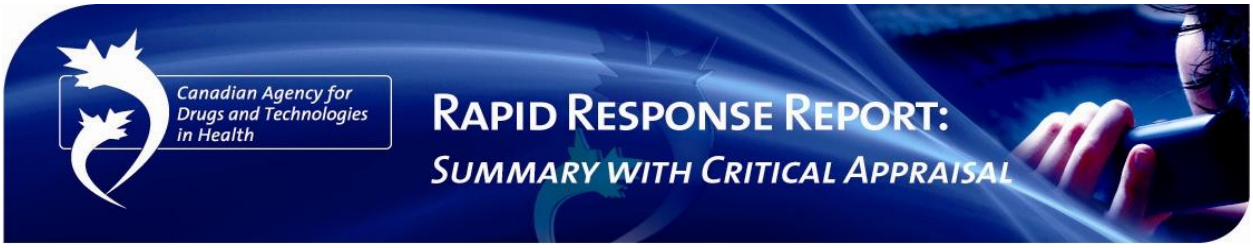


TITLE: Metabolic Monitoring and Interventions for Reducing Metabolic Syndrome in Patients Treated with Atypical Antipsychotics: A Review of the Clinical Evidence

DATE: 21 July 2011

CONTEXT AND POLICY ISSUES:

Metabolic syndrome commonly refers to a group of risk factors that occur together that increase the risk of coronary artery disease, stroke and type 2 diabetes.[1] There is no universal consensus on the precise definition of metabolic syndrome.[2] Some common features in the definitions of metabolic syndrome include high blood pressure, above normal blood sugar (or glucose), large waist circumference, low high density lipoprotein (HDL) cholesterol, and high triglycerides.[1,2] In this report, the definition for metabolic syndrome by the American Heart Association and the National Heart, Lung, and Blood Institute was used.[1] As such, metabolic syndrome is defined as the presence of at least three of the following signs: blood pressure $\geq$ 130 per 85 mmHg, fasting blood glucose (sugar) $\geq$ 100 mg per deciliter (dl), waist circumference of $\geq$ 40 inches for men or $\geq$ 35 inches for women, HDL < 40 for men mg per dl and HDL< 50 mg per dl for women, or triglycerides $\geq$ 150 mg per dl.[1]

Metabolic syndrome has been observed as an adverse effect of treatment with atypical antipsychotics (AAPs) after as little as 10 weeks of treatment.[3-5] AAPs include aripiprazole, clozapine, olanzapine, quetiapine, and risperidone.[4,6,7] As well, clozapine and olanzapine have been frequently linked with risk factors of metabolic syndrome such as hyperglycemia, and dyslipidemia.[2,8,9] To a lesser extent, quetiapine and risperidone have been associated with the same risk factors of metabolic syndrome.[2] Finally, there is a low potential for hyperglycemia or adverse events on lipid profiles in treatments with aripiprazole.[10]

According to the National Cholesterol Education Program definition of metabolic syndrome[11] the prevalence of metabolic syndrome in a population of patients from 17 to 55 years old treated with clozapine in an outpatient setting was 53.8% compared with 20.7% in the general population.[6] The prevalence of metabolic syndrome in patients treated with other AAPs in various clinical settings was not identified in the literature.

The purpose of this review is to examine the clinical evidence regarding the monitoring and interventions to prevent or manage metabolic syndrome in patients treated with aripiprazole, clozapine, olanzapine, quetiapine, and risperidone.

RESEARCH QUESTIONS:

1. What is the clinical evidence for interventions to prevent or manage metabolic syndrome in adult patients treated with atypical antipsychotics?

2. What is the clinical evidence for metabolic monitoring in adult patients treated with atypical antipsychotics?

KEY MESSAGE:

Limited evidence is available on the interventions which treat metabolic risk factors. Low quality studies and inconsistent reporting of clinical outcomes make it difficult to draw definitive conclusions on the optimal intervention to prevent or manage metabolic syndrome.

METHODS:

Literature search strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2011, Issue 6), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated list of major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type for research question number 1. Methodological filters were applied to research questions number 1 and 2 to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2006 and Jun 22, 2011.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full text publications for the final article selection, according to the selection criteria outlined in Table 1.

Table 1: Selection Criteria

Population	Adult patients on atypical antipsychotics. Specific medications of interest include as follows: 1. Aripiprazole (Abilify) 2. Clozapine 3. Olanzapine (Zyprexa) 4. Quetiapine (Seroquel) 5. Risperidone
Intervention	Q1: Metabolic monitoring, such as waist circumference, blood pressure, glucose and, cholesterol levels Q2: Various interventions to manage or prevent metabolic syndrome (for example, health education and training)

Comparator	Q1 and Q2: No comparator
Outcomes	Q1: Types of metabolic monitoring and frequency of monitoring for risk factors[1] (see signs and tests section) Q2: Reduction of metabolic syndrome The following signs within an acceptable range: Blood pressure Waist circumference Glucose levels HDL cholesterol Triglycerides
Study Designs	Health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials (RCTs)

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or included in at least one selected systematic review, involved irrelevant study designs or were published before 2006.

Critical Appraisal of Individual Studies

The quality of the included systematic review was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool,[12] and RCTs were critically appraised with the Downs and Black Checklist.[13]

SUMMARY OF EVIDENCE:

Quantity of Research Available

The literature search generated 667 citations. Upon screening 635 citations were excluded and 32 potentially relevant articles were identified were for full-text review. An additional five potentially relevant reports were identified through the grey literature search. Of the 37 potentially relevant articles**,** 25 articles did not meet the inclusion criteria. As a result, six systematic reviews and meta-analyses[7,14-18] and six RCTs were included in this review.[19-24] Additional articles of potential interest are provided in the appendix.

Summary of Study Characteristics

Detailed study characteristics, critical appraisal of studies and findings and author's conclusions are provided in appendices 2, 3and 4.

Country of Origin

Of the six included systematic reviews, three were from the USA[15-17] two were from the United Kingdom[7,18] and one was from India.[14] The systematic reviews included RCTs conducted in numerous countries. Four RCTs included in this review were conducted in the USA,[19,21,23,24] and a single RCT was conducted in Finland[22] and India[20], respectively.

Study Setting

The systematic reviews did not specify the setting in which the included studies were conducted. Three RCTs were conducted at urban mental health centres.[19,20,22] One RCT was conducted in a psychiatric clinic of a tertiary care hospital.[20] Two RCTs did not specify the health care setting,[19,23] including one multicenter RCT.[23]

Patient Population

The study population in three systematic reviews was limited to adult patients[7,14,17] and three reviews include studies with adults and children[15,16,18] The trials that reported clinical outcomes for adult patients will be discussed in this report. The systematic reviews included patients with the following mental illnesses- schizophrenia, schizoaffective disorder, bipolar disorder, psychotic disorder, schizotypal, depression, and personality disorder.[7,14-18]

The patient population in the RCTs ranged from 18 to 65 years of age.[19-24] In addition, the trials included patients with schizophrenia (including first episode schizophrenia), schizoaffective disorder or an unspecified "serious mental condition."[19-24] Two RCTs included a mix of inpatients and outpatients.[19,20]

Interventions and Comparators

The interventions and comparators in the systematic reviews and RCTs will be described. Four systematic reviews included studies that compared metformin with placebo.[7,14-16] Two systematic reviews included studies that compared metformin and sibutramine versus metformin and placebo [18] or placebo alone.[16] Two systematic reviews included studies that compared metformin and lifestyle interventions with lifestyle interventions and placebo and placebo alone.[16,18] One systematic review included studies that compared switching from treatment with olanzapine or risperidone to aripiprazole and studies that compared switching from olanzapine to quetiapine.[7] One systematic review included studies that compared combinations of dietary counseling, physical activity counseling, and/or behavioural components with unspecified standard or routine care, nutrition education, unspecified control groups, metformin only, metformin and lifestyle interventions, lifestyle interventions and placebo, and placebo only.[18]

Four RCTs compared individual pharmacological interventions (modafinil, orlistat, topiramate, sibutramine) with placebo.[19,20,22,24] One study involved patients previously treated with any schizophrenia or schizoaffective disorder intervention including individuals randomized to risperidone or olanzapine treatments.[23] One study compared aripiprazole with olanzapine, quetiapine, risperidone involving patients with unknown previous use of AAPs.[21]

Outcomes measures

Three RCTs reported measures of blood pressure.[19,20,24] Three systematic reviews [7,17,18] and four RCTs[19,20,22,24] reported measures of fasting blood glucose or blood glucose or sugar. Five systematic reviews[7,14-16,18] and one RCT[24] reported measures of waist circumference. Three systematic reviews [7,16,18] and four RCTs[19,22-24] reported measures of HDL, and four systematic reviews[7,16-18] and five RCTs[19,20,22-24] reported measures of triglycerides.

Summary of Critical Appraisal

The quality of evidence varied, but was generally low. Four of the six systematic reviews included a comprehensive literature.[7,15-17] It, however, was unclear if the grey literature was searched in any of the included systematic reviews. Most of the systematic reviews had poor or incomplete reporting of the metabolic outcomes in the individuals trials. The study findings of the same trials were reported inconsistently across several systematic reviews. Two systematic reviews stated that the data were extracted by at least two independent reviewers.[17,18] In addition, publication bias was assessed in two of the six systematic reviews.[7,15]

Among the six RCTs, none stated how allocation was concealed. In addition, none of the studies provided power calculations to determine the minimum sample size needed to detect a minimum clinically important difference for any of the metabolic risk factors. Furthermore, none of the studies provided information the process used to randomize participants (for example, participants randomized based on a random number sequence). Five out of the six RCTs studies blinded participants and investigators in the randomization process.[19,20,22-24] Four RCTs reported the results of the per-protocol analyses. [19,20,22,24] One RCT reported the results intention to treat (ITT) analysis (ITT analysis not described).[21] For one RCT it was unclear if the results of the per-protocol of ITT analysis were reported for one study.[23]

Summary of Findings

The primary outcomes of the included studies were as follows: weight reduction/loss,[15,18,24] weight gain,[14] weight gain prevention,[17] weight or body weight,[7] serum or fasting glucose,[16] body mass index (BMI),[14,15,20] waist circumference (WC),[14-16] homeostatic model assessment of insulin resistance (HOMA-IR),[15,19] blood pressure,[20] weight change,[19,22] total cholesterol,[19] non-high density lipoproteins (HDL),[19] HDLs,[19] and triglycerides.[19]

Blood Pressure (BP)

Three RCTs[19,20,24] measured BP in the patient population. Henderson et al.[19] reported no significant differences in BP between clozapine and modafinil versus placebo. Narula et al.[20] compared olanzapine and topiramate (100 mg per day) versus olanzapine and placebo (placebo) in a RCT. They reported a significant difference between groups in systolic BP ($p=0.012$). After 12 weeks, the topiramate group had a mean systolic BP of [mean $\pm$ standard deviation (SD)]=117.88$\pm$7 and the placebo group had a mean systolic BP of (mean $\pm$ SD)= 122.5$\pm$ 7.71.[20] They reported a significant difference between groups in diastolic BP ($p=0.014$).[20] After 12 weeks, the topiramate group had a mean diastolic BP of (mean $\pm$ SD)= 77.94 $\pm$ 4.8 and the placebo group had a mean diastolic BP of (mean $\pm$ SD)= 81.41$\pm$ 6.2. Henderson et al.[24] in a RCT compared clozapine and sibutramine to clozapine and placebo.[24] They observed no significant differences in BP between groups.[24]

Fasting Blood Glucose or Blood Glucose (FBG or BG)

Two systematic reviews[7,17] and four RCTs[19,20,22,24] included a measure of FBG or BG. One systematic review and meta-analysis by Mukundan et al.,[7] indicated a significant decrease in FBG when switching from olanzapine to aripiprazole or quetiapine [-2.53, 95% confidence interval (CI) -2.94 to -2.11].[7] Gabriele et al.[17] reported a significant decrease in BG that compared diet, and physical activity versus an unspecified control group in one RCT. In the same systematic review another RCT comparing diet, physical activity and behavioral components (food records) with metformin, metformin and lifestyle interventions and placebo in patients treated with clozapine, olanzapine, risperidone, or quetiapine in the included primary studies. The BG decreased from -7.54 to -12.00% ($p<0.05$) in patients on AAPs.[17] In the same review, another RCT reported no significant difference between diet, physical activity and exercise rewards versus an unspecified control group.[18]

No significant differences in FBG between groups were reported in a RCT that compared olanzapine and modafinil with olanzapine alone and placebo.[19] Narula et al.[20] in a RCT found a significant difference in FBG when they compared olanzapine and topiramate versus olanzapine and placebo ($p<0.001$). After 12 weeks, the mean FBG in topiramate group had a mean FBG of ($\pm$ SD)= 78.24 $\pm$ 6.7 and the mean of the placebo group was (mean $\pm$ SD)=88.47 $\pm$ 12.0. Joffe et al.[22] reported no significant differences between groups in FBG when they compared clozapine or olanzapine and orlistat (360 mg per day) versus clozapine or olanzapine and placebo.[22] As well, Henderson et al. observed no significant differences in BG between clozapine and sibutramine (10 mg per day) versus clozapine and placebo.[24]

Waist Circumference (WC)

Five systematic reviews[7,14-16,18] and one RCT[24] measured the WC in the study population. One systematic review and meta-analysis[14] reported a significant difference in WC between patients treated with olanzapine and metformin versus those treated with olanzapine or on placebo ($p<0.00001$). The weighted mean difference was 1.42 (95% CI 0.29 to 3.13) cm lower for the metformin compared to placebo.[14] Mukundan et al.[7] reported no significant difference in WC between patients switching from olanzapine to aripiprazole versus staying on olanzapine in one RCT included in their systematic review. Ehret et al.[15] reported a significant decrease in WC in adults treated with olanzapine, clozapine, risperidone or quetiapine and metformin versus the same AAPs and placebo [WMD (95% CI)= -1.64, (95% CI -3.11 to -0.18]. Miller et al.[16] in a systematic review found a significant decrease in WC for patients treated with olanzapine and metformin alone or in combination with lifestyle changes versus olanzapine with lifestyle changes and placebo or placebo only. One RCT in the same review reported no significant change in WC in olanzapine and metformin group versus olanzapine with placebo (data were not provided).[16] A third RCT in the same review that compared olanzapine and metformin versus olanzapine and placebo reported significant changes in WC (data were not provided).[16] A systematic review by Bushe et al.[18] included five studies that measured the WC in the patient population. Four of the five studies reported no significant difference in WC between olanzapine or clozapine and metformin versus olanzapine or clozapine and placebo.[18] One study observed that metformin and lifestyle changes were more effective in decreasing waist circumference than metformin ($p=0.03$), lifestyle changes only ($p< 0.001$) or placebo ($p< 0.001$).[18] All interventions were added to treatment with olanzapine, clozapine or risperidone.[18]

No significant differences in WC between the clozapine and sibutramine cohort versus clozapine and placebo were found in one RCT.[24]

High Density Lipoproteins (HDLs)

Three systematic reviews[7,16,18] and five RCTs[19,20,22-24] included HDLs as a clinical outcome. One systematic review reported no difference in HDLs between patients switching from olanzapine to quetiapine versus staying on olanzapine. Another systematic review by Miller et al.[16] found a significant increase in HDLs in one of the included RCTs that compared olanzapine and metformin versus olanzapine and placebo (data were not provided). Bushe et al.[18] in a systematic review reported in two included RCTs that compared olanzapine and metformin to olanzapine and placebo found significant increases in HDLs in one RCT (p=0.001), while one study found no significant decreases in HDLs.

One RCT by Henderson et al.[19] compared olanzapine and modafinil versus olanzapine and placebo. They reported no significant differences in HDLs between groups.[19] Henderson et al.[24] compared clozapine and sibutramine with clozapine and placebo in another RCT and found no significant differences in HDLs between groups.[24] Another RCT compared olanzapine and topiramate with olanzapine and placebo,[20] and they also reported no significant difference in HDLs between groups. Joffe et al.[22] compared clozapine or olanzapine and orlistat with olanzapine and placebo in a RCT, and observed no significant differences between groups in HDLs.[22] One RCT by Kelly et al.[23] trial that compared olanzapine versus risperidone in patients who were treated previously for schizophrenia and schizoaffective disorder and/or were previously treated with olanzapine or risperidone reported no significant differences in HDLs between groups.[23]

Triglycerides

Triglycerides are a type of fat in the bloodstream and fat tissue, and high levels of triglycerides can contribute to the hardening and narrowing of your arteries.[25] Triglycerides were measured in three systematic reviews[7,16,17] and five RCTs.[19,20,22-24] Mukundan et al.[7] reported no significant difference in triglycerides based on results in one study that compared switching from olanzapine to quetiapine versus continued treatment on olanzapine. A systematic review by Miller et al.[16] also found no significant difference between olanzapine and metformin alone or in combination with lifestyle changes or sibutramine intervention versus olanzapine and placebo (data were not provided). Gabriele et al.[17] noted a significant difference in the percentage decrease of triglycerides between groups that compared dietary counseling, physical activity and/or behavioral components versus an unspecified control group or metformin, metformin and lifestyle interventions and/or placebo in three included RCTs.[17] The difference in triglycerides between groups was measured as a percentage decrease in triglycerides of -20.68 to -29.56 ($p< 0.05$).

One RCT reported no significant differences in triglycerides in patients treated with olanzapine and modafinil versus those treated with olanzapine alone and placebo.[19] Narula et al.[20] compared olanzapine and topiramate versus olanzapine and placebo in a RCT, and they reported no significant differences in triglycerides across the groups.[20] Another RCT measured triglycerides in patients treated with clozapine or olanzapine and orlistat versus monotherapy with the same AAPs and placebo but did not report the results.[22] Kelly et al.[23] compared olanzapine with risperidone in patients previously treated for schizophrenia and schizoaffective disorder. They reported no significant differences between groups. Henderson et al.[24] observed no significant differences between groups in a RCT that compared clozapine and sibutramine versus clozapine alone and placebo.[24]

Change in Metabolic Syndrome Status

Owen et al.[21] compared aripiprazole versus a control group that included patients treated with quetiapine, risperidone, and olanzapine in an open label RCT. The study population also included patients with schizophrenia and metabolic syndrome. At the end of treatment, 64% of patients in the aripiprazole group and 86% patients in the control group had metabolic syndrome.[21]

Monitoring for Risk factors of Metabolic Syndrome

The systematic reviews did not provide details on the frequency of monitoring risk factors for metabolic syndrome. Several RCTs may offer some insight on the frequency of monitoring for metabolic risk factors. Three RCTs[19,20,24] measured BP and the frequency of monitoring ranged from every two to 12 weeks. In four RCTs[19,20,22,24] that measured FBG or BG, the frequency of monitoring for FBG or BG ranged from every four to 12 weeks. One RCT[24] monitored WC every 12 weeks. Five RCTs[19,20,22-24] monitored HDLs and triglycerides the frequency of monitoring ranged from two to 12 weeks.

Limitations

Several systematic reviews presented incomplete information. For instance, a description of the control groups was not provided in one systematic review.[17] Furthermore, when the same study was included in several systematic reviews, the outcomes were reported inconsistently across the reviews. Subsequently, the lack of standard reporting of clinical outcomes makes it difficult to compare study findings between individual RCTs.

It should be noted that none of the included systematic reviews or RCTs were powered to detect changes in the risk factors of metabolic syndrome. Many of the SRs included a small number of studies involving the population of interest in this report (see Appendix 2). No account was provided in any of the RCTs on how many patients were included from the original source population and how allocation concealment was performed. Also, two RCTs did not report the number of patients taking each AAP monotherapy during the study.[21,22]

The generalizability of study results may be limited as some of the RCTs included in the systematic reviews limited the population to specific ethnic groups. For example some studies were restricted to the Chinese population.[7,15,16] It is possible that the response to the treatment of metabolic risk factors may differ in other patient populations. The included RCTs had a duration that ranged from eight to 16 weeks, which may not be long enough to observe changes in the risk factors that would prevent or effectively treat metabolic syndrome. In addition, only one of the included studies addressed if patients in the trial experienced any change in their metabolic syndrome status after treatment. It is difficult to draw meaningful conclusions on interventions that reduce metabolic syndrome without any information on disease status. Moreover, relevant studies on aripiprazole, as the intervention, were not identified in the literature search. A conclusion, therefore, on the impact of metabolic syndrome with this treatment cannot be drawn.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

It is difficult to draw definitive conclusions on the interventions for risk factors for metabolic syndrome. The most frequently studied AAP for metabolic risk factor included in this report is

olanzapine. None of the included RCTs and systematic reviews studies metabolic risk factors was related to aripiprazole. There is insufficient evidence on which specific intervention may have clinical benefits on individual metabolic risk factors. Topiramate may be associated with a decrease in systolic and diastolic BP. However, sibutramine or modafinil added to treatment with olanzapine had no significant difference on BP.

Switching from olanzapine to aripiprazole or quetiapine may be associated with a significant decrease in FBG. There is some evidence to suggest that switching from olanzapine to quetiapine or aripiprazole is associated with a decrease in FBG. There is also some evidence to suggest that a combination of dietary counseling, physical activity and behavioural components may be beneficial in decreasing blood glucose. In addition, topiramate added to a treatment with an AAP may be associated with a significant decrease in blood glucose. There is no evidence to suggest that modafinil, orlistat or sibutramine are associated with lower FBG when treated with AAP monotherapy.

It is unclear if metformin in combination with AAP monotherapy has any benefit on decreasing WC, however, metformin and lifestyle changes may have some benefit on decreasing WC in combination with AAP monotherapy. There is no evidence to suggest that switching from olanzapine to aripiprazole is associated with a decrease in WC. There is no evidence to suggest that sibutramine is associated with a decrease in WC in combination with AAP monotherapy. There is insufficient clinical evidence on the most effective treatment to decrease WC.

Topiramate is one intervention that may be associated with an increase in HDLs while being with an AAP monotherapy. The evidence on the association between HDLs and sibutramine, and orlistat, while being treated with an AAP monotherapy, is lacking. A combination intervention of diet, physical activity and behavioural changes may be associated with decrease triglycerides in combination with other AAPs. Metformin and sibutramine in combination may prevent some of the increase in triglycerides while being treated with AAPs.

The frequency of monitoring for metabolic risk factors ranged from two to 12 weeks for BP, FBG, WC, HDL, and triglycerides. It is important to note that the longest study duration was 16 weeks. As a result, it is unclear whether the frequency of monitoring should change beyond 16 weeks.

Most RCTs in this review were of low quality. Inconsistent reporting in the systematic reviews and RCTs also makes it difficult to draw firm conclusions on the short-term and long-term impact of interventions to prevent or manage metabolic syndrome for patients treated with aripiprazole, clozapine, olanzapine, quetiapine, or risperidone. A universal definition of metabolic syndrome would help to standardize the reporting of clinical findings and, subsequently, increase the comparability of these studies.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES:

1. PubMed health [Internet]. Atlanta: A.D.A.M., Inc.; 2011. Metabolic syndrome; 2010 Apr 19 [cited 2011 Jul 13]. Available from: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0004546/

2. Narasimhan M, Raynor J. Evidence-based perspective on metabolic syndrome and use of antipsychotics. Drug Benefit Trends. 2010;22(3):77-88.

3. Saddichha S, Manjunatha N, Ameen S, Akhtar S. Metabolic syndrome in first episode schizophrenia - a randomized double-blind controlled, short-term prospective study. Schizophr Res. 2008 Apr;101(1-3):266-72.

4. Ellinger LK, Ipema HJ, Stachnik JM. Efficacy of metformin and topiramate in prevention and treatment of second-generation antipsychotic-induced weight gain. Ann Pharmacother. 2010 Apr;44(4):668-79.

5. Hermes E, Nasrallah H, Davis V, Meyer J, McEvoy J, Goff D, et al. The association between weight change and symptom reduction in the CATIE schizophrenia trial. Schizophr Res. 2011 May;128(1-3):166-70.

6. Lamberti JS, Olson D, Crilly JF, Olivares T, Williams GC, Tu X, et al. Prevalence of the metabolic syndrome among patients receiving clozapine. Am J Psychiatry. 2006 Jul;163(7):1273-6.

7. Mukundan A, Faulkner G, Cohn T, Remington G. Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems. Cochrane Database Syst Rev. 2010;(12):CD006629.

8. Baptista T, Uzcategui E, Rangel N, El FY, Galeazzi T, Beaulieu S, et al. Metformin plus sibutramine for olanzapine-associated weight gain and metabolic dysfunction in schizophrenia: a 12-week double-blind, placebo-controlled pilot study. Psychiatry Res. 2008 May 30;159(1-2):250-3.

9. Rege S. Antipsychotic induced weight gain in schizophrenia:mechanisms and management. Aust N Z J Psychiatry. 2008 May;42(5):369-81.

10. Newcomer JW, Meyer JM, Baker RA, Eudicone JM, Pikalov A, Vester-Blokland E, et al. Changes in non-high-density lipoprotein cholesterol levels and triglyceride/high-density lipoprotein cholesterol ratios among patients randomized to aripiprazole versus olanzapine. Schizophr Res. 2008 Dec;106(2-3):300-7.

11. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001 May 16;285(19):2486-97.

12. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2011 Jul 15];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

13. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2011 Jul 15];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

14. Praharaj SK, Jana AK, Goyal N, Sinha VK. Metformin for olanzapine-induced weight gain: a systematic review and meta-analysis. Br J Clin Pharmacol. 2011 Mar;71(3):377-82.

15. Ehret M, Goethe J, Lanosa M, Coleman CI. The effect of metformin on anthropometrics and insulin resistance in patients receiving atypical antipsychotic agents: a meta-analysis. J Clin Psychiatry. 2010 Oct;71(10):1286-92.

16. Miller LJ. Management of atypical antipsychotic drug-induced weight gain: focus on metformin. Pharmacotherapy. 2009 Jun;29(6):725-35.

17. Gabriele JM, Dubbert PM, Reeves RR. Efficacy of behavioural interventions in managing atypical antipsychotic weight gain. Obes Rev. 2009 Jul;10(4):442-55.

18. Bushe CJ, Bradley AJ, Doshi S, Karagianis J. Changes in weight and metabolic parameters during treatment with antipsychotics and metformin: do the data inform as to potential guideline development? A systematic review of clinical studies. Int J Clin Pract. 2009 Dec;63(12):1743-61.

19. Henderson DC, Freudenreich O, Borba CP, Wang X, Copeland PM, Macklin E, et al. Effects of modafinil on weight, glucose and lipid metabolism in clozapine-treated patients with schizophrenia. Schizophr Res. 2011 May 10. Epub ahead of print.

20. Narula PK, Rehan HS, Unni KE, Gupta N. Topiramate for prevention of olanzapine associated weight gain and metabolic dysfunction in schizophrenia: a double-blind, placebo-controlled trial. Schizophr Res. 2010 May;118(1-3):218-23.

21. A 16-Week, Multicenter, Randomized, Open-Label Study to Assess the Effects of Aripiprazole Versus Other Atypical Antipsychotics in the Treatment of Schizophrenic Patients with Metabolic Syndrome [Internet]. New York: Bristol-Myers Squibb; 2009. [cited 2011 Jul 8]. Available from: http://ctr.bms.com/pdf/CN138-489.pdf

22. Joffe G, Takala P, Tchoukhine E, Hakko H, Raidma M, Putkonen H, et al. Orlistat in clozapine- or olanzapine-treated patients with overweight or obesity: a 16-week randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2008 May;69(5):706-11.

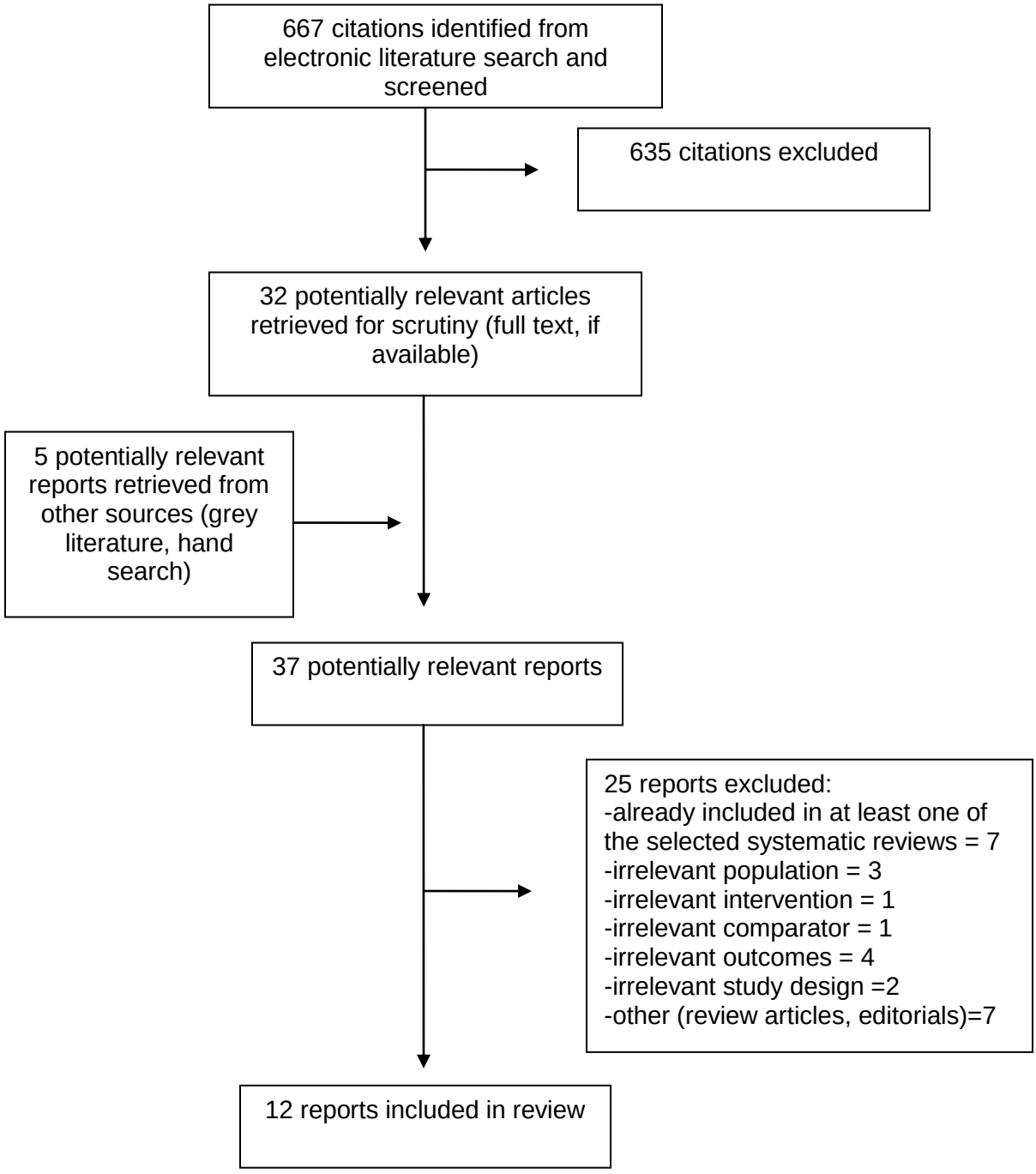
23. Kelly DL, Conley RR, Love RC, Morrison JA, McMahon RP. Metabolic risk with second-generation antipsychotic treatment: a double-blind randomized 8-week trial of risperidone and olanzapine. Ann Clin Psychiatry. 2008 Apr;20(2):71-8.

24. Henderson DC, Fan X, Copeland PM, Borba CP, Daley TB, Nguyen DD, et al. A double-blind, placebo-controlled trial of sibutramine for clozapine-associated weight gain. Acta Psychiatr Scand. 2007 Feb;115(2):101-5.

25. MedlinePlus [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2011. Triglycerides; 2011 [cited 2011 Jul 19]. Available from: http://www.nlm.nih.gov/medlineplus/triglycerides.html

APPENDICES:

Appendix 1: Selection of Included Studies



Appendix 2: Summary of Included Study Characteristics

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator(s)	Relevant Clinical Outcomes for Mets Measured
Praharaj et al. (2011)[14], India	Systematic review and meta-analysis	Four DB, RCTs (n=224) adult patients with schizophrenia, schizoaffective disorder, or bipolar disorder **AAPs include**: Olanzapine 5-20 md/day (for all patients)	metformin 750 to 2250 mg/day(four trials)	placebo (four trials)	WC
Mukundan et al. (2010)[7] United Kingdom	Systematic review and meta-analysis	Four DB, RCTs Three DB, RCTs included patients taking atypical antipsychotics (n=617) Adult patients with schizophrenia or schizoaffective disorder **AAPs include:** olanzapine, risperidone, quetiapine, and aripiprazole	switching from typicals or atypical antipsychotics (olanzapine or risperidone) to aripiprazole 30 mg via three methods of initiation (one trial) one treatment arm switching from olanzapine to quetiapine (mean modal dose = 16.9 mg/day) with the other arm (one trial) switching to aripiprazole monotherapy (mean dose= 16.9 mg/day), (one trial)	staying on olanzapine (mean dose= 15.9 to 16.9 mg/day) (2 trials)	cholesterol, HDL, triglycerides, fasting blood glucose WC

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator(s)	Relevant Clinical Outcomes for Mets Measured
Ehret et al. (2010)[15] USA	Systematic review and meta-analysis	Six RCTs, placebo controlled patients taking metformin including adults and children 4 RCTs including adults receiving treatment for 12 to 16 weeks (n=274) **AAPs include**: olanzapine, clozapine, risperidone, quetiapine, sulpiride	metformin 750 to 2,250 mg/day (four trials)	placebo (four trials)	WC
Miller et al. (2009)[16] USA	Systematic review	Eight DB, RCTs including children and adults 4 RCTs including only adult patients with schizophrenia, or bipolar disorder (n=278) **AAPs include:** olanzapine, risperidone, clozapine,	metformin alone 750-2250 mg/day (2 trials) metformin 750 mg/day alone or + lifestyle modifications(one trial) metformin 850-1700 mg/day + sibutramine 10-20 mg/day (one trial)	placebo (three trials) placebo only or/+ lifestyle modification (one trial)	HDL, triglycerides and WC

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator(s)	Relevant Clinical Outcomes for Mets Measured
Gabrielle et al. (2009)[17] USA	Systematic review	16 non-RCTs and RCTs Ten RCTs (n=694) adult patients with schizophrenia, schizoaffective disorder, psychotic disorder, bipolar disorder, schizotypal, depression, and personality disorder **AAPs include:** olanzapine, risperidone, clozapine, and quetiapine	dietary counseling components, PA counseling, and/or behavioural component s for 12 weeks to 18 months (10 trials)	standard/ routine care (unspecified) (5 trials), 2hr nutrition education group (one trial), control group with food and exercise diaries (one trial), control group (unspecified) (two trials), metformin, metformin lifestyle, placebo (one trials)	Triglycerides, cholesterol and glucose
Bushe et al. (2009)[18] United Kingdom	Systematic review	11 studies with children and adult patients randomized, DB Seven studies included adult patients only (n= 339) with schizophrenia or bipolar disorder **AAPs include:** risperidone,(2.7 mg/day), olanzapine (5.3 - 11.5 mg/day), clozapine (115-196.8 mg/day),	metformin 500 mg to 2550 mg./day (five trials) metformin 750mg/day+ lifestyle intervention (one trial) metformin 850-3400 mg/day+ sibutramine 10-40 mg/day (one trial)	lifestyle intervention+ placebo or placebo only placebo only (one trial) placebo, (5 trials) metformin +placebo (one trial)	WC, lipids, FG, HDL

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator(s)	Relevant Clinical Outcomes for Mets Measured
Henderson et al. (2011)[19] USA	DB, RCT, eight week, placebo-controlled	N= 35 schizophrenia or schizoaffective disorder DSM-IV, Adults age 20-64 **AAP**: clozapine for at least 6 months with a stable dose for one month prior to the trial for all patients	modafinil 100-300 mg/day	Placebo	BP (baseline ,2,4,6,8), Glucose, HDL, LDL, total cholesterol, triglycerides (baseline, week 4, and week 8)
Narula et al. (2010)[20] India	DB, RCT, 12 week, placebo-controlled	N=72 Adults with ICD-10 diagnosis of schizophrenia **AAP:** olanzapine for all patients	olanzapine (5-20 mg/day)+ topiramate (50-100mg/day) (n=33)	olanzapine (5-20 mg/day)+placebo (n=34)	FBG, Triglycerides, Systolic BP, Diastolic BP
Owen (2009)[21] USA	RCT, 16 week, open-label	N=51 schizophrenia and mets (ATP-III-A) Adults (age 22 to 62)	aripiprazole (n=26)	Olanzapine, quetiapine, risperidone (n=25)	Proportion with Mets at end of treatment,
Joffe et al. (2008)[22] Finland	DB, placebo controlled, 16 week, RCT	N= 81 adults (age 18 to 65) with a serious mental condition **AAP:** clozapine or olanzapine stable for at least 4 weeks before the trial for all patients	orlistat (n=35) 360mg /day (3x 120 mg with meals)	placebo (n=36)	fasting glucose, total cholesterol, HDL, and triglycerides (monitored at 0,,8,16 weeks)
Kelly et al. (2008) et al.[23] USA	Double blind, 8 week, RCT	N= 377 patients with DSM-IV diagnosed schizophrenia and schizoaffective disorder (age 18-64) outpatients or inpatients (if hospitalized <4 weeks)	olanzapine (5-20 mg/day) (n= 188)	risperidone (2-6 mg/day) (n= 189)	HDL, triglycerides,

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator(s)	Relevant Clinical Outcomes for Mets Measured
Henderson et al. (2007)[24] USA	double blind,, placebo-controlled, 12 week, RCT	N=21 DSM-IV diagnosed schizophrenia 18-65 years, stable on dose of clozapine for 4 months **AAP:** clozapine for all patients	sibutramine (n=11) (10-15 mg/day (dose escalation from 10 to 15 mg over 4 weeks)	placebo (n= 10)	WC, glucose, total cholesterol, HDL triglycerides, systolic BP, diastolic BP (baseline and week 12)

AAPs=Atypical Antipsychotics, ATP-III-A= Adult Treatment Panel III BP= Blood Pressure, DB= double blind, DSM-IV= Diagnostic and Statistical Manual of Mental Disorders IV, FBG= Fasting Blood Glucose, FG = Fasting Glucose , HDL= High Density Lipoproteins, RCT=Randomized Controlled Trial, WC= Waist Circumference.

Appendix 3: Summary of Critical Appraisal

First Author, Publication Year, Country	Strengths	Limitations
Systematic Reviews		
Praharaj et al. (2011)[14], India	• Explicit inclusion criteria • Methodological assessment of quality of included studies conducted	• Literature search time frame was not specified • Studies designed to assess prevention of weight gain were pooled with studies designed to assess weight loss • No assessment of publication bias
Mukundan et al. (2010)[7], United Kingdom	• Comprehensive literature search • Appropriately applied statistical tests for heterogeneity and pooled studies when it was appropriate	• Restricted the populations to patients with schizophrenia or schizophrenia like illness taking AAPs only • Data extraction was not done independently by at least two reviewers
Ehret et al. (2010)[15] USA	• Data extraction conducted by two independent reviewers • Methodological assessment of study quality of included studies conducted and only studies deemed high quality were included (Jadad Score $\geq$ 3)	• Heterogeneity was present by individual study findings were pooled (I^2> 83.9%) • No information on the mental health status of the patients (for example, mental illnesses diagnosed were not provided) • Including only trials that met the Jadad score cutoff may limit generalizability [15]
Miller et al. (2009)[16] USA	• Detailed descriptions of the included studies was presented	• Unclear inclusion and exclusion criteria • It is unclear how the data were extracted • Little data provided and incomplete reporting of study results • Publication status and bias not assessed
Gabrielle et al. (2009)[17] USA	• Included 10 RCTs with a clear and concise summary of study characteristics • The only systematic review included that evaluated non-pharmacological interventions	• No information provided on data extraction • No assessment for publication bias conducted • Study is focused on weight gain or weight changes with little discussion or interpretation of metabolic outcomes (SBP, DBP, Triglycerides, cholesterol, glucose)
Bushe et al. (2009)[18] United Kingdom	• Comprehensive literature search • Clear, detailed data presented for included studies	• Unclear if data was extracted independently by at least two reviewers • Unclear if grey literature was searched • Unclear how the scientific quality of studies was assessed
Randomized Controlled Trials		

Henderson et al. (2011)[19] USA	• Described reasons patients were excluded from the study and/ or lost to follow up • Numerous relevant metabolic outcomes are recorded	• Sample size (n=39) and no power calculations are provided • Description of methods to blind investigators and participants not provided
Narula et al. (2010)[20] India	• Population included inpatients and outpatients • Numerous relevant metabolic outcomes • Provide a description of reasons for exclusion at screening and patients excluded/lost to follow up during the trial	• Provided per protocol analysis only
Owen (2009)[21] USA	• Included four AAPs (aripiprazole, olanzapine, quetiapine, and risperidone)	• No information provided on the number of patients treated with the other atypical medications (olanzapine, quetiapine, and risperidone) • One metabolic outcome measured Investigators, participants and analysts not blinded
Joffe et al. (2008)[22] Finland	• Exclusion criteria and the reasoning behind the criteria were provided (for example possible confounding effect on weight and other metabolic issues)	• No information on the dose of clozapine or olanzapine used during the trial • No statistical methods used to account for multiple comparisons increasing the risk a significant relationship was found by chance [22]
Kelly et al. (2008) et al.[23] USA	• Multiple relevant metabolic outcomes • Direct comparison of two AAPs (risperidone and olanzapine) • Sample size (n=377	• Industry sponsored study • Study duration (8 weeks) • It is unclear if the study was powered to detect differences on metabolic factors between risperidone and olanzapine
Henderson et al. (2007)[24] USA	• Multiple relevant metabolic outcomes	• No dose information on clozapine provided • Sample size (n=21)

AAPs=Atypical Antipsychotics, DBP= Diastolic Blood Pressure, RCTs=Randomized Controlled Trials, SBP= Systolic Blood Pressure

Appendix 4: Summary of Findings and Authors' Conclusions

First Author, Publication Year, Location	Main Study Findings	Authors' Conclusions
Systematic Reviews		
Praharaj et al. (2011)[14], India	From a random effects model in WC was reported WMD (weighted mean difference) = 1.42 (95% CI 0.29 to 3.13, p<0.00001) cm lower with metformin compared to placebo at 12 weeks.	Metformin use is justified in patients experiencing olanzapine-induced weight gain with no contraindication [14]
Mukundan et al. (2010) [7], United Kingdom	There was no significant difference in HDL levels for patients who switched from olanzapine to quetiapine; no difference was observed in triglycerides in the two groups (switch to quetiapine or staying olanzapine) in one trial. In the one trial HDL, levels increased by 1.7% (n=80, SE 1.8) in the aripiprazole group and decreased by 5.9% (n=7.6, SE 1.7) in the olanzapine group. The p-value was 0.002. FBG showed a significant decrease switch to aripiprazole or quetiapine from olanzapine (2 RCTs, -2.53, 95% CI -2.94 to -2.11, n= 280)	The authors indicated to switch from antipsychotic medications to a treatment with a lower potential for causing weight gain or metabolic problems to manage effectively metabolic adverse effects. Data, however, are weak due to few trials, small samples, and poor reporting too; better trials with higher power are needed.
Ehret et al. (2010)[15] USA	Four studies included in a subgroup analysis reported a weight a decrease in waist circumference of 1.64 cm,(WMD -1.64, 95% CI -3.11 to -0.18)	The study results suggested metformin may reduce metabolic risks in patients treated with AAPs.
Miller et al. (2009)[16] USA	No significant differences were reported in HDL, or triglycerides. One study reported a significant decrease in waist circumference (no data provided), one study reported significant increase in waist circumference (no data provided)	The results did not provide clear substantial evidence that metformin, as added to atypical antipsychotic use, will decrease weight gain and improve metabolic effects, although the findings are encouraging.
Gabrielle et al. (2009)[17] USA	The results from three RCTs that measured changes in triglycerides were not pooled. These studies reported significant decreases in triglycerides ranging from -20.68 to -29.56 % during a course of treatment for studies with follow-up ranging from 10 weeks to 18 months (p< 0.05). The three RCTs that measure changes in cholesterol were not pooled. Only one study with an 18 month follow up period reported significant decreases in cholesterol -12.10% (p<0.05)	"As length of intervention increases, the benefits of the intervention on metabolic risk factors increases, the benefits of the intervention on these outcomes also appears to increase." (p.450)
Bushe et al. (2009)[18] United Kingdom	Data were not pooled for any of outcomes. Five RCTs measured changes or decreases in WC. Four of the five studies reported no significant differences in waist circumference in groups taking metformin. One study reported metformin and lifestyle changes were superior for decreasing waist circumference compared to metformin alone (p<0.03), lifestyle alone (p<0.0001) or placebo (p<0.0001). Three RCT reported on lipid related outcomes. One study reported no significant between group differences on lipids. One study reported HDL-C	There is insufficient evidence to conclude definitively that metformin should be used as an adjunct to weight and lifestyle programs for patients with schizophrenia. Conclusions may only be applied to olanzapine investigated in cohorts with patients of specific ethnicities.

First Author, Publication Year, Location	Main Study Findings	Authors' Conclusions
	increased significantly for patients using metformin and clozapine compared to placebo and clozapine (p=0.0001), while the other reported HDL-C decreased for patients using metformin and olanzapine significantly decreased HDL-C compared to placebo and olanzapine. Fasting glucose was recorded in all six RCTs including adult patients taking metformin. Five studies did not report any significant difference in serum glucose between clozapine or olanzapine (alone or with sibutramine) and metformin groups versus clozapine or olanzapine (or and metformin) and placebo. One study reported metformin and lifestyle was significantly superior to placebo to placebo on FG (p=0.0006); metformin was superior to lifestyle or placebo only (p<0.0001) and lifestyle alone was significantly superior to placebo only (p<0.001) No significant between group differences were reported for triglycerides or total cholesterol in the three trials with measures of lipids that reported on metformin alone (and with sibutramine and olanzapine) or clozapine or olanzapine alone.	
Randomized Controlled Trials		
Henderson et al. (2011)[19] USA	There were no significant differences for any of the metabolic outcomes for the modafinil group compared to placebo (BP, FBG, HDL, and triglycerides were included).	There were no significant effects of from modafinil on any on anthropometric measures or glucose and lipid metabolism.
Narula et al. (2010)[20] India	The olanzapine and topiramate group showed a significant decrease after 12 weeks in FBG (mg%), Triglycerides (mg%), HDL (mg%) systolic BP (mm Hg), and diastolic BP (mmHg) compared to olanzapine control group.	This study demonstrates that low dose topiramate (100 mg/day) can prevent olanzapine associated weight gain. It allows displays topiramate can prevent the development metabolic adverse events associated with olanzapine use such as hyperglycemia, hypercholesterolemia and hypertriglyceridemia.
Owen (2009)[21] USA	Non-HDL cholesterol mean % change difference between the aripiprazole group and the control group (olanzapine, quetiapine, and risperidone) is -11.28 (95% CI -19.14 to -2.66). Proportion of patients with metabolic syndrome at the end of treatment aripiprazole group 64% and the control group 86%	Aripiprazole treatment was well tolerated in patients with metabolic syndrome.
Joffe et al. (2008)[22] Finland	No significant differences were observed between the orlistat and placebo groups after 16 weeks in total cholesterol, LDL, HDL, or fasting glucose.	Orlistat may be a safe treatment for obese or overweight patients using clozapine or olanzapine, but without a hypoclaroic diet, the effect is modest and may be only observed in men.

First Author, Publication Year, Location	Main Study Findings	Authors' Conclusions
Kelly et al. (2008) et al.[23] USA	A significant difference was observed between the risperidone and olanzapine groups was observed for triglycerides after eight weeks (p<0.0001) with the risperidone group having displaying a decrease in triglycerides and the olanzapine group presenting an increase in triglycerides. At week 8 subjects on olanzapine had a significant increase in TC (p<0.001), while subjects on risperidone had a significant decrease in TC p<0.0001) However, no significant difference were observed between the risperidone and olanzapine groups for TC,HDL-C.	Results confirm SGA are associated with weight gain and olanzapine is associated with weight gain to a greater extent than risperidone.
Henderson et al. (2007)[24] USA	After 12 weeks, no significant differences were observed for WC, glucose, total cholesterol, HDL, triglycerides, systolic and diastolic BPs.	This study indicates that, sibutramine added to a behavioural nutrition program, there are no significant benefits in weight loss or any other metabolic parameters in patients with schizophrenia or schizoaffective disorder treated with clozapine.

AAPs=Atypical Antipsychotics, BP= Blood Pressure, CI=Confidence Interval, FBG= Fasting Blood Glucose, FG = Fasting Glucose , HDL= High Density Lipoproteins, HDL-C= High Density Lipoprotein Cholesterol, LDL= Low Density Lipoproteins, RCT=Randomized Controlled Trial, SGA= Second Generation Antipsychotics, SE=Standard Error, WC= Waist Circumference, WMD= Weight Mean Difference

Appendix 5: Additional Articles

Interventions for Preventing or Managing Metabolic Risk Factors (Non-randomized studies and guidelines)

1. Park T, Usher K, Foster K. Description of a healthy lifestyle intervention for people with serious mental illness taking second-generation antipsychotics. Int J Ment Health Nurs. 2011 May 12. PubMed: PM21564457

2. Maayan L, Correll CU. Management of antipsychotic-related weight gain. Expert Rev Neurother. 2010 Jul;10(7):1175-200. PubMed: PM20586697

3. Poulin MJ, Chaput JP, Simard V, Vincent P, Bernier J, Gauthier Y, et al. Management of antipsychotic-induced weight gain: prospective naturalistic study of the effectiveness of a supervised exercise programme. Aust N Z J Psychiatry. 2007 Dec;41(12):980-9. PubMed: PM17999270

4. Spurling RD, Lamberti JS, Olsen D, Tu X, Tang W. Changes in metabolic parameters with switching to aripiprazole from another second-generation antipsychotic: a retrospective chart review. J Clin Psychiatry. 2007 Mar;68(3):406-9. PubMed: PM17388710

5. Faulkner G, Cohn TA. Pharmacologic and nonpharmacologic strategies for weight gain and metabolic disturbance in patients treated with antipsychotic medications. Can J Psychiatry. 2006 Jul;51(8):502-11. PubMed: PM16933587

Monitoring for Metabolic Risk Factors (Non-randomized studies and guidelines)

6. Hoffmann VP, Case M, Stauffer VL, Jacobson JG, Conley RR. Predictive value of early changes in triglycerides and weight for longer-term changes in metabolic measures during olanzapine, ziprasidone or aripiprazole treatment for schizophrenia and schizoaffective disorder post hoc analyses of 3 randomized, controlled clinical trials. J Clin Psychopharmacol. 2010 Dec;30(6):656-60. PubMed: PM21105275

7. Mackin P, Waton T, Watkinson HM, Gallagher P. A four-year naturalistic prospective study of cardiometabolic disease in antipsychotic-treated patients. Eur Psychiatry. 2010 Oct 29. PubMed: PM21036552

8. Ingole S, Belorkar NR, Waradkar P, Shrivastava M. Comparison of effects of olanzapine and risperidone on body mass index and blood sugar level in schizophrenic patients. Indian J Physiol Pharmacol. 2009 Jan;53(1):47-54. PubMed: PM19810576

9. Waterreus AJ, Laugharne JD. Screening for the metabolic syndrome in patients receiving antipsychotic treatment: a proposed algorithm. Med J Aust. 2009 Feb 16;190(4):185-9. PubMed: PM19220182

10. Morrato EH, Cuffel B, Newcomer JW, Lombardo I, Kamat S, Barron J. Metabolic risk status and second-generation antipsychotic drug selection: a retrospective study of commercially insured patients. J Clin Psychopharmacol. 2009 Feb;29(1):26-32.
PubMed: PM19142103

11. Peh AL. Safety monitoring of patients on atypical antipsychotics. Qual Saf Health Care. 2008 Dec;17(6):469-72.
PubMed: PM19064665

12. Hsu C, Ried LD, Bengtson MA, Garman PM, McConkey JR, Rahnavard F. Metabolic monitoring in veterans with schizophrenia-related disorders and treated with second-generation antipsychotics: findings from a Veterans Affairs-based population. J Am Pharm Assoc (2003). 2008 May;48(3):393-400.
PubMed: PM18595825

13. Jennex A, Gardner DM. Monitoring and management of metabolic risk factors in outpatients taking antipsychotic drugs: a controlled study. Can J Psychiatry. 2008 Jan;53(1):34-42.
PubMed: PM18286870

14. Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. J Clin Psychiatry. 2007;68 Suppl 4:8-13.
PubMed: PM17539694

15. Torres DM. Evidence-based monitoring for metabolic syndrome in clients with chronic schizophrenia. J Healthc Qual. 2007 Mar;29(2):48-56.
PubMed: PM17465171

16. Weissman EM, Zhu CW, Schooler NR, Goetz RR, Essock SM. Lipid monitoring in patients with schizophrenia prescribed second-generation antipsychotics. J Clin Psychiatry. 2006 Sep;67(9):1323-6.
PubMed: PM17017817

Other Article

17. Jin H, Meyer J, Mudaliar S, Henry R, Khandrika S, Glorioso DK, et al. Use of clinical markers to identify metabolic syndrome in antipsychotic-treated patients. J Clin Psychiatry. 2010 Oct;71(10):1273-8.
PubMed: PM21062616