### Table 1. Eligibility Criteria

<table>
<thead>
<tr>
<th></th>
<th><strong>Inclusion</strong></th>
<th><strong>Exclusion</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>People with schizophrenia on antipsychotic agents</td>
<td>All others on antipsychotic agents</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Second generation antipsychotics</td>
<td></td>
</tr>
<tr>
<td><strong>Comparison group</strong></td>
<td>First generation antipsychotics</td>
<td></td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Metabolic syndrome</td>
<td>Studies measuring only individual metabolic syndrome criteria</td>
</tr>
<tr>
<td><strong>Exposure time</strong></td>
<td>$\geq 3$ months</td>
<td>$&lt; 3$ months</td>
</tr>
<tr>
<td><strong>Search period</strong></td>
<td>January 1990-May 2011</td>
<td>Prior to January 1990</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Randomized controlled trials</td>
<td>Cross sectional studies</td>
</tr>
<tr>
<td></td>
<td>Prospective cohort studies</td>
<td>Case reports</td>
</tr>
<tr>
<td></td>
<td>Retrospective cohort studies</td>
<td></td>
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</tbody>
</table>
Table 2. Definitions of Metabolic syndrome

<table>
<thead>
<tr>
<th>American Heart Association adapted National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP IIIa) criteria</th>
<th>International Diabetes Federation (IDF) criteria 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three of following five criteria required for diagnosis of metabolic syndrome:</td>
<td>Required: Elevated waist circumference according to ethnicity specific values (<em>Table 3</em>) AND</td>
</tr>
<tr>
<td>1. Elevated waist circumference ($\geq 102$ cm in men and $\geq 88$ cm in women)</td>
<td>Two of the following four criteria required for diagnosis of metabolic syndrome:</td>
</tr>
<tr>
<td>2. Elevated fasting triglycerides ($\geq 150$mg/dL)</td>
<td>1. Elevated fasting triglycerides ($\geq 150$mg/dL) or specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td>3. Reduced HDL ($&lt; 40$ mg/dL in men and $&lt; 50$ mg/dL in women)</td>
<td>2. Reduced HDL ($&lt; 40$ mg/dL in men and $&lt; 50$ mg/dL in women) or specific treatment for this lipid abnormality</td>
</tr>
<tr>
<td>4. Elevated blood pressure ($\geq 130/85$ mm Hg) or on antihypertensive medication</td>
<td>3. Elevated blood pressure ($\geq 130/85$ mm Hg) or on antihypertensive medication</td>
</tr>
<tr>
<td>5. Elevated fasting glucose ($\geq 100$ mg/dL) or on insulin or hypoglycemic medication</td>
<td>4. Elevated fasting glucose ($\geq 100$ mg/dL) or on insulin or hypoglycemic medication</td>
</tr>
</tbody>
</table>
Table 3. Ethnic specific values for waist circumference

<table>
<thead>
<tr>
<th>Country/Ethnic group</th>
<th>Waist circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Europoids</strong></td>
<td></td>
</tr>
<tr>
<td>For USA, ATP III values (≥102 cm males; ≥88 cm female) are likely to continue to be used for clinical purposes</td>
<td>Male: ≥ 94 cm</td>
</tr>
<tr>
<td></td>
<td>Female: ≥ 80 cm</td>
</tr>
<tr>
<td><strong>South Asians</strong></td>
<td>Male: ≥ 90 cm</td>
</tr>
<tr>
<td></td>
<td>Female: ≥ 80 cm</td>
</tr>
<tr>
<td><strong>Chinese</strong></td>
<td>Male: ≥ 90 cm</td>
</tr>
<tr>
<td></td>
<td>Female: ≥ 80 cm</td>
</tr>
<tr>
<td><strong>Japanese</strong></td>
<td>Male: ≥ 90 cm</td>
</tr>
<tr>
<td></td>
<td>Female: ≥ 80 cm</td>
</tr>
<tr>
<td><strong>Ethnic South and Central Americans</strong></td>
<td>Use South Asian recommendations until data is available</td>
</tr>
<tr>
<td><strong>Sub-Saharan Africans</strong></td>
<td>Use European data until data is available</td>
</tr>
<tr>
<td><strong>Eastern Mediterranean and Middle East (Arab) populations</strong></td>
<td>Use European data until data is available</td>
</tr>
</tbody>
</table>

Adapted from Table 2 of IDF Consensus Worldwide Definition of the Metabolic Syndrome booklet.
C. Search strategy

I searched four electronic databases including MEDLINE via PUBMED, BIOSIS, Cumulative Index to Nursing and Allied Health (CINAHL), and The Cochrane Library (Appendix 1). These databases were chosen on the recommendation of a health sciences librarian. I used Medical Subject Headings (MeSH) terms when possible and used key word searches where applicable (Table 4). These terms were then combined in several ways with Boolean operators. The searches were then limited to articles written in the “English Language.”

The search criteria were limited to articles published between January 1990 to May 2011. Additional articles were identified using a hand search of reference lists of select articles. Reference lists of review articles on metabolic syndrome in schizophrenia patients were manually searched for other relevant citations.

All of the citations were imported into the citation manager RefWorks. Within RefWorks, citations were consolidated and duplicate articles from the various database searches were discarded.

Table 4. Key words used in database searches

<table>
<thead>
<tr>
<th>Key Words</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic agents</td>
</tr>
<tr>
<td>Atypical OR Second generation</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Metabolic syndrome X</td>
</tr>
</tbody>
</table>
D. Study Selection

I reviewed all abstracts resulting from the database and hand searches. For a systematic review, in an ideal situation, there would have been at least another reviewer, however, for this review, I was the solitary reviewer. I then attempted to retrieve full text articles corresponding to abstracts meeting the initial inclusion criteria using online and text resources from the University of North Carolina at Chapel Hill, Duke University and North Carolina State University. Retrieved full text articles underwent review and data abstraction.

E. Data Abstraction and Synthesis

A standardized data abstraction form was created using Microsoft Excel in order to be consistent and comprehensive when conducting quality assessments and analysis of results. I abstracted the following data from each included study: study type; year study was conducted; location; study population; description of intervention; sampling method; number of participants; type of comparison group; measured outcomes; length of follow up; definition of metabolic syndrome used; potential study bias; description of internal and external validity; overall quality of the study.

I created standardized evidence tables to describe the included studies and answer the proposed question. Findings of the review were qualitatively synthesized instead of quantitatively (meta-analysis) due to the small number of studies that met inclusion criteria and the methodological heterogeneity of the included studies. In particular I
concentrated on the available evidence for the question presented in this review and the overall consistency of the evidence.

F. Quality Assessment

The quality of the evidence, internal validity, and external validity assessments of each of the articles was made using criteria adapted from the United States Preventive Services Task Force (USPSTF) of the Agency for Healthcare Research and Quality (AHRQ). Tables 5 and 6 describe the specific criteria for internal and external validity respectively. Table 7 describes how overall quality was determined based on internal and external validity ratings.
### Table 5. Criteria for assessing internal validity adapted from USPSTF 12

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
</table>
| 1. Initial assembly of comparable groups. | a. RCT: Randomization adequate, equal distribution potential confounders  
  b. Cohort: considered potential confounders and adequately adjusted for these |
| 2. Maintenance of comparable groups throughout study. |                                                                                                                                           |
| 3. Important differential loss to follow-up or overall high loss to follow-up. |                                                                                                                                           |
| 4. Measurements are equal, valid, and reliable |                                                                                                                                           |
| 5. Clear definition of interventions |                                                                                                                                           |
| 6. Outcomes are clearly defined and all important outcomes are considered |                                                                                                                                           |
| 7. Analysis: | a. RCT: Intention to treat analysis  
  b. Cohort: Adjustment for potential confounders |

**Ratings**

- **Good:** Meets all criteria; Initial groups are comparable and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to groups; interventions are spelled out clearly; all important outcomes are considered; appropriate attention to confounders in the analysis. For RCTs, an intention to treat analysis is used.

- **Fair:** Generally comparable groups initially assembled; some differences with follow-up; measurement instruments are acceptable and generally applied equally; some but not all important outcomes are considered; some but not all confounders are accounted for. For RCTs, an intention to treat analysis is used.

- **Poor:** Studies given this rating have any of the following fatal flaws. Groups assembled initially are not close to being comparable or maintained; unreliable or invalid measurement instruments used or not applied equally among groups; key confounders are given little to no attention. For RCTs, intention to treat analysis is lacking.
Table 6. Criteria for assessing external validity adapted from USPSTF 12

| Criteria | 1. **Study population:** The degree to which the people who were involved as subjects in the study constitute a special population because they were selected from a larger eligible population. The following are features of the study population and the study design that may cause experience in the study to be different from what would be observed in the general population.  
   a. Demographics: age, gender, ethnicity, education, income  
   b. Comorbidities: frequency of co-morbid conditions in study population  
   c. Refusal rate: refusal rate among eligible study subjects is high, making the enrollees in the study unrepresentative  
   d. Adherence: run-in phase, frequent contact to monitor adherence; features of the study itself that make study participants comply with intervention that may be different than in a clinically observed population  
   e. Stage in natural history of the disease  
   f. Source and intensity of recruitment: The sources for recruiting subjects for the study and/or the effort and intensity of recruitment may distort the characteristics of the study subjects in ways that could increase the effect of the intervention as it is observed in the study.  
2. **Situation:** The degree to which the clinical experience in the situation in which the study was conducted is likely to be reproduced in other settings.  
3. **Providers:** The degree to which the providers in the study have the skills and expertise likely to be available in general settings

| Ratings | **Good:** The study differs minimally from the US primary care population/situation/providers and only in ways that are unlikely to affect the outcome; it is highly probable (>90%) that the clinical experience with the intervention observed in the study will be attained in the US primary care setting.  
**Fair:** The study differs from the US primary care population/situation/providers in a few ways that have the potential to affect the outcome in a clinically important way; it is only moderately probable (50%-89%) that the clinical experience with the intervention in the study will be attained in the US primary care setting.  
**Poor:** The study differs from the US primary care population/situation/providers in many way that have a high likelihood of affecting the clinical outcomes; the probability is low (<50%) that the clinical experience with the intervention observed in the study will be attained in the US primary care setting. |
**Table 7. Overall Quality**

<table>
<thead>
<tr>
<th>Quality Level</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Quality</td>
<td>• Good internal and external validity</td>
</tr>
<tr>
<td>Fair Quality</td>
<td>• Good internal validity with fair external validity</td>
</tr>
<tr>
<td></td>
<td>• Fair internal validity with Good external validity</td>
</tr>
<tr>
<td></td>
<td>• Fair internal and external validity</td>
</tr>
<tr>
<td>Poor Quality</td>
<td>• Fair internal validity with poor external validity</td>
</tr>
<tr>
<td></td>
<td>• Poor internal validity with fair external validity</td>
</tr>
<tr>
<td></td>
<td>• Poor internal and external validity</td>
</tr>
</tbody>
</table>
Results

A. Literature Search

The literature search identified 349 potentially relevant citations. 346 citations were found through electronic database searches and 3 articles were found through a targeted hand search. The initial Medline search identified 180 total abstracts. CINAHL, BIOSIS, and COCHRANE searches identified 68, 88, and 10 abstracts respectively. Twenty-three duplicate articles were identified across the searches and were discarded, resulting in 326 unique and potentially relevant citations (Figure 1).

I reviewed these 326 abstracts and excluded 314 articles (96%) for reasons including: inappropriate study design, metabolic syndrome was not the measured outcome, abstract was unavailable, second generation antipsychotics were not used as the intervention. I attempted to retrieve the 12 remaining articles using resources from the University of North Carolina at Chapel Hill, Duke University, and North Carolina State University. 3 of the articles were not accessible; therefore 9 articles underwent full text review.

Upon full text review, 7 of the 9 articles were excluded. Three of the excluded articles focused on comparing individual metabolic syndrome criteria (e.g. lipid and fasting glucose levels) between first- and second generation antipsychotics instead of metabolic syndrome. One study was excluded because the authors calculated incidence rate of developing diabetes instead of measuring incidence rate of developing metabolic syndrome. One study was excluded because the authors did not compare development of metabolic syndrome between first- and second-generation antipsychotics. The final
two studies that were excluded measured prevalence of developing metabolic syndrome instead of incidence \(^8,^{18}\).

The remaining two articles met eligibility criteria and were included for data abstraction and included in this review \(^{19,20}\). The results of the literature search are depicted in Figure 1.
Figure 1. Results of literature search

- Titles and abstracts identified through database searches: n=346
- # of additional records identified through targeted hand search: n=3

Unique citations included in RefWorks: n=326

- Citations Excluded by Abstract Review: n=314
- Unable to retrieve Full Text: n=3

Full Text retrieved: n=9

- Citations Excluded by Full Text Review: n=7

Articles included in review: n=2
  - 1 randomized controlled study
  - 1 cohort study
B. Description of the Included Studies

Both of the included studies were published in 2008. One of the studies, a randomized controlled trial was conducted in the United States and the other, a prospective cohort study, was conducted in Belgium. The study from Belgium was restricted to patients from one site. The study from the United States included participants from 57 different sites across the country including university clinics, state mental health agencies, VA Medical Centers, private nonprofit agencies, independent practice sites, and mixed system sites.

Both of the included studies defined metabolic syndrome using the adapted guidelines set by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP IIIa). The measured outcome in both studies was metabolic syndrome. The treatment intervention in one study included more than one second generation antipsychotic compared to one first generation antipsychotic. The other study compared the intervention of several second generation antipsychotics with high potency first generation antipsychotics. The descriptive characteristics of the two included studies are depicted in Table 8.
### Table 8. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>First Author</th>
<th>De Hert 19</th>
<th>Meyer 20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year Published</strong></td>
<td>2008</td>
<td>2008</td>
</tr>
</tbody>
</table>
| **Study Location** | University Centre St. Jozef, Kortenberg, Belgium. | United States- 57 sites  
- 16 university clinics,  
- 10 state mental health agencies  
- 7 VA Medical Centers  
- 6 private nonprofit agencies  
- 4 independent practice sites  
- 14 mixed system sites |
| **Study Design** | Prospective cohort | Randomized controlled trial |
| **Length of follow up time** | 3 years | 3 months |
| **Number of Participants** | Historic: 148  
Current: 148  
Total: 296 | Source: 933  
All classifiable:660  
Fasting: 281 |
| **Metabolic syndrome criteria used** | NCEP ATP-III a | NCEP ATP-III a |
| **Intervention (SGA)** | Amisulpride  
Aripiprazole  
Clozapine  
Olanzapine  
Risperidone  
Quetiapine | Olanzapine  
Risperidone  
Quetiapine  
Ziprasidone |
| **Comparison (FGA)** | High potency FGAs  
- Butyrophenones  
- Diphenylbutylperidines  
- Thioxanthenes | Perphenazine |
| **Measured Outcome** | Metabolic Syndrome | Metabolic Syndrome |

**Abbreviations:** SGA: Second generation antipsychotic agent; FGA: First generation antipsychotic agent; NCEP ATP-IIIa: Adapted National Cholesterol Education Program Adult Treatment Panel III criteria
C. Quality and Results of the Included Studies

De Hert, Schreurs, Sweers et al. 19

In their 2008 article in Schizophrenia Research, the authors compared two different cohorts (historic and current) of patients with schizophrenia admitted for their first episode of psychosis.

The historic cohort was derived from an original cohort of 1119 consecutive patients diagnosed with schizophrenia or schizoaffective disorder admitted for their first episode of psychosis to two treatment and rehabilitation wards at University Centre St. Jozef, Kortenberg, Belgium between 1973 and 1992 21. Laboratory testing for HDL cholesterol was not available until 1984; therefore the historic cohort only included patients after this point. Furthermore, only patients with schizophrenia were included in the final study population. Of the 301 patients admitted between 1984 and 1995, there was complete laboratory data for all metabolic criteria for 148 patients prior to start of treatment and these patients were included as the study population.

The concurrent cohort was derived from a prospective cohort of consecutive patients admitted to the study between 2000 and 2006 at their first episode of psychosis in either in- or out-patient settings at a university psychiatric hospital and its affiliated facilities 22. De Hert, Schreurs, Sweers et al. matched the 148 patients from the historic cohort for age and sex with 148 patients in the current cohort.
At baseline measurement of the two cohorts, prior to starting antipsychotic treatment, the historic and current cohorts’ prevalence of metabolic syndrome were similar, 5.7% and 5.6% respectively. After 3 years of follow-up, the investigators of this study found that the incidence of metabolic syndrome had risen in both cohorts, but significantly more so in the second generation antipsychotic treated current cohort (historic: 9.8% vs. current: 27.8%). Of the 148 patients in each of the cohorts at the start of this study, complete data was available for 122 (historic cohort) and 108 (current cohort) patients after 3 years.

Internal Validity

The authors of this study did consider some of the potential confounders (age and sex) and adjusted for these when they assembled the current cohort to match the historic cohort. However, this comparability was not maintained throughout the study as there was loss to follow up in both cohorts. Specifically, the current cohort was younger at admission into the study and had a shorter duration of follow up (shorter amount of time on medication).

To classify metabolic syndrome in the historic cohort, waist circumference was calculated using BMI and a “conservative conversion factor” which questions the accuracy of that variable in the historic cohort. If the conversion factor was too conservative, then subjects who potentially had metabolic syndrome might have been misclassified making the reported incidence over 3 years for the historic cohort to be lower than it actually is. Another limitation is that compared to the time period of the historic cohort, we are now more concerned about metabolic syndrome and the potential
of medications to cause changes to individual metabolic parameters which may result in
closer monitoring of patients in the current cohort presenting a bias in measurement.

Another limitation is that the authors did not collect data on compliance to medications in
both cohorts. Non-compliance to the medications might differential measurement bias
especially if some of the drugs have worse side effects than the others. Therefore, it
would have been helpful to have information to quantify the specific effect of non-
compliance. The authors of this study provided clear definition of interventions and
outcomes. They considered qualitatively the effect of confounding by differences in age
and duration of treatment between the two cohorts in their discussion. Follow up period
was over three years which is fairly long in duration to appreciate long term effects of the
medications. This study was given a “fair” rating for internal validity.

*External Validity*

This study was conducted at one site in Belgium which limits the generalizability of the
results. People included in the study were of similar ethnic background (>95% Caucasian
and of native Belgian origin). The definition of metabolic syndrome used in this study
(NCEP IIIa) does not differentiate between different ethnic groups. Even when using the
IDP criteria where ethnicity is considered for waist circumference, criteria for USA
populations are the same as the ATP IIIa values. For European populations, however,
there is a lower threshold for diagnosis of central obesity. Given these definitions, the
results can be considered to be conservative in diagnosis of metabolic syndrome and
applicable to other ethnic groups.
Participants in this investigation were drug-naïve patients with schizophrenia, presenting with their first episode of psychosis. Therefore, these results are not as applicable to patients with schizophrenia who are in a later stage of the disease, having been on antipsychotic medications for several years. Lastly, another limitation to the generalizability of this study was that the size of the study population was fairly small. This study was given a “fair” rating for external validity.

**Overall quality**

There were some important limitations to consider with this study, including some loss of comparability between cohorts, loss to follow up, accuracy/validity of waist circumference measurements, and generalizability of results due to size of study population, study location, and number of study sites. For these concerns, this study was given a “fair” rating for overall quality.
Meyer, Davis, Goff et al. 20

In their 2008 article in Schizophrenia research, Meyer, Davis, Goff et al. used data from phase I of the Clinical Antipsychotic Trials of Intervention and Effectiveness (CATIE) Schizophrenia trial to compare metabolic syndrome status in schizophrenia patients treated with antipsychotic medications. Subjects in this trial were randomized to one of five treatments: olanzapine, risperidone, quetiapine, ziprasidone, and perphenazine. Baseline measures were completed prior to start of antipsychotic medication and follow up measures were completed at 3 months.

Fasting measures were collected at both baseline and at 3 months for 281 subjects. To have larger sample size, the authors created a cohort of non-fasting subjects whose metabolic syndrome status could be classified ("all classifiable cohort") using modified metabolic syndrome criteria (n=660). These two cohorts had similar demographics at baseline. The authors reported prevalence measures of metabolic syndrome however enough data was reported in the article to determine incidence (Tables 9 and 10).

In the fasting cohort, the overall incidence of metabolic syndrome over the 3 month period for those treated with second generation antipsychotics was 4.5% and for those treated with the first generation antipsychotic (perphenazine), there was a reduction in overall incidence by 3.8%. For those treated with perphenazine, the number of cases decreased from 22 (baseline) to 20 (3 months). Within the second generation antipsychotic groups, there was variability. The largest difference was between those treated with olanzapine and ziprasidone, the incidence of metabolic syndrome by the 3
month period was 9.5% in the olanzapine treated group and a decrease in incidence in the ziprasidone treated group by 9.7%.

In the larger “all classifiable” cohort, the overall incidence of metabolic syndrome, over the 3 months, for those treated with second generation antipsychotics was 1.5% and for those treated with the first generation antipsychotic (perphenazine) was 0.8%. Once again there was great variability in the second generation treatment groups. Only olanzapine had a positive incidence at 9.1%. Of the remaining second generation treatment groups, there were no new cases of metabolic syndrome in the risperidone treated group, one less case in the quetiapine group and finally, ziprasidone had the largest decrease in cases (6 cases) with a decrease in incidence by 7.8%.
# Table 9. Results of fasting cohort

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (n=278)</th>
<th>Baseline prevalence</th>
<th># cases at baseline(^a)</th>
<th>3 month prevalence</th>
<th># of total cases at 3 months(^b)</th>
<th>Incident cases at 3 months(^c)</th>
<th>Incidence (%)(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>74</td>
<td>0.419</td>
<td>31</td>
<td>0.514</td>
<td>38</td>
<td>7</td>
<td>9.5</td>
</tr>
<tr>
<td>Risperidone</td>
<td>54</td>
<td>0.370</td>
<td>20</td>
<td>0.426</td>
<td>23</td>
<td>3</td>
<td>5.6</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>67</td>
<td>0.388</td>
<td>26</td>
<td>0.433</td>
<td>29</td>
<td>3</td>
<td>4.5</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>31</td>
<td>0.484</td>
<td>15</td>
<td>0.387</td>
<td>12</td>
<td>-3</td>
<td>-9.7</td>
</tr>
<tr>
<td>Total SGA</td>
<td>226</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGA: Perphenazine</td>
<td>52</td>
<td>0.423</td>
<td>22</td>
<td>0.385</td>
<td>20</td>
<td>-2</td>
<td>-3.8</td>
</tr>
</tbody>
</table>

**Abbreviations:** SGA: Second generation antipsychotic agent; FGA: First generation antipsychotic agent

# Table 10. Results of the “all classifiable” cohort

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (n=660)</th>
<th>Baseline prevalence</th>
<th># cases at baseline(^a)</th>
<th>3 month prevalence</th>
<th># of total cases at 3 months(^b)</th>
<th>Incident cases at 3 months(^c)</th>
<th>Incidence (%)(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>164</td>
<td>0.348</td>
<td>57</td>
<td>0.439</td>
<td>72</td>
<td>15</td>
<td>9.1</td>
</tr>
<tr>
<td>Risperidone</td>
<td>147</td>
<td>0.306</td>
<td>45</td>
<td>0.306</td>
<td>45</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>143</td>
<td>0.378</td>
<td>54</td>
<td>0.371</td>
<td>53</td>
<td>-1</td>
<td>-0.7</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>77</td>
<td>0.377</td>
<td>29</td>
<td>0.299</td>
<td>23</td>
<td>-6</td>
<td>-7.8</td>
</tr>
<tr>
<td>Total SGA</td>
<td>531</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGA: Perphenazine</td>
<td>129</td>
<td>0.372</td>
<td>48</td>
<td>0.380</td>
<td>49</td>
<td>1</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**Abbreviations:** SGA: Second generation antipsychotic agent; FGA: First generation antipsychotic agent

Note: The following represents calculations used in Tables 9 and 10.

a. \# of cases at baseline = n* Baseline prevalence
b. \# of cases at 3 months = n* 3 month prevalence
c. Incident cases at 3 months = \# of cases at 3 months - \# of cases at baseline
d. Incidence (%) = [(Incident cases at 3 months) ÷ n] * 100%
**Internal Validity**

Meyer, Davis, Goff et al. clearly defined the interventions as well as the outcomes in this study. Randomization to the five antipsychotic medications was conducted under double blind conditions. The authors compared baseline demographics between the fasting cohort (n=281), the larger “all classifiable” cohort (n=660), and the source population of all the subjects in the CATIE phase 1 trial with some data at baseline and 3 months (n=933). Within these cohorts, there were no differences in baseline demographics. The authors however failed to report baseline demographics within the different treatment arm which is a significant limitation as we do not know how comparable the treatment arms are to each other. The authors did report the baseline prevalence of each of the metabolic criteria for the different treatment arms in the fasting cohort; the criteria were fairly comparable between all groups.

Another limitation is that baseline data on length of previous antipsychotic use was not collected. Subjects who may have a longer exposure to metabolically effecting antipsychotics will more likely have metabolic syndrome. If these subjects are unequally randomized, the results may be skewed towards the treatment arm with more subjects that were exposed for a longer period of time prior to start of the study. Additionally, the authors did not do an intention to treat analysis, severely limiting this readers’ ability to determine whether randomization was intact throughout the study.

For the fasting cohort, the measurements were equal, valid, and reliable. For the “all classifiable” cohort, there are some questions about the measurements used for
classification of metabolic syndrome. This cohort included patients that had non-fasting data. Of the five metabolic syndrome criteria, serum glucose and triglycerides are affected by fasting status. For serum glucose, the authors considered the criteria to have been met if the subject was currently taking hypoglycemic medications or insulin or if the random glucose level was ≥200mg/dl which met the American Diabetes Association definition for DM. Furthermore, glucose criteria was not considered met if the random glucose was <100 mg/dl. For triglyceride levels, the criterion was considered not met if the random triglyceride level was <150 mg/dl. Additionally, any subject not taking anti-diabetic medication, with a random glucose value between 100-199 mg/dl and random triglyceride level ≥150 mg/dl were not considered either positive or negative for metabolic criteria. These modified criteria could potentially lead to underestimation of incidence as some people who may actually have metabolic syndrome are classified as not having metabolic syndrome.

This study was given a rating of “poor” for inappropriately comparing the initially assembled groups, not conducting an intention to treat analysis, and concerns of unequal and invalid measurements.

External Validity

Data for this study were collected at 57 sites in the United States in various different settings increasing the generalizability of the results. The fasting cohort was limited by the small size of each of the treatment groups. As mentioned previously, the length of prior treatment with other antipsychotic medications was unknown; therefore we cannot
determine the stage of the disease of the participants in this study. In regard to situation and providers, they can be easily reproduced in the general settings. This study was given a “fair” rating.

*Overall Quality*

Given the considerable limitations of this study resulting in “poor” internal and “fair” external validity, this study was given a “poor” overall quality rating.

**D. Principal Findings of this Review**

In summary, one study\(^1\) found a significantly higher incidence of metabolic syndrome in those taking second generation antipsychotics than in those taking first generation antipsychotics. This study was given an overall quality rating of “fair.” The other study\(^2\) showed mixed results. In one cohort of fasting patients, they found a higher incidence of metabolic syndrome in those treated with second generation antipsychotics, whereas in the other cohort using non-fasting criteria, the authors found a small difference in overall incidence between first- and second-generation antipsychotics, with slightly higher incidence in the second generation antipsychotic group. This study was given an overall quality rating of “poor” due to some significant limitations in internal and external validity.
Discussion

A. Synthesis of Results

There is poor to fair evidence that there is increased incidence of developing metabolic syndrome in patients with schizophrenia being treated with second generation antipsychotics when compared to patients with schizophrenia treated with first generation antipsychotics. Of the two studies included in this systematic review, one was of fair quality and the other was of poor quality.

B. Secondary results

The study by Meyer, Davis, Goff et al. 20, which was given a poor quality rating, also found differences in incidence of developing metabolic syndrome between individual second generation antipsychotic treatments. They found that olanzapine was associated with an increased incidence of developing metabolic syndrome over a 3 month period over the remaining second generation antipsychotics under study (risperidone, quetiapine, ziprasidone).

C. Limitations of review

This review has several limitations. Firstly, the search for relevant articles was limited to only include English-language articles. Antipsychotic medications are the primary source of treatment for schizophrenia and as such there may be studies that are published in other languages that may be appropriate for answering the question proposed in this systematic review. Therefore, this review might be slightly limited by excluding these articles.
Additionally, this systematic review was limited to currently published literature. There are likely unpublished data and ongoing trials studying incidence of metabolic syndrome in antipsychotic treated schizophrenic patients and these was not included in this review. Furthermore, there were 3 articles identified by the abstract review that were not able to be retrieved. Exclusion of these articles limits the comprehensiveness of this systematic review.

D. **Recommendations for future research**

The two studies included in this review had several limitations. For future research, there is a need for a more optimally constructed and conducted study. Randomized controlled trials would work best as specific interventions and controls can be assigned randomly and confounders can be limited easily at the start of the studies. Non-randomized cohort trials could also be appropriate as long as there is proper control of confounders. In order to best determine if people with schizophrenia treated with second generation antipsychotics have a higher incidence of developing metabolic syndrome, we must first start with schizophrenia patients that are drug naïve presenting with their first episode of psychosis. These patients would not have any prior antipsychotic use limiting confounding effects from different drugs.

Although follow-up of 3 months is a requirement for this review, in general, patients with schizophrenia are treated of long periods of time; therefore, a longer follow up period would be more appropriate. The ideal follow up period would be the lifetime of the
included patients. This is because drug-naïve, first episode of psychosis patients with schizophrenia tend to be young and healthy. Furthermore, the risk of metabolic syndrome increases with age and needs to be considered in the study. In other words, differential risk across first generation antipsychotics and second generation antipsychotics should be evaluated over the course of the disease process of schizophrenia.

In terms of interventions, some studies have indicated the variable effects of different second generation antipsychotics on metabolic parameters (weight gain, impaired fasting glucose)\(^6\). One of the studies included in this review randomized people to four different second generation antipsychotics, but only randomized to one first generation antipsychotic agent\(^20\). Ideally, we would randomize patients to several commonly used second generation antipsychotic agents and several first generation antipsychotic agents. This would enable comparison of the drug class effects of first- and second-generation antipsychotics as well as the differential effects of individual agents.

Additionally, much of the literature on this topic is in smaller sample sizes from one site. This limits the generalizability of the results to a larger population in different locations. Therefore, it would preferable to conduct a multi-site, multi-national study utilizing a large study population.
E. Conclusions

In conclusion, the available evidence is insufficient to determine whether treatment with second generation antipsychotic agents results in a higher incidence of developing metabolic syndrome than treatment with first generation antipsychotic agents in patients with schizophrenia. Nonetheless, there is need for future studies with better design as current studies are not of good quality.

I have described areas in future research that would improve on the current available literature and have described an ideal study which could be readily conducted if funding were not an issue. A long-term, large, multi-site, multi-national, randomized controlled trial would be very expensive. Drug companies which have the funds would not be interested in this study as the study is looking for adverse effects of medications. Therefore, funding for the study would have to come from a source such as the NIH. Funding for such an extensive study is further limited by the current status of the economy. The limited numbers of studies included in this review are likely due in part to barriers in cost.

Metabolic syndrome and schizophrenia are chronic conditions for which treatment is long term. They both have a significant effect on the quality of life of those that are affected. The second generation antipsychotic medications have only been on the market for the past two decades and long-term effects of these medications are only now being realized. Therefore, only with more studies of better quality, can we determine the specific effect of antipsychotic medications on developing metabolic syndrome.
Appendix I. Search Strategy

1. PubMed Search using MeSH headings and keywords:

   ("Antipsychotic Agents"[Mesh] OR "antipsychotic agents"[MeSH Terms] OR
   ("antipsychotic"[All Fields] AND "agents"[All Fields]) OR "antipsychotic
   agents"[All Fields] OR "antipsychotic"[All Fields] OR "antipsychotic
   agents"[Pharmacological Action]) OR ("antipsychotic agents"[MeSH Terms] OR
   ("antipsychotic"[All Fields] AND "agents"[All Fields]) OR "antipsychotic
   agents"[All Fields] OR "antipsychotics"[All Fields] OR "antipsychotic
   agents"[Pharmacological Action])) AND (atypical[All Fields] OR "second
   generation"[All Fields])) AND ("Metabolic Syndrome X"[Mesh] OR "metabolic
   syndrome"[All Fields]) AND (English[lang])

2. CINAHL via EBSCO host:

   Boolean/Phrase: (MH “Antipsychotic Agents +”) AND (MH “Metabolic
   Syndrome X+”)

3. BIOSIS and The Cochrane Library:

   “Antipsychotic Agents” AND “Metabolic Syndrome”
### Appendix 2. Evidence table of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>De Hert (^{19})</th>
<th>Meyer (^{20})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year Published</td>
<td>2008</td>
<td>2008</td>
</tr>
<tr>
<td>Study Design</td>
<td>2 cohorts- prospective</td>
<td>RCT</td>
</tr>
<tr>
<td>Selection bias</td>
<td>Dropouts: Historic: 26  Current: 40</td>
<td>Did not conduct intention to treat analysis</td>
</tr>
<tr>
<td></td>
<td>Historic: older and longer</td>
<td>Baseline demographics and characteristics between treatment arms were not discussed in the study</td>
</tr>
<tr>
<td></td>
<td>Current: younger, and shorter duration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Did not collect exact drugs, switches over time between agents or eventual polypharmacy in historic cohort</td>
<td></td>
</tr>
<tr>
<td>Measurement bias</td>
<td>Used a conversion to calculate waist circumference from BMI for Historic cohort.</td>
<td>For all classifiable cohort: Modified criteria for impaired fasting glucose and triglycerides</td>
</tr>
<tr>
<td></td>
<td>Lab techniques have changed over time. We are more careful now about metabolic syndrome and so we look for it more</td>
<td>The duration of baseline antipsychotic use was not measured-important as those with longer exposure to more metabolically offending agents might have been randomized unequally to the different treatment arms.</td>
</tr>
<tr>
<td>Internal validity (Good, Fair, Poor)</td>
<td>Fair</td>
<td>Poor</td>
</tr>
<tr>
<td>External validity</td>
<td>Fair:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• &gt;95% Caucasian and of native Belgian origin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• One hospital center</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Small sample size</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 57 sites in US. Large study.-generalizable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Small sample size of treatment groups in fasting cohort</td>
<td></td>
</tr>
<tr>
<td>Quality of the Study</td>
<td>Fair</td>
<td>Poor</td>
</tr>
</tbody>
</table>
REFERENCES


