

# Reprise: The effect of metformin on anthropometrics and insulin resistance in patients receiving atypical antipsychotic agents: A meta-analysis

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## ABSTRACT

Atypical antipsychotics are well-established agents for the treatment of various psychiatric illnesses, although they are associated with adverse metabolic effects. There have been a few methodologically sound studies that have assessed the approach of adding metformin to atypical antipsychotics to reduce body weight. A systematic literature review of MEDLINE, EMBASE, and Cochrane was performed from the earliest possible dates to December 31, 2008. Metformin was found to be associated with a decrease in weight, waist circumference, bmi, and insulin resistance ( $p < 0.005$ ). The data supports the consideration of metformin for the reduction of metabolic effects developed from the atypical antipsychotics in clinical practice. Ultimately, additional rigorous controlled trials with the various antipsychotics and at different time points in the development of the metabolic effects are needed.

## KEYWORDS

metformin, atypical antipsychotics, metabolic effects

## ORIGINAL CITATION

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 Psych*;2010;71:1286-92.

## INTRODUCTION

Atypical Antipsychotics are well-established medications for the treatment of various psychiatric illnesses, although they are associated with adverse metabolic effects. The Diabetes Prevention Program has demonstrated metformin can reduce body weight and prevent diabetes. There have been a few methodologically sound studies that have evaluated the strategy of adding metformin to atypical antipsychotics to reduce body weight. To help characterize more completely the impact of metformin on anthropometrics and insulin resistance in patients taking atypical antipsychotics, our research team performed a meta-analysis of the completed randomized controlled trials.

## METHODS

### Statistics Notes

$I^2$  statistic is interpreted as the percentage of variability due to **heterogeneity between studies** rather than sampling error of each study

Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?

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Our team performed a systematic literature review of MEDLINE, EMBASE, and Cochrane from the earliest possible

dates to December 31, 2008. Studies were included in the analysis if they were randomized, placebo-controlled trials of metformin in patients taking atypical antipsychotics. The studies had to report weight, body mass index (BMI), waist circumference, insulin resistance, and/or the development of type 2 diabetes mellitus.

The mean change in weight, BMI, waist circumference, and insulin resistance from baseline were treated as continuous variables. The weighted mean difference was calculated as the difference between the mean in the metformin and the placebo groups. The incidence of new-onset type 2 diabetes mellitus was treated as a dichotomous variable, and the weighted averages were reported as relative risks with associated 95% confidence intervals. The statistical heterogeneity was addressed using the  $I^2$  statistic.

Visual inspection of funnel plots and Egger's weighted regression statistics were used to assess for the presence of publication bias. Additionally, subgroup and sensitivity analyses were done to assess the effect of clinical or methodological heterogeneity were conducted to determine the varying degrees of prior exposure to atypical antipsychotics before randomization to metformin, the differences between adults and children, reanalyzing the results excluding studies with a Jadad score  $< 3$ .

## RESULTS

A total of six trials met all inclusion criteria, although one trial required the continuous data be treated as if the data came from two separate trials. Thus, the results are based upon a meta-analysis of seven randomized metformin versus

placebo comparisons. Trials meeting the inclusion criteria are outlined in Table 1.

**Table 1: Characteristics of Included Studies**

References	Atypical Antipsychotic(s)	Metformin Dose (mg/day)	Follow-Up Length (weeks)
Wu et al, 2008 (n=37)	Olanzapine	750	12
Wu et al, 2008a (n=64)	Clozapine, olanzapine, risperidone, sulpiride	750	12
Wu et al, 2008b (n=64)	Clozapine, olanzapine, risperidone, sulpiride	750	12
Arman et al, 2008 (n=32)	Risperidone	1000	12
Baptista et al, 2007 (n=72)	Olanzapine	850-2250	12
Klein et al, 2006 (n=30)	Olanzapine, quetiapine, risperidone	850	16
Baptista et al, 2006; Baptista et al, 2007 (n=37)	Olanzapine	850-1700	14

Results of the analysis are outlined in Table 2. Metformin also demonstrated a trend toward reducing the risk of developing diabetes mellitus (3 trials, n=203, RR, 0.30, p=.13). For each subgroup analyses, there was no change in direction of effects.

**Table 2: Results of the Meta-Analysis**

Variable	Data	Result
Weight	6 trials, n = 336, WMD = 3.16 kg	decrease, p = 0.002
BMI	6 trials, n = 336, WMD = 1.21 kg/m <sup>2</sup>	decrease, p = 0.0001
Waist circumference	5 trials, n = 304, WMD = 1.99 cm	decrease, p < 0.005
Insulin resistance	5 trials, n = 295, WMD = 1.71	decrease, p < 0.004

## DISCUSSION

Our analysis suggests metformin has beneficial but modest effects on anthropometrics and insulin sensitivity when prescribed to patients receiving various atypical antipsychotics. In the paper, our research team describes the proposed mechanism of metformin's effect on insulin sensitivity as the underlying mechanism for the reported weight loss and the decreased proportion of new cases of

diabetic development. Additionally, we discuss how the current data does not allow us to assess whether metformin has differing abilities to attenuate/prevent metabolic disturbances when combined with different antipsychotics.

The data does support the consideration of metformin for the reduction of metabolic effects developed from the atypical antipsychotics in clinical practice. Ultimately, additional rigorous controlled trials with the various antipsychotics and at different time points in the development of the metabolic effects are needed.

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### How to cite this editor-reviewed article

Ehret MJ. Reprise: The effect of metformin on anthropometrics and insulin resistance in patients receiving atypical antipsychotic agents: A meta-analysis. *Ment Health Clin [Internet]*. 2011;1(1):6-7. Available from: <http://dx.doi.org/10.9740/mhc.n74803>