

A Meta-Analysis of Randomized Control Trial on the Efficacy of Second Generation Antipsychotics

Aschalew Alemu Marie*¹ Hailemeskel Mekonen² Shewatateke Gedamu³

1.Internal Medicine Department, School Of Medicine, Addis Ababa University, Addis Ababa, Ethiopia

2.Pharmacology Department, School Of Medicine, Addis Ababa University, Addis Ababa, Ethiopia

3.Pharmacology Department, Medical Faculty Jimma University, Jimma, Ethiopia

Abstract

Over the past decade, second-generation antipsychotic medications have become the first-line treatment for schizophrenia. But efficacy of second generation antipsychotic compared with first generation antipsychotic in patients with schizophrenia has not been sufficiently addressed. The study objective was to perform a meta-analysis of randomized trials compare the efficacy of second generation antipsychotic (SGAs) vs. first generation antipsychotics (FGAs). Searches were conducted for randomized, blinded studies comparing one or more of nine second- generation antipsychotics in the treatment of schizophrenia with first generation antipsychotic which published from 2003 till 2013 from nature, Pubmed central, and henari website. The primary outcome measure was change in total score on the Positive and Negative Syndrome Scale; secondary outcome measures were positive and negative symptom subs cores. The results were combined in comprehensive meta- analysis version 2 software. The analysis included 9 studies, the meta-analysis comparing FGAs and SGAs using change in total PANSS, score, the odds ratio is 1.407 with 95 % confidence interval of 1.016-1.948 z- value of 2.055 and p-value 0.04(p<0.05) indicating the result of analysis is statistically significant. The odds ratio is falls above 1 indicating the patient treated with second generation antipsychotic were more likely reduce total PANSS score than first generation antipsychotic. In conclusion, Second generation antipsychotic is superior in reducing total PANSS score than first generation antipsychotic. Regard to resperidone and olanzapine, they are homogenous in reducing total PANSS score.

Keywords: Efficacy, antipsychotic, second generation antipsychotic, first generation antipsychotic, PANSS score, meta-analysis.

1. Introduction

Schizophrenia is a heterogeneous syndrome characterized by perturbations of language, perception, thinking, social activity, affect, and volition. Schizophrenia has a worldwide prevalence of 1%; Schizophrenia causes social disability and also carries a high mortality. It has a strikingly high suicide rate of 10%, the early age at onset and its chronic nature means that schizophrenia is an expensive medical condition to health care systems and to society in general (Lean, Bchir, & Pajonk, 2003) (Brown, 2001) (Greens, Kern, & Heaton, 2004).

Recovery" in schizophrenia must be defined as both functional (occupational & social) recovery as well as symptomatic recovery. Thus successful treatments for schizophrenia must show that they decrease: unemployment, social isolation, medical adverse effects, psychotic relapse, hospitalization, and suicide. Unfortunately, apart from antipsychotic medication, most of the other treatments for schizophrenia haven't consistently shown that they bring about both functional and symptomatic recovery. Early diagnosis and lifelong treatment on antipsychotic medication is absolutely essential for recovery from schizophrenia (Mental health, 2013).

The exact causes of schizophrenia and bipolar disorder are not fully known (Jones, et al., 2006). However, they are linked to changes in chemicals in the brain that influence behavior, mood, and thinking. The dopamine hypothesis of schizophrenia is the most fully developed theory of causation for this disorder, and until recently, it has been the foundation for the rationale underlying drug therapy for this disease. However, the dopamine hypothesis does not account for some important observations. If an abnormality of dopamine physiology were solely responsible for the pathogenesis of schizophrenia, antipsychotic drugs would do a much better job in treating patients. As it is, they are only partially effective for most and ineffective for some patients (Carpenter & Koenig, 2008) (Lasley, 2001).

Antipsychotic medications are used to treat a number of psychiatric disorders, including schizophrenia, bipolar mania, dementia, and psychotic depression along with other drugs (AHRQ, 2010). Antipsychotics work by affecting chemicals involved in the pathogenesis of the disease. Antipsychotics are commonly categorized into two classes. First-generation antipsychotics (FGAs), also known as "typical antipsychotics," were developed in the 1950s. Second-generation antipsychotics (SGAs), also known as "atypical antipsychotics," emerged in the 1980s. To date, FGAs have been classified according to their chemical structure, which includes serotonin-dopamine antagonists and multi-acting receptor-targeted antipsychotics, whereas SGAs have been categorized according to their pharmacological properties as dopamine partial agonists (AHRQ, 2010) (Setta, et al., 2012).

The first was the discovery of chlorpromazine, serendipitously, in 1952 in Paris by Laborit, Delay and Deniker,

who were the first to observe that this compound, which had been expected to be no more than a highly sedative antihistamine to relieve agitation, controlled delusions and hallucinations, and was, thus, the first antipsychotic drug. Numerous drugs with a similar mechanism of action were then quickly discovered (Meltzer, October 2012).

First-generation antipsychotics (FGAs), also known as neuroleptics or conventional antipsychotics, cause extrapyramidal side effects, including rigidity, bradykinesia, tremor, and akathisia (restlessness) most likely a few cases of neuroleptic malignant syndrome (NMS). They also frequently lead to tardive dyskinesia—hyperkinetic, involuntary movements most readily observed in the face and extremities. This would be especially true in elderly and post-menopausal patients (Potkin, Cohen, & Panagides, 2007). The antagonism of dopamine in the mesolimbic–mesocortical system is thought to be the basis of the therapeutic actions of these antipsychotic drugs, while antagonism of the nigrostriatal system is the major factor in the extrapyramidal side effects (EPS) seen with these agents (Ananth, Burgoyne, Gadasalli, & Aquino, 2001;) (Tuunainen, Wahlbeck, & Gilbody, 2002) (Gründer, Hippus, & Carlsson, 2009).

The prior concern with tardive dyskinesia as a result of neuroleptic treatment is diminished to some extent now that it is so rarely seen because of the introduction of, and near ubiquitous use of, atypical antipsychotic drugs (Potkin, Cohen, & Panagides, 2007). In addition to blocking 5-HT_{2A} receptors Second generation also work by blocking D₂ receptor but bind more loosely than dopamine to the dopamine D₂ receptor and have dissociation constants higher than that for dopamine. Thus atypical antipsychotics clinically help patients by transiently occupying D₂ receptors and then rapidly dissociating to allow normal dopamine neurotransmission. This keeps prolactin levels normal, spares cognition, and obviates EPS (Seeman, 2004).

Though second generation antipsychotics generally have lower risk of motor side effects, they are associated with significant weight gain, elevated lipids and have been associated with the development of type 2 diabetes, besides atypical antipsychotics are expensive comparing with the older agent (AHRQ, 2010). Increasing numbers of reports concerning diabetes, ketoacidosis, hyperglycaemia and lipid dysregulation in patients treated with second-generation (or atypical) antipsychotics have raised concerns about a possible association between these metabolic effects and treatment with these medications. Moreover, antagonism of dopamine's neurohormonal action in the anterior pituitary accounts for the hyperprolactinemia associated with antipsychotic administration. Thus, the same pharmacodynamics action may have distinct psychiatric, neurological, and endocrinological outcomes (Newcomer, 2005).

Atypical or second-generation antipsychotics (SGAs) were hailed as a major advance, principally because of their lower liability for EPSs. The first atypical drug, clozapine, is the most efficacious of all antipsychotics but is restricted to treatment resistant schizophrenia because of adverse effects. Over the past decade, second-generation antipsychotic medications have become the first-line treatment for schizophrenia (Rahman O. , 2011).

Atypical antipsychotic drugs are more frequently used and prescribed to a great extent than typical antipsychotic drugs everywhere in the world. e.g. 18% in UK, 42% in Italy, 62% in USA but less than 2% in Palestine. According to other findings from the 2004–05 Medical Expenditure Panel Survey, an estimated 2 million adult patients in the United States were prescribed an antipsychotic medication, three-quarters of whom were taking an SGA. In 2003, an estimated \$2.82 billion were spent in the country on these medications, with SGAs accounting for 93 percent of this expenditure. There were some very interesting findings for these drugs' use pattern. In one key finding, it has observed that most of the psychiatric patients were receiving atypical antipsychotics (61.46%) – either alone or in combination and this class is dominant in use in comparison to the typical antipsychotic drugs. Even single atypical antipsychotic drug was received by a large number of patients (23.44%) in comparison to typical antipsychotic single agent use (8.33%) (Jones, et al., 2006) (Setta, et al., 2012) (Rahman O. , 2011).

The introduction of a second generation of antipsychotic drug has created a large literature concerning their therapeutic value and tolerability. Recently there has been concern over the reliability of this literature. The effects of pharmaceutical industry funding, publication bias, the appropriateness of first-generation comparators (particular haloperidol) and a range of other methodological issues have come under close scrutiny. Thus therapeutic differences between the other SGAs and FGAs are less certain (Terry, Goldberg, Robert, & Goldman, 2007) (Leucht, Corves, Arbter, Engel, Li, & Davis, 2009). Two systematic reviews showed that the 2 groups of drugs are generally equivalent in terms of efficacy against positive symptoms, whereas another study found evidence of superiority for SGAs. Claims of superiority for SGAs in terms of the treatment of negative symptoms, cognitive enhancement, fewer EPSs, and improved subjective experience and tolerability have led to a general shift away from FGAs in the treatment of schizophrenia (Miller, 2004).

However, no clear evidence that atypical antipsychotics are more effective or are better tolerated than typical antipsychotics. Consequently this meta-analysis compared the efficacy and safety of second-generation antipsychotics with a first-generation antipsychotic in the treatment of psychosis.

2. Method

2.1. Selection and Study Characteristics

In this study randomized control clinical trial of patients with psychosis is selected which published from 2003 till 2013 written in English that compare second generation antipsychotic with either first generation antipsychotics or another second generation antipsychotic and a dose response comparison of FGAs and SGAs.

2.2. Literature Search Strategy

The data bases which were searched for the free and full articles were nature, Pubmed central, and henari; the preferences for those data bases were the availability of free full articles and the existence of user name and password for the database website. In addition to these database literature were searched using Google search engines by using the following search terms; efficacy, second generation antipsychotic, second generation antipsychotic versus first generation antipsychotic and efficacy of antipsychotic.

2.3. Exclusion criteria

A study that was done before 2003 were not used as data source in this meta-analysis, in addition to this, articles not written in English and not free of charges are not included.

2.4. Principal Outcome

Odds ratios were calculated from the positive and negative syndrome scale (PANSS) or, when that was not available, total PANSS score is calculated by addition of its component from the addition of positive symptom sub-score, negative symptom sub-score and General Psychopathology scale. Heterogeneity was calculated to ensure that the outcome variable was reasonably normally distributed.

2.5. Data collection

Data were extracted from both text and tables of the original papers.

2.6. Data Extraction

The number of participant, the mean change in PANSS score, sample size and the mean change in positive and negative symptom sub-score data of all studies included in the meta- analysis were extracted.

2.7. Statistical Analysis

Statistical analysis was performed with comprehensive meta- analysis version 2 software which Compute the odds ratio automatically, perform the meta-analysis quickly and accurately create high-resolution forest plots.

3. Result

3.1. Description of Studies

Twenty free and full randomized control trials study were selected from the initial search that compare first generation antipsychotics with second generation antipsychotics, five studies with no or inadequate randomization; four studies with no appropriate drug group and that used only groups of second generation do not include either resperidone or olanzapine ; and two studies with no usable data. The meta-analysis included nine studies among them six were used to compare typical and atypical antipsychotics and five were used to compare atypical resperidone with olanzapine. The studies used PANSS and other outcome measure for their comparison.

Among the six randomized controlled trial selected for the comparison of first generation and second generation antipsychotics one trial were conducted in 2008; two trial conducted in 2006; one trial conducted in 2005; one trial conducted in 2004 and one trial conducted in 2003 [Table 1].

Five studies present data from different phases of the clinical antipsychotic Trials of intervention to conduct comparison between second generation antipsychotic resperidone and olanzapine [Table 2].

3.2. Results of the meta-analysis

The meta-analysis comparing FGAs and SGAs using change in total PANSS, score, the odds ratio is 1.407 with 95 % confidence interval of 1.016-1.948 z- value of 2.055 and p-value 0.04($p < 0.05$) indicating the result of analysis is statistically significant. The odds ratio is falls above 1 indicating the patient treated with second generation antipsychotic were more likely reduce total PANSS score than first generation antipsychotic[Fig 1].

The odds ratio of first-generation antipsychotic versus second-generation antipsychotic using only change in positive symptom sub score is shown in Figure 2. It should be noted the odds ratio is greater than one (1.319 with 95% confidence interval of 0.717-2.427) but p-value is 0.373 $> p < 0.05$ the difference in reduction of positive symptom sub score is not statistical significant. Similar result also observed on the meta- analysis using negative symptom sub score, odds ratio 1.195 with 95% confidence interval of 0.518-2.755 p- value

0.076($p>0.05$) and z- value 0.417 Figure 3.

The Meta analysis of risperidone versus olanzapine that included four studies shows a difference in change in total PANSS score but statistically is not significant p- value 0.157 ($p>0.05$). The odds ratio is 1.397 with 95% confidence interval of 0.879-2.221 and z- value is 1.415. Similar result was found in comparing the two drugs using change in positive symptom sub score indicated odds ratio is 1.491 with 95 % confidence interval of 0.795-2.797 p -value and z- value is 0.213($p>0.05$) and 1.246 respectively which is not statistically significant. But using the outcome change in negative syndrome sub score the meta-analysis is in the favour of risperidone the analyzed odds ratio is 0.617 with 95% confidence interval of 0.290-1.311; p-value 0.209 ($P>0.05$) and z- value is -1.256 [Figure 4, Figure 5 and Figure 6).

4. Discussion

The introduction of a second generation of antipsychotic drug has created a large literature concerning their therapeutic value and tolerability. Recently there has been concern over the reliability of this literature. In this meta-analysis first generation and second generation (typical and atypical) antipsychotics drugs and among atypical risperidone and olanzapine were compared using studies that uses PANSS score, positive symptom sub score and negative symptom sub score for their outcome measure.

Randomized control trial (RCT) investigated efficacy through a variety of different outcome criteria like the positive and negative syndrome scale (PANSS), the brief psychiatric rating scale (BPRS) and the clinical global rating (CGR). However, this meta-analysis uses the PANSS to compare groups of antipsychotic drugs as outcome criteria because the availability of this outcome measure in most study.

The PANSS is used for measuring symptom severity following a 45-minute clinical interview with the patient and reviewing relevant reports from family members and hospital workers. Each of 30 symptoms is rated from 1 (absent) to 7 (extreme). Symptoms are grouped into three subscales: positive symptoms (i.e., delusions, conceptual disorganization, hallucinations, hyperactivity, grandiosity, suspiciousness or persecution, and hostility), negative symptoms (i.e., blunted affect, emotional withdrawal, poor rapport, passive or apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking), and general psychopathology symptoms (i.e., somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance).

A study that was done in 2006 by Jones PB, et al. indicated that there is little difference between the two groups of drug and meta analysis done in 2003 by Davis JM et al. indicated in their work that there is difference between typical and atypical antipsychotic drugs and concluded that second generation antipsychotic superior than first generation antipsychotic (Jones, et al., 2006) (Davis, Chen, & Glick, 2003). The result of this meta-analysis consistent with Davis JM et al. the odds ratio is 1.407 with 95 % confidence interval of 1.016-1.948 z- value of 2.055 and p-value 0.04($p<0.05$).

The older, typical neuroleptics are effective antipsychotic agents with neurologic side effects involving the extrapyramidal motor system. Typical neuroleptics block the dopamine-2 receptor. All atypical neuroleptics block dopamine and serotonin receptors; other neurochemical effects so that this additional serotonin receptor blockage may be given additional advantage for second generation antipsychotic to become superior to first generation antipsychotic in total change in PANSS score. Other explanations for the findings include the study participants in the first generation antipsychotic hand was compared with out prophylactic anticholinergic , because some extrapyramidal side effects , described as akinesia or akinetic depression that are responsive to anticholinergic, can emerge without telltale parkinsonian features. Thus these symptoms can be indistinguishable from negative symptoms of schizophrenia this gives an unfair advantage to second generation antipsychotic (Rosenheck, Effectiveness Versus Efficacy of Second-Generation Antipsychotics: Haloperidol Without Anticholinergics as a Comparator, 2005) (Kahn, et al., 2008).

In addition the meta-analysis comparing positive symptom sub score and negative symptom sub score is not statistical significant the odds ratio is greater than one (1.319 with 95% confidence interval of 0.717-2.427) but p-value is 0.373 $> p-0.05$. Similar result also observed on the meta- analysis using negative symptom sub score, odds ratio 1.195 with 95% confidence interval of 0.518-2.755 p- value 0.076($p>0.05$) and z- value 0.417. PANSS include 30 assessment questions of which Of the 30 items included in the PANSS, 7 constitute a Positive Scale, 7 a Negative Scale and the remaining 16 a General Psychopathology Scale thus, the superiority of second generation may be due to general psychopathology scale and the analysis used only three studies.

Regard to differences between the different second-generation antipsychotics, for example CATIE(C) and two meta-analyses (Leucht, Corves, Arbter, Engel, Li, & Davis, 2009) (Davis, Chen, & Glick, 2003) conclude that there is small difference among the groups of atypical antipsychotics drugs and another study conclude that there were no differences between the treatment group with regards to PANSS score. In this meta-analysis no significant differences in efficacy were noted among the different atypical agents (risperidone and

olanzapine) the odds ratio is 1.397 with 95% confidence interval of 0.879-2.221 and z- value is 1.415. The pattern of outcomes in terms of positive symptoms sub score and negative symptom score paralleled that of the PANSS total score.

In deciding on the choice of antipsychotic drugs for the treatment of psychosis not only the magnitude of the efficacy differences measured by reduced PANSS outcome other characteristics like medication cost, the appearance of side effect because the efficacy of a medication can be interpreted only in the context of its adverse effect profile and patient past response should be predetermined to obtain optimal benefit from the drug. Generally the focus of treatment with antipsychotics is no longer only symptom reduction alone, but well-being therapy and improvement of quality of life. And this study should be further strengthened by different studies using different rating scales. Variation in treatment evaluations using outcome measurement and patient populations across studies makes it difficult to draw well-founded conclusions from this meta-analysis

5. Conclusion

Second generation antipsychotic is superior in reducing total PANSS score than first generation antipsychotic. Regard to risperidone and olanzapine, they are homogenous in reducing total PANSS score. On the other hand the risks of weight gain and metabolic side effects with some second-generation antipsychotics needs of closely monitoring weight, glucose and lipid levels, and liver functioning. In general side effect, individual response and cost of a drug should be considered in addition to reduction the total PANSS score for the choice of antipsychotic drug.

6. Recommendation

Since PANSS is not the only indicator of efficacy of antipsychotic it is recommended to do another meta-analysis using the brief psychiatric rating scale (BPRS) and, the clinical global rating with large number of studies to come with a better conclusion. And the choice should be an individual one based on the particular profiles of the individual drug and on the patient's preferences.

ACKNOWLEDGEMENTS

The authors would like to thank Addis Ababa University, College health sciences for financial support to execute this work.

Reference

- Mental health*. (2013). Retrieved November 29, 2013, from Mental Health: <http://www.mentalhe.com/dis/p20-ps01.html>
- AHRQ. (2010). *Comparative Effectiveness of First and Second Generation Antipsychotics in the Pediatric and Young Adult Populations*. Retrieved November 12, 2013, from <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=453&pageaction=displayproduct>
- Ananth, J., Burgoyne, K., Gadasalli, R., & Aquino, S. (2001;). How do the atypical antipsychotics work? *J Psychiatry Neurosci*, 26, 385–394.
- Brown, S. (2001). Excess mortality of schizophrenia : a meta-analysis. *Br J Psychiatry*, 171, 502-508.
- Carpenter, W., & Koenig, J. (2008). The evolution of drug development in schizophrenia : past issues and future opportunities. *Neuropsychopharmacology*, 33, 2061-2079.
- Davis, J., Chen, N., & Glick, I. (2003). A meta-analysis of the efficacy of second generation antipsychotics. *Arch Gen Psychiatry*, 60, 553–64.
- Greens, M., Kern, R., & Heaton, R. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophrenia Res*, 72, 41-51.
- Gründer, G., Hippus, H., & Carlsson, A. (2009). The "atypicality" of antipsychotics A concept re-examined and re-defined. *Nat Rev Drug Disc*, 8, 197–202.
- Jones, P., Barnes, T., Davies, L., Dunn, G., Lloyd, H., Hayhurst, K., et al. (2006). Randomized controlled trial of the effect on quality of life of second -vs first generation antipsychotic drugs in schizophrenia: cost Utility of the Latest Antipsychotic Drugs in Schizophrenia study (Cut LASS1). *Arch Gen Psychiatry*, 63, 1079-1087.
- Kahn, R., Fleischhacker, W., Boter, H., Davidson, M., Vergouwe, Y., Keet, I., et al. (2008). Effectiveness of antipsychotic drugs in firstepisode schizophrenia and schizophreniform disorder: an open randomized clinical trial. *Lancet*, 371, 1085-97.
- Keefe, R., Seidman, L., Christensen, B., Hamer, R., Sharma, T., Sitskoorn, M., et al. (2004). Comparative Effect of Atypical and Conventional Antipsychotic Drugs on Neurocognition in First-Episode Psychosis: A Randomized, Double-Blind Trial of Olanzapine Versus Low Doses of Haloperidol. *Am J Psychiatry*, 161, 985–995.

- Lasley, M. (2001). *Antipsychotic Drugs in pharmacology with clinical Applications*. Washington, American.
- Lean, M., Bchir, M., & Pajonk, F. (2003). Patients on A typical Antipsychotic Drugs Another high risk group for type 2 diabetes. *Diabetes Care*, 26, 1597-1605.
- Leucht, S., Corves, C., Arbter, D., Engel, R., Li, C., & Davis, J. (2009). Second-generation versus first-generation antipsychotic drugs for schizophrenia: a Meta-analysis. *Lancet*, 3, 31–41.
- Lieberman, J., Tollefson, G., Tohen, M., Green, A., Gur, R., Kahn, R., et al. (2003). Comparative Efficacy and Safety of Atypical and Conventional Antipsychotic Drugs in First-Episode Psychosis: A Randomized, Double-Blind Trial of Olanzapine Versus Haloperidol. *Am J Psychiatry*, 160, 1396–1404.
- McEvoy, J., Lieberman, J., Perkins, D., Hamer, R., Gu, H., Lazarus, A., et al. (2007). Efficacy and Tolerability of Olanzapine, Quetiapine, and Risperidone in the Treatment of Early Psychosis: A Randomized, Double-Blind 52-Week Comparison. *Am J Psychiatry*, 164, 1050–1060.
- Meltzer, H. (October 2012). Clozapine: Balancing Safety with Superior Antipsychotic Efficacy. *Clinical Schizophrenia & Related Psychoses*, 1, 134-144.
- Miller, D. (2004). Atypical Antipsychotics: Sleep, Sedation, and Efficacy Prim Care Companion. *J Clin Psychiatry*, 6[*suppl 2*], 3–7.
- Newcomer, J. (2005). Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*, 19 *Suppl 1*, 1-93.
- Potkin, S., Cohen, M., & Panagides, J. (2007). Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry*, 68, 1492-1500.
- Rahman, O. (2011). . An overview on the trends of typical and atypical antipsychotic drugs' use in Bangladesh. *Asian Journal of Psychiatry*, 4, 71–72.
- Rahman, O. (2011). An overview on the trends of typical and atypical antipsychotic drugs' use in Bangladesh. *Asian Journal of Psychiatry*, 4, 71–72.
- Rosenheck, R. (2005). Effectiveness Versus Efficacy of Second-Generation Antipsychotics: Haloperidol Without Anticholinergics as a Comparator. *PSYCHIATRIC SERVICES* ♦ <http://ps.psychiatryonline.org>, 56, No. 1(1-4).
- Rosenheck, R., Leslie, D., Sindelar, J., Miller, E., Lin, H., Stroup, T., et al. (2006). Cost-Effectiveness of Second-Generation Antipsychotics and Perphenazine in a Randomized Trial of Treatment for Chronic Schizophrenia. *Am J Psychiatry*, 163, 2080–2089.
- Schooler, N., Rabinowitz, J., Davidson, M., Emsley, R., Harvey, P., Kopala, L., et al. (2005). Risperidone and Haloperidol in First-Episode Psychosis: A Long-Term Randomized Trial. *Am J Psychiatry*, 162, 947–953.
- Seeman, P. (2004). Atypical Antipsychotics: Mechanism of Action. *focus the journal of lifelong learning in psychiatry winter*, Vol. II, No. 1, 1-5.
- Setta, A., Mousavi, S., Spooner, C., Schouten, J., Pasichnyk, D., Armijo-Olivo, S., et al. (2012). *First-generation versus Second-generation Antipsychotics in Adults: comparative Effectiveness*. *Comparative Effectiveness Review*. Retrieved october 21, 2013, from <http://www.ncbi.nlm.nih.gov/books/NBK107254/>
- Sevy, S., Robinson, D., Sunday, S., Napolitano, B., Miller, R., McCormack, J., et al. (2011). Olanzapine vs. Risperidone in Patients with First-Episode Schizophrenia and a Lifetime History of Cannabis Use Disorders: 16-Week Clinical and Substance Use outcomes. *Psychiatry Res*, 188(3), 310–314.
- Sikich, L., Frazier, J., McClellan, J., Findling, R., Vitiello, B., Ritz, L., et al. (2008). Double-Blind Comparison of First- and Second-Generation Antipsychotic in Early-Onset Schizophrenia and Schizoaffective Disorder: Findings From the Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS) Study. *Am J Psychiatry*, 165, 1420–1431.
- Stroup, T., Lieberman, J., McEvoy, J., Swartz, M., Davis, S., Capuano, G., et al. (2007). Effectiveness of Olanzapine, Quetiapine, and Risperidone in Patients With Chronic Schizophrenia After. *Am J Psychiatry*, 164, 415–427.
- Terry, E., Goldberg, T., Robert, S., & Goldman, R. (2007). Cognitive Improvement After Treatment With Second-Generation Antipsychotic Medications in First-Episode Schizophrenia Is It a Practice Effect? *Arch Gen Psychiatry*, 64(10), 1115-1122.
- Tuunainen, A., Wahlbeck, K., & Gilbody, S. (2002). Newer atypical antipsychotic medication in comparison to clozapine: A systematic review of randomized trials. *Schizophr Res*, 56, 1–10.

Table and figure Legends

Table 1 Description of studies selected for the comparison of first generation and second generation antipsychotics drug.

Serial Number	Author	Participants		Follow Up Periods
		FGAS	SGAS	
1	(Jones, et al., 2006)	99	86	52 weeks
2	(Sikich, et al., 2008)	40	76	8 weeks
3	(Schooler, et al., 2005)	264	264	30 weeks
4	(Lieberman, et al., 2003)	132	131	12 weeks
5	(Rosenheck, et al., 2006)	256	1168	18 months
6	(Keefe, et al., 2004)	78	89	12 weeks

Table 2 Description of studies selected for the comparison of two second generation antipsychotics resepridone vs olanzapine.

Serial Number	Author	Participants		Follow Up Periods
		Resperidone	Olanzapine	
1	(Rosenheck, et al., 2006)	332	328	18 months
2	(Sikich, et al., 2008)	41	35	8 weeks
3	(Sevy, et al., 2011)	21	28	16 weeks
4	(Stroup, et al., 2007)	38	39	15 months
5	(McEvoy, et al., 2007)	37	37	52 weeks

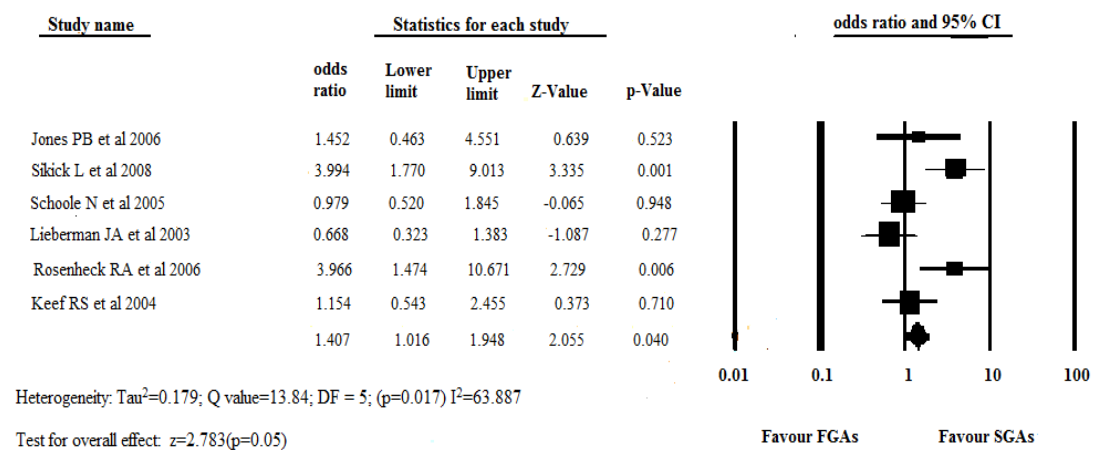


Figure 1 A meta-analysis of first generation antipsychotics VS Second generation antipsychotics, outcome: change in total PANSS score

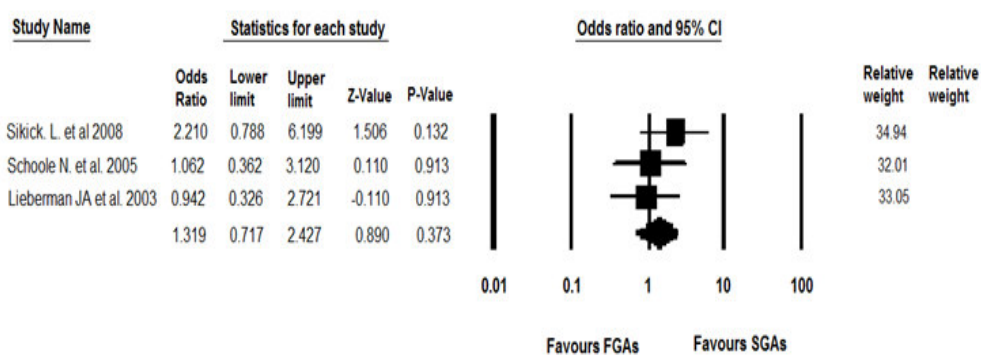


Figure 2 A meta-analysis of first generation antipsychotics VS second generation antipsychotics, outcome: change in positive symptom sub-score

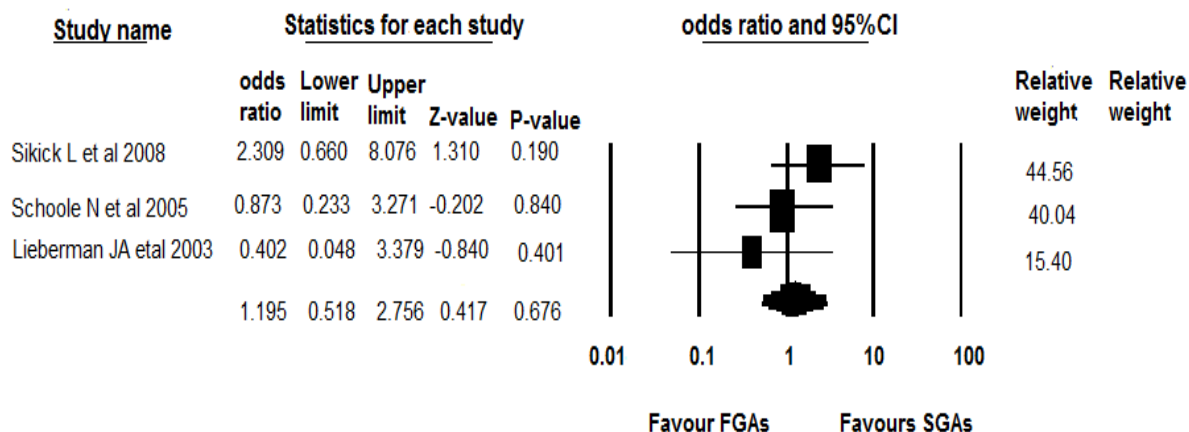


Figure 3 A meta-analysis of first generation antipsychotics VS second generation antipsychotics, outcome: change in negative symptom subs-score

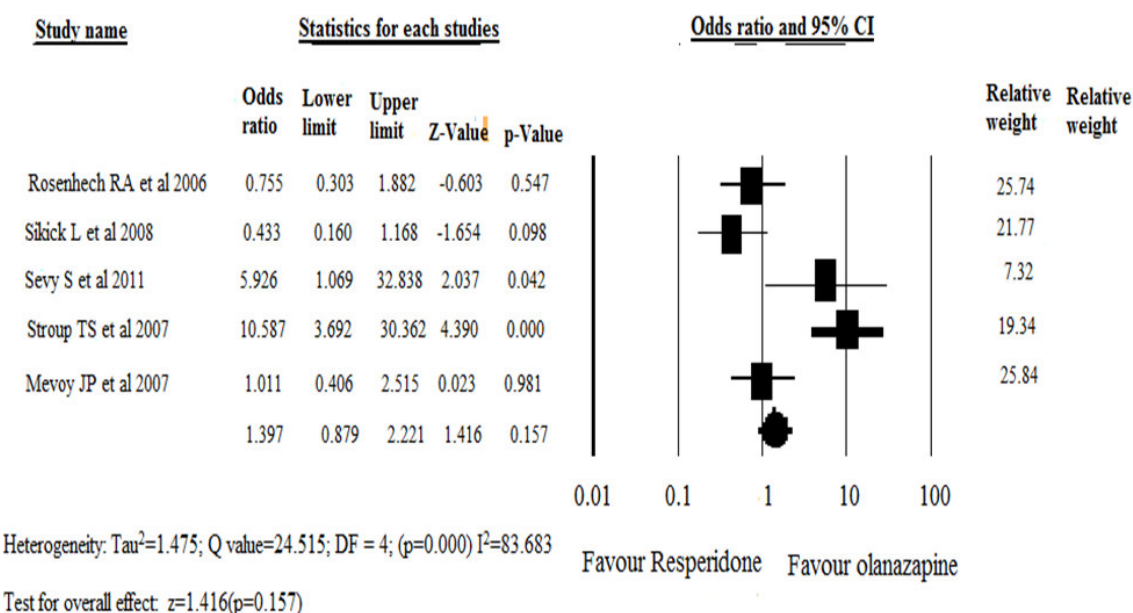


Figure 4 A meta-analysis of first generation resperidone VS olanzapine, outcome: change in total PANSS score

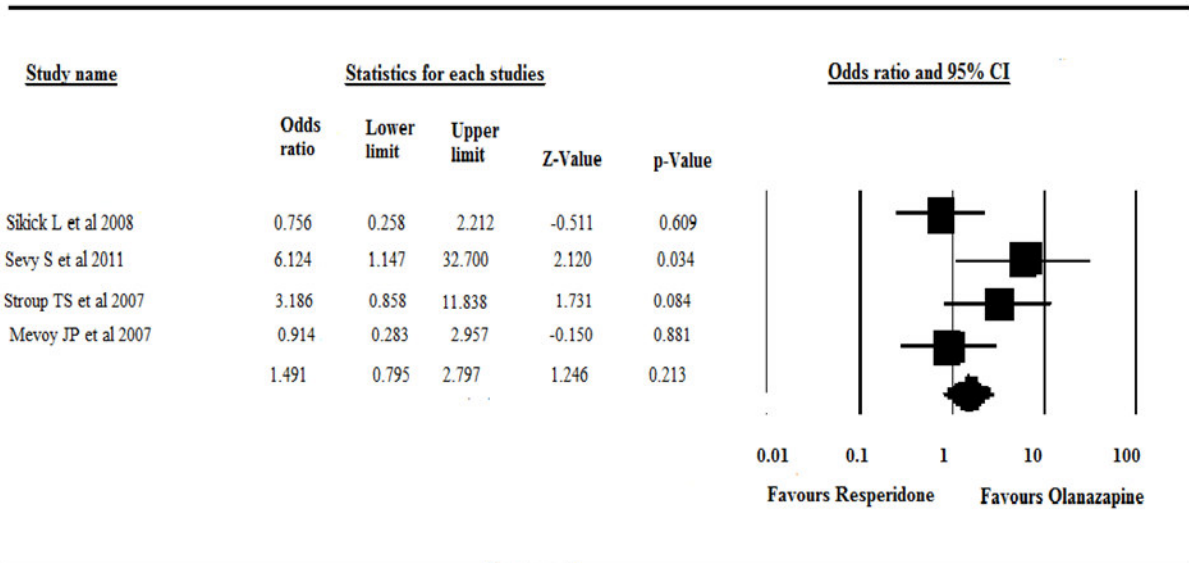


Figure 5 A meta-analysis of resperidone VS olanzapine, outcome: change in positive symptom sub-score

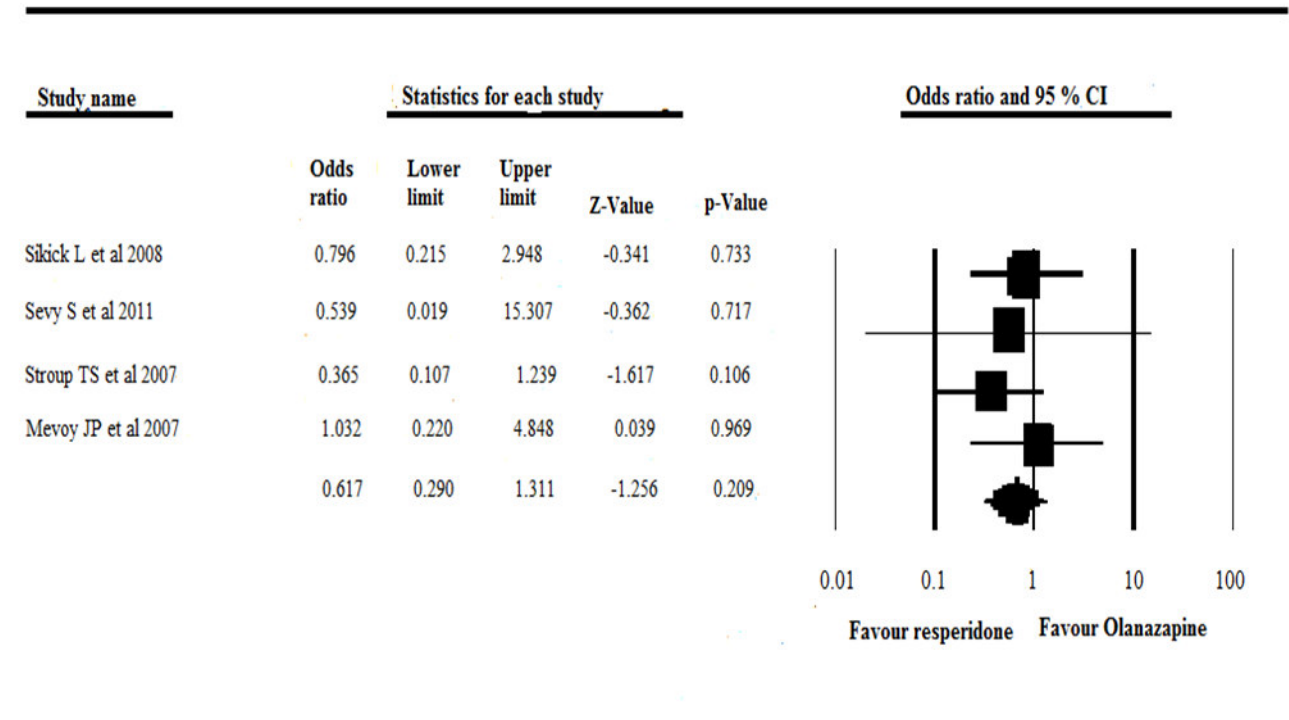


Figure 6 A meta-analysis or resperidone VS olanzapine: change in negative symptom sub-score