The Effect of Metformin on Anthropometrics and Insulin Resistance in Patients Receiving Atypical Antipsychotic Agents: A Meta-Analysis

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Context: In the Clinical Antipsychotic Trials of Intervention Effectiveness, atypical antipsychotics (AAPs) were found to be associated with weight gain and impairment of glucose metabolism. While metformin has been shown to attenuate weight gain and insulin resistance, not all studies have shown a benefit in the reduction of antipsychotic-induced weight gain and insulin resistance.

Objective: To characterize metformin's impact on anthropometrics and insulin resistance in patients taking AAPs.

Data sources: A systematic literature search of MEDLINE, EMBASE, and Cochrane CENTRAL was conducted from the earliest possible date through December 31, 2008. The search was performed using the following Medical Subject Headings and text keywords: *metformin*, *biguanide(s)*, *in combination with neuroleptic(s)*, *neuroleptic drug(s)*, *antipsychotic(s)*, *dopamine antagonist(s)*, *atypical antipsychotic(s)*, *psychotropic(s)*, *risperidone*, *olanzapine*, *quetiapine*, *ziprasidone*, *sulpiride*, *clozapine*, *iloperidone*, *aripiprazole*, *paliperidone*, *melperone*, *bifeprunox*, *amisulpride*, *zotepine*, and *sertindole*.

Study selection: Six of 62 identified studies (N = 336 participants) met our inclusion criteria: randomized, placebo-controlled trials of metformin in patients taking AAPs with data on weight, body mass index (BMI), waist circumference, insulin resistance (determined using the homeostasis model assessment of insulin resistance [HOMA-IR]), and/or a diagnosis of diabetes.

Data extraction: Data were independently abstracted by 2 investigators; disagreements were resolved through discussion or by a third investigator using a standardized data abstraction tool. For continuous endpoints, the weighted mean difference (WMD) of the change from baseline with 95% CI was calculated as the difference between the mean in the metformin and placebo groups. For categorical endpoints, the pooled relative risk (RR) with 95% CI was calculated. A random-effects model was used for all analyses.

Data synthesis: Compared to placebo, the metformin group had significantly reduced weight (WMD, 3.16 kg; $P = .0002$), BMI (WMD, 1.21 kg/m^2; $P = .0001$), waist circumference (WMD, 1.99 cm; $P = .005$), and HOMA-IR (WMD, 1.71; $P = .004$). The reduction in risk of diabetes was not statistically significant (RR, 0.30; $P = .13$).

Conclusions: This analysis suggests that using metformin in patients treated with AAPs may reduce metabolic risks. Additional randomized controlled trials are needed, but available data support consideration of this intervention in clinical practice.

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Atypical antipsychotics (AAPs) are well-established agents for the treatment of psychiatric illness.[1] However, they are associated with adverse metabolic effects and with an increased risk of cardiovascular disease, obesity, reductions in insulin sensitivity, and type 2 diabetes mellitus. Moreover, their overall effectiveness may be limited by the impact of these side effects on adherence.[2]

The Diabetes Prevention Program has provided data that show that metformin reduces body weight and prevents diabetes.[3] Baptista[4] first proposed the use of metformin in AAP-treated patients to reduce body weight in 1999. Since then, a few methodologically sound studies evaluating this strategy have been conducted; however, these studies have been of only short duration and small sample size.[5–11] To characterize more completely the impact of metformin on anthropometrics and insulin resistance in patients taking AAPs, we performed a meta-analysis of randomized controlled trials.

METHOD

Study Selection

A systematic literature search of MEDLINE (1966 through December 31, 2008), EMBASE (1990 through December 31, 2008), and Cochrane CENTRAL was conducted. The search was performed using the following Medical Subject Headings and text keywords: *metformin*, *biguanide(s)*, *in combination with neuroleptic(s)*, *neuroleptic drug(s)*, *antipsychotic(s)*, *dopamine antagonist(s)*, *atypical antipsychotic(s)*, *psychotropic(s)*, *risperidone*, *olanzapine*, *quetiapine*, *ziprasidone*, *sulpiride*, *clozapine*, *iloperidone*, *aripiprazole*, *paliperidone*, *melperone*, *bifeprunox*, *amisulpride*, *zotepine*, and *sertindole*. For our MEDLINE search, we used the Cochrane Collaboration's Highly Sensitive Search Strategy sensitivity-maximizing version.[12] The McMaster University Health Information Research Unit search strategy was used for the EMBASE search.[13] No language restrictions were imposed. In addition, a manual search of references from primary or review articles was performed to identify relevant trials. Two investigators (M.E., C.I.C.) independently reviewed potentially relevant articles.

Studies were included if they were randomized, placebo-controlled trials of metformin in patients taking AAPs that

reported weight, body mass index (BMI), waist circumference, insulin resistance (determined using the homeostasis model assessment of insulin resistance [HOMA-IR] calculated as HOMA-IR = [fasting insulin in μU/mL × fasting blood glucose in mg/dL] ÷ 405; a value of 1.0 is considered normal, with increasing values depicting worsening insulin sensitivity),[14] and/or the development of type 2 diabetes mellitus.

Validity Assessment

The following methodological features relevant to the control of bias were assessed: randomization, double-blinding, and description of withdrawals and dropouts. Using these criteria, Jadad scores were calculated to aid in the identification of reports with overall weaker study methodologies (scores < 3).[15] All trials were reviewed and graded by 2 investigators (M.E., C.I.C.), with disagreement resolved through discussion.

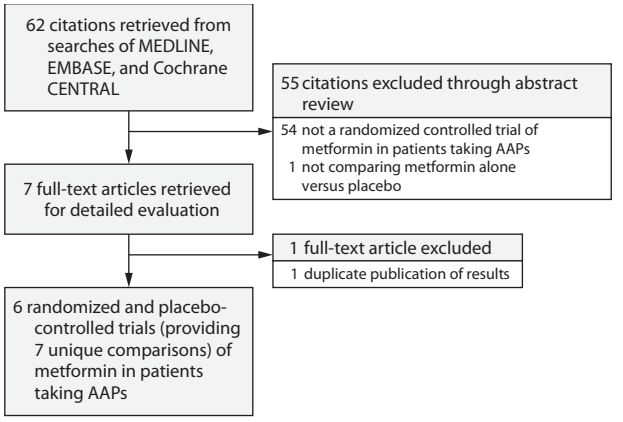
Data Abstraction

Using a standardized data abstraction tool, 2 reviewers (M.E., M.L.) independently collected data, with disagreement resolved through discussion or by a third investigator (C.I.C.). The following information was obtained from each trial: author identification, year of publication, study design and aforementioned quality criteria, source of study funding, study population (including study inclusion and exclusion criteria and baseline anthropometric and insulin resistance data), sample size, duration of patient follow-up, metformin and AAP dose and duration, use of concurrent lifestyle modification, and effect on outcome parameters (weight, BMI, waist circumference, HOMA-IR, and incidence of new-onset diabetes).

Statistical Analysis

The mean change in weight, BMI, waist circumference, and HOMA-IR from baseline was treated as a continuous variable, and the weighted mean difference (WMD) was calculated as the difference between the mean in the metformin and placebo groups. A DerSimonian and Laird[16] random-effects model was used in calculating the WMD and its 95% CI. The net changes in each of these study parameters were calculated as the difference (metformin minus placebo) of the changes (baseline minus follow-up) in the mean values (also referred to as the change score). When variances for net changes were not reported directly in a study, it was calculated from CIs, *P* values, or individual variances for intervention and placebo groups. For parallel trials, in which variance for paired differences were reported separately for each group, we calculated a pooled variance for net change by standard methods. When the variance for paired differences was not reported, we calculated it from variances at baseline and at the end of follow-up using a correlation coefficient of 0.5.[17] The incidence of new-onset type 2 diabetes mellitus was treated as a dichotomous variable. Weighted averages were reported as relative risks (RRs) with associated 95% CIs. As with WMDs, a DerSimonian and Laird[16] random-effects model was used in calculating RRs and 95% CIs.

Figure 1. Flow Diagram of Study Identification, Inclusion, and Exclusion



Abbreviation: AAPs = atypical antipsychotics.

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.[12]

Subgroup and sensitivity analyses to assess the effect of clinical or methodological heterogeneity were conducted. Included trials varied as to the degree of prior exposure to AAPs before randomization to metformin (ie, trials assessed either the prevention or attenuation of metabolic disturbances due to AAPs), with some trials enrolling AAP-naive patients and others requiring prolonged exposure. Furthermore, some trials were conducted in adults while others were in children or adolescents. Since data suggest that the previously untreated and/or the young may be particularly vulnerable to AAP-induced metabolic disturbances,[18,19] we conducted subgroup analyses whereby studies enrolling (1) previously AAP-treated and AAP-untreated patients and (2) adults and children/adolescents were analyzed separately. Finally, studies of poorer methodological quality may exhibit inaccurate treatment effects. Including only higher quality studies may result in increased internal validity but could reduce external validity of the analysis.[12] To reconcile this issue, sensitivity analysis was performed whereby the meta-analysis results were reanalyzed excluding studies with a Jadad score < 3.[15]

All statistics were performed using StatsDirect statistical software, version 2.4.6 (StatsDirect Ltd, Cheshire, England). A *P* value of < .05 was considered statistically significant in all cases.

RESULTS

Study Characteristics

A total of 6 trials met all inclusion criteria[5–11] (Figure 1). A trial by Wu and colleagues[6] randomly assigned patients to metformin or placebo and the presence or absence of aggressive lifestyle modification using a 2 × 2 factorial design, necessitating continuous data be treated as if the data came from 2 separate trials, 1 comparing metformin to placebo

Table 1. Characteristics of Included Randomized, Double-Blind, Placebo-Controlled Trials of Metformin in Patients Taking Atypical Antipsychotics

Reference (n)[a]	Inclusion Criteria of Note	AAP(s)	Baseline Anthropometrics and HOMA-IR[b]	Metformin Dose (mg/d)	Follow-Up (wk)	Concurrent Lifestyle Modification[c]	Jadad Score[d]
Wu et al,[5] 2008 (n = 37)	Chinese adults; no antipsychotic agent in past 3 mo	Olanzapine	Weight = 55.7, 56.5; BMI = 21.3, 21.6; WC = 76.5, 75.8; HOMA-IR = 1.7, 1.6	750	12	Standardized inpatient diets (not necessarily designed for weight control)	2, 2, 1 (5)
Wu et al,[6] 2008 (n = 64)	Chinese adults; > 10% weight gain during < 12 mo taking AAP; no lifestyle intervention group	Clozapine, olanzapine, risperidone, sulpiride	Weight = 64.7, 64.6; BMI = 24.6, 24.5; WC = 83.8, 83.5; HOMA-IR = 6.4, 5.8	750	12	2 × 2 factorial study; arms that did not receive lifestyle modification	2, 1, 1 (4)
Wu et al,[6] 2008 (n = 64)	Chinese adults; > 10% weight gain during < 12 mo taking AAP; lifestyle intervention group	Clozapine, olanzapine, risperidone, sulpiride	Weight = 64.6, 64.7; BMI = 24.6, 24.6; WC = 83.9, 83.6; HOMA-IR = 6.2, 6.2	750	12	2 × 2 factorial study; arms that received psycho-educational, dietary (AHA Step-2 diet), and exercise programs	2, 1, 1 (4)
Arman et al,[7] 2008 (n = 32)	< 20 y of age taking AAP for an undisclosed period of time	Risperidone	Weight = 35.2, 29.8; BMI = 17.4, 17.0; WC = NR, NR; HOMA-IR = NR, NR	1,000	12	None	1, 2, 0 (3)
Baptista et al,[8] 2007 (n = 72)	Adults taking AAP > 4 mo	Olanzapine	Weight = 66.2, 65.6; BMI = 25.0, 26.2; WC = 89.6, 91.3; HOMA-IR = 3.4, 3.3	850–2,250	12	Recommendations for healthy food and physical exercise to control weight at baseline	2, 2, 1 (5)
Klein et al,[9] 2006 (n = 30)	Children and adolescents; weight gain > 10% during < 12 mo taking AAP	Olanzapine, quetiapine, risperidone	Weight = 67.7, 74.3; BMI = 26.7, 28.7; WC = 89.4, 88.0; HOMA-IR = 5.1, 4.8	850	16	Patient-specific nutritional counseling by a dietician at baseline and every 4 wk	1, 2, 1 (4)
Baptista et al,[10] 2006; Baptista et al,[11] 2007 (n = 37)	Prior treatment with both oral and depot typical agent for 30.7 ± 10.1 y; switching oral agent to AAPs, maintained taking depot (mean age: 47 y)	Olanzapine	Weight = 58.3, 59.4; BMI = 23.1, 23.0; WC = 86.0, 84.1; HOMA-IR = 4.5, 4.9	850–1,700	14	Counseling for balanced diet of 2,500–3,000 kcal/d	2, 1, 1 (4)

[a]Number of participants evaluated for the weight endpoint, each study's primary endpoint. Other endpoints may have had fewer study participants.
[b]Presented as metformin value(s) at baseline, placebo value(s) at baseline. Weight is reported in kg, BMI in kg/m^2, and WC in cm.
[c]Lifestyle modifications (or lack thereof) were applied equally to the metformin and placebo groups.
[d]Reported as points for randomization (0–2 points), blinding (0–2 points), withdrawal and dropout reporting (0–1 points), and total Jadad score in parentheses.
Abbreviations: AAP = atypical antipsychotic, AHA = American Heart Association, BMI = body mass index, HOMA-IR = homeostasis model assessment of insulin resistance, NR = not reported, WC = waist circumference.

in the presence of lifestyle modification and another comparing metformin to placebo in the absence of lifestyle modification. Thus, this report is based upon a meta-analysis of 7 randomized metformin versus placebo comparisons. Of note, 3 studies evaluating the effect of metformin on metabolic disturbances in AAP-treated patients were excluded because they lacked a control group, and another study was excluded because it compared the combination of metformin and sibutramine to placebo.[20–23] All included trials enrolled patients receiving AAPs that were at least moderately associated with metabolic disturbances and randomly assigned them to treatment with either metformin (dosing range, 750 to 2,250 mg/d) or placebo for a period of 12 to 16 weeks (Table 1).[5–11] All trials were double-blind, placebo-controlled, parallel trials, and the median Jadad score was 4 (range, 3 to 5), suggesting that the included trials had relatively high internal validity. Two trials (2 comparisons) were conducted entirely in children and/or adolescents,[7,9] with the remaining trials limited to adults.[5,6,8,10,11] Four trials (5 comparisons) enrolled participants taking AAPs prior to randomization,[6–9] many of whom were specifically enrolled patients who had established metabolic disturbances.[6,8,9] The remaining 2 trials were limited to patients naive to AAP treatment,[5,10] although they may have been exposed to typical/first-generation antipsychotic agents in the past.[10] The type and degree of concomitant lifestyle modification varied among included trials, ranging from no modification to intensive psycho-education, dietary, and exercise modification.[6,7]

Quantitative Data Synthesis

In the meta-analysis, metformin, compared to placebo, significantly reduced weight (6 trials, n = 336 participants; WMD, 3.16 kg; $P = .0002$), BMI (6 trials, n = 336 participants; WMD, 1.21 kg/m^2; $P = .0001$), waist circumference (5 trials, n = 304 participants; WMD, 1.99 cm; $P = .005$), and HOMA-IR values (5 trials, n = 295 participants; WMD, 1.71; $P = .004$; Figure 2). In each analysis, significant statistical heterogeneity was noted ($I^2 \geq 83.9\%$ for all). While not reaching statistical significance, metformin also demonstrated

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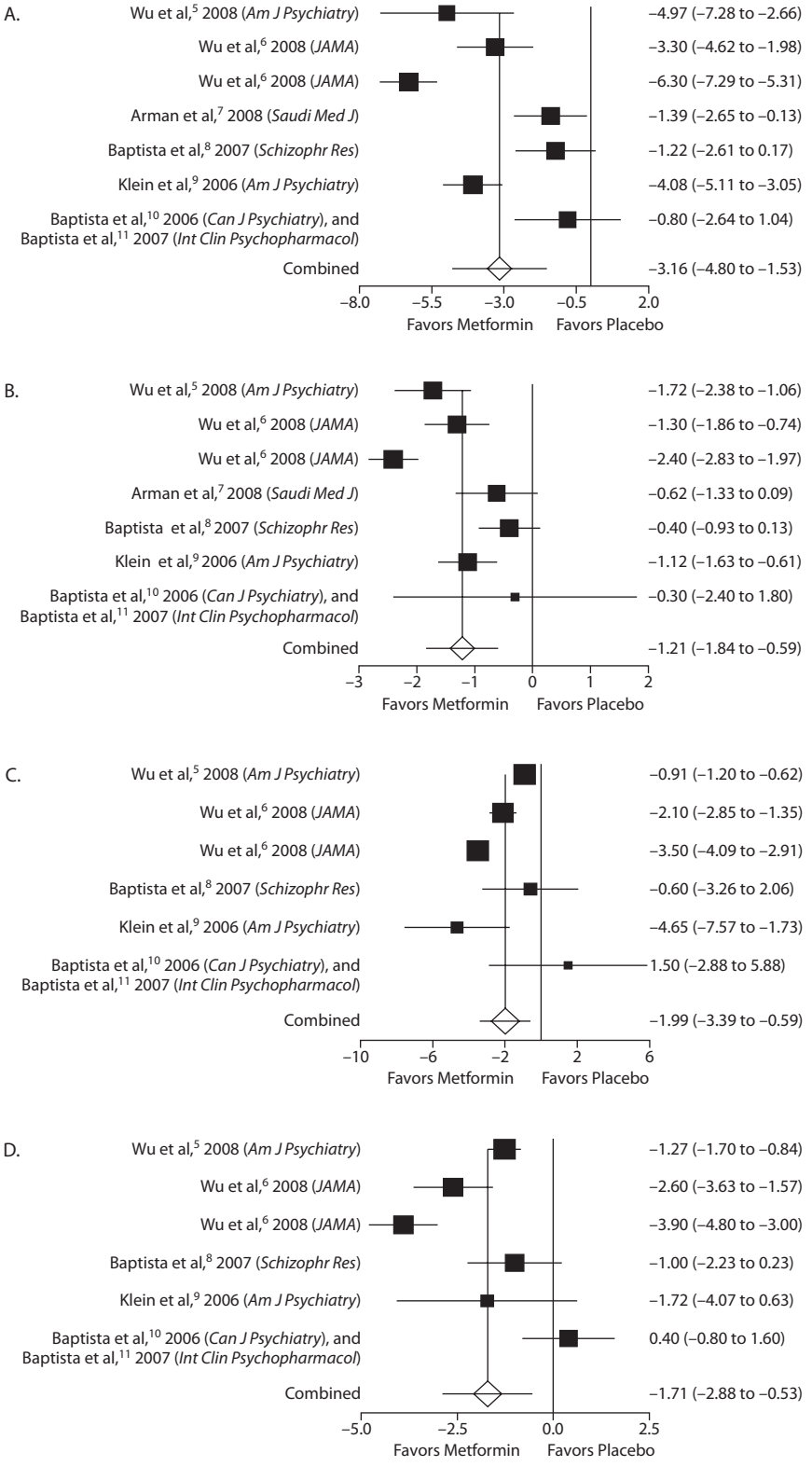
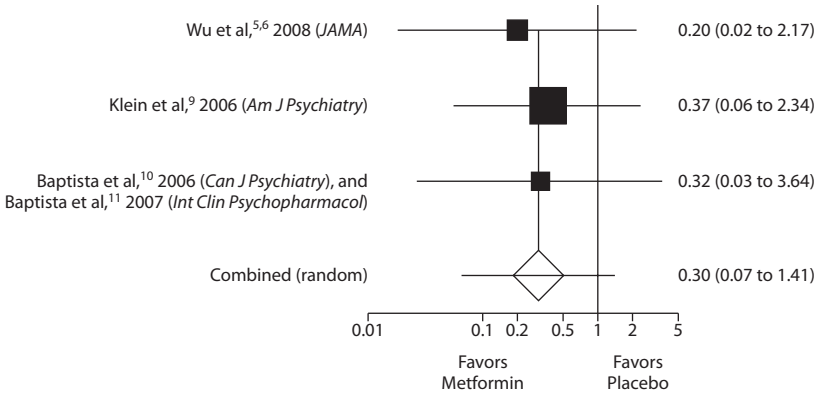
Figure 2. Forest Plots Depicting the Effect of Metformin on (A) Body Weight (kg), (B) Body Mass Index (kg/m^2), (C) Waist Circumference (cm), and (D) HOMA-IR (unitless)[a]



[a]All results reported as weighted mean differences and 95% CIs using a random-effects model.
Abbreviation: HOMA-IR = homeostasis model assessment of insulin resistance.

Figure 3. Forest Plots Depicting the Effect of Metformin on Patients' Risk of Developing Type 2 Diabetes Mellitus[a]



[a]Result reported as a relative risk and 95% CIs using a random-effects model.

Table 2. Results of Subgroup and Sensitivity Analyses

Subgroup or Sensitivity Analysis	Body Weight, kg		BMI, kg/m^2		Waist Circumference, cm		HOMA-IR	
	WMD	95% CI	WMD	95% CI	WMD	95% CI	WMD	95% CI
All trials	−3.16	−4.80 to −1.53	−1.21	−1.84 to −0.59	−2.04	−3.32 to −0.76	−1.71	−2.88 to −0.53
Adults	−3.33	−5.62 to −1.04	−1.34	−2.20 to −0.49	−1.64	−3.11 to −0.18	−1.70	−2.99 to −0.42
Children/adolescents	−2.76	−5.40 to −0.12	−0.93	−1.41 to −0.46	−4.65	−7.57 to −1.73	−1.72	−4.07 to 0.63
New exposure to AAP	−2.82	−6.91 to 1.26	−1.37	−2.57 to −0.18	−0.74	−1.96 to 0.48	−0.53	−2.16 to 1.09
Previous exposure to AAP	−3.29	−5.20 to −1.38	−1.18	−1.94 to −0.43	−2.73	−3.97 to −1.50	−2.41	−3.79 to −1.03

Abbreviations: AAP = atypical antipsychotic, BMI = body mass index, HOMA-IR = homeostasis model assessment of insulin resistance, WMD = weighted mean difference.

a trend toward reducing the risk of developing diabetes (3 trials, n = 203 participants; RR, 0.30; $P = .13$; Figure 3). No statistical heterogeneity was noted for this analysis ($I^2 = 0\%$). The reviews of funnel plots (not shown) and Egger's weight regression suggest a lower likelihood of publication bias for all analyses ($P = .30$, .39, .53, .81, and .70, respectively).

In the subgroup analyses, there was no change in direction of effect, although in some analyses, the differences were not statistically significant (Table 2). Sensitivity analysis was not conducted since all trials had a Jadad score > 2.

DISCUSSION

This systematic review and meta-analysis of 6 randomized, placebo-controlled trials suggests that metformin has beneficial but modest effects on anthropomorphics and insulin sensitivity when administered to patients taking AAPs.[5–11] These benefits appear to apply to adults and adolescents/children and to patients with metformin given at AAP initiation or after metabolic disturbances were observed. While a trend ($P = .13$) toward a reduction in new-onset diabetes was observed with metformin administration, the short duration and small sample size of available trials make it impossible to determine if this trend is due to chance alone.

Statistical heterogeneity was observed in all analyses ($I^2 > 83.9\%$) except for the one evaluating metformin's effect on preventing type 2 diabetes mellitus ($I^2 = 0\%$). Potential explanations for the observed heterogeneity include differences in clinical population (eg, ethnicity [American or Chinese]; age [adult or child/adolescent]; degree of insulin resistance; and inclusion of lean, untreated, or overweight or obese patients on treatment) or methodological study characteristics (eg, diet in a Chinese hospital with or without a dietary intervention may be fundamentally different than that of an outpatient in the United States). While the percentage of variation across trials due to heterogeneity rather than chance was high in each analysis, it appeared that the observed heterogeneity was more likely due to disagreement on the magnitude rather the direction of effect.

Previous studies have demonstrated the efficacy of metformin in reducing body weight from baseline (2.1 kg vs 0.1 kg for placebo; $P < .001$) and in the prevention of overt type 2 diabetes mellitus (relative risk reduction, 31%; 95% CI, 17% to 43% compared to placebo) in patients not taking AAPs, albeit not to the same extent as vigorous lifestyle modification.[4] Metformin's effect on insulin sensitivity (as evidenced by the aggregate 1.71-point reduction seen in HOMA-IR) has been proposed as the underlying mechanism for the reported weight loss and the decreased proportion of new cases of diabetes development.[4,24] This mechanism seems a particularly plausible explanation for those studies enrolling patients with significant insulin resistance (higher mean HOMA-IR values and/or overweight/obese patients). Metformin may also yield beneficial metabolic effects through

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its ability to decrease hepatic glucose output or by inducing gastrointestinal adverse effects, although the latter is less likely to explain the benefits seen in included studies, since significant numbers of withdrawals due to metformin adverse effects were not reported, and dropouts were often not included in efficacy analyses. Moreover, when gastrointestinal effects did occur and patients remained on treatment, the adverse effects were typically reported as mild and were addressed through dosage modification.[5–11]

There are different levels of metabolic risk among the AAPs. For example, clozapine and olanzapine have the highest risk, quetiapine and risperidone have moderate risk, and ziprasidone and aripiprazole have the least risk for metabolic disturbances.[25] All trials included in our meta-analysis evaluated metformin's effect on patients taking an AAP associated with at least a moderate risk of metabolic disturbances (clozapine, olanzapine, quetiapine, risperidone, or sulpiride). Although, often, patients in a study could have been taking more than 1 antipsychotic with different risks of development of metabolic disturbances.[6,9] Unfortunately, the currently available data do not allow us to assess whether metformin has differing abilities to attenuate/prevent metabolic disturbances when combined with different antipsychotics.

There are additional limitations to our meta-analysis. First, as with any meta-analysis, the potential for publication bias is a concern[12]; however, Egger's statistic *P* values and visual inspection of our analyses' funnel plots suggest that publication bias in this meta-analysis is less likely. Secondly, because the trials in this review were of short duration (12–16 weeks of follow-up), we cannot assess the potential benefits of longer-term use. However, many of the trials indicated that the benefit of metformin is evident early in therapy.[5,6,9] A search of the clinicaltrials.gov registry identified 2 ongoing, longer-term (24 weeks) studies (NCT00617240 and NCT00682448),[26,27] but results from these trials will not be available for at least a year. Lifestyle modification as an intervention varied greatly among included trials, and we could not assess its impact on our results. It is noteworthy that detailed review of the trial by Wu and colleagues[6] suggests an additive benefit of metformin even in patients receiving vigorous lifestyle modification. This finding is important because previous studies concluded that the benefits of behavioral interventions in patients taking AAPs were limited to small reductions in weight.[28] Finally, it should be noted that the short study durations and paucity of safety data reported did not allow us to assess a benefit:risk comparison of metformin in this unique population. While metformin is generally well tolerated, gastrointestinal side effects often occur, and clinicians must be wary of rare but serious adverse effects, including lactic acidosis.[29]

CONCLUSIONS

This analysis suggests that using metformin in patients treated with AAPs may reduce metabolic risks. As there have been only a handful of rigorous studies evaluating this topic, additional randomized controlled trials are needed. While the available data support consideration of this intervention in clinical practice, due to effect size considerations and a lack of safety data in this population, either a dechallenge from the offending AAP or enactment/re-enforcement of lifestyle modification would appear to be a more prudent strategy.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), iloperidone (Fanapt), metformin (Glucophage, Glumetza, and others), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal and others), sibutramine (Meridia), ziprasidone (Geodon).

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