**Comparative effects of 18 antipsychotics on metabolic function in schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis**

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**RESEARCH IN CONTEXT**

**Evidence before this study**

It has been proposed that antipsychotic drug treatment causes glucose dysregulation and lipid disturbance, thereby contributing to development of the metabolic syndrome in patients with schizophrenia. However, the relative degree to which metabolic alterations occur in treatment with different antipsychotics remains unclear. Furthermore, it is currently unknown whether baseline patient characteristics can predict metabolic dysregulation, while the association between metabolic change and change in psychopathology remains uncertain. To address these issues, we performed a systematic search for published network meta-analyses (NMAs) on the field. We searched Pubmed using the keywords: ‘schizophrenia AND antipsychotic AND (glucose OR cholesterol OR triglycerides OR metabolic)’, from inception until 19 July 2019 and without language restriction. Selection criteria were: NMAs of randomized blinded trials examining antipsychotic treatment of patients with schizophrenia, where outcomes were change in glucose, cholesterol, or triglyceride levels. Studies in any language were considered. Of the 664 studies retrieved, 1 NMA was identified, although this examined only a single parameter (glucose). No studies examined baseline predictors of metabolic change, nor the relationship between metabolic change and change in psychopathology.

**Added value of this study**

Our findings demonstrate differences between antipsychotics in terms of their metabolic side effects, and identify increased age, male gender, and non-Caucasian ethnicity as possible risk factors for antipsychotic-induced metabolic dysregulation. Furthermore, we have identified strong evidence that antipsychotic-associated improvements in psychopathology are associated with metabolic disturbance.

**Implications of all the available evidence**

Considering the increased prevalence of metabolic syndrome, cardiovascular disease, and cardiovascular mortality in schizophrenia, data from this study may be used to inform antipsychotic-prescribing, especially in the at-risk groups we have identified. However, clinical decisions to preferentially use an antipsychotic with fewer metabolic side effects should consider that clinical improvement appears to be associated with development of these side effects.

**ABSTRACT**

**Background:** Antipsychotic-treatment is associated with metabolic disturbance. However, the relative degree to which metabolic alterations occur in treatment with different antipsychotics remains unclear. Furthermore, predictors of metabolic dysregulation are poorly understood, and association between metabolic-change and change in psychopathology is uncertain. As such, we aimed to compare and rank antipsychotics based on their metabolic side-effects, identify physiological and demographic predictors of antipsychotic-induced metabolic dysregulation, and determine the relationship between change in psychotic symptoms and change in metabolic parameters with antipsychotic treatment.

**Methods:** We searched Medline, EMBASE and PsychINFO from inception until June 30, 2019. We included blinded randomised controlled trials (RCTs) comparing 18 antipsychotics and placebo in acute-treatment of schizophrenia. We performed frequentist random-effects network meta-analyses (NMAs) to investigate treatment-induced changes in body weight, BMI, total/LDL/HDL-cholesterol, triglycerides, and glucose. We performed meta-regressions to examine relationships between metabolic change and age/gender/ethnicity/baseline-weight/baseline-metabolic parameter level. We examined the association between metabolic change and psychopathology change by estimating the correlation between symptom severity change and metabolic parameter change.

**Outcomes:** Of 6532 citations, 100 RCTs met inclusion criteria, including 25,952 patients. Median treatment-duration was 6-weeks. According to our NMAs, mean differences for weight-gain compared to placebo ranged from -0.23 (95% CI: -0.83, 0.36) for best (haloperidol) to +3.01kg (1.78, 4.24) for worst (clozapine); for BMI from -0.25 (-0.68, 0.17) for best (haloperidol) to +1.07kg/m2 (0.90, 1.25) for worst (olanzapine); for total-cholesterol from -0.09 (-0.24, 0.07) for best (cariprazine) to +0.56mmol/L (0.26, 0.86) for worst (clozapine); for LDL-cholesterol from -0.13 (-0.21, -0.05) for best (cariprazine) to +0.20mmol/L (0.14, 0.26) for worst (olanzapine); for HDL-cholesterol from +0.05 (0.00, 0.10) for best (brexpiprazole) to -0.10mmol/L (-0.33, 0.14) for worst (amisulpride); for triglycerides from -0.01 (-0.10, 0.08) for best (brexpiprazole) to +0.98mmol/L (0.48, 1.49) for worst (clozapine); for glucose from -0.29 (-0.55, -0.03) for best (lurasidone) to 1.05mmol/L (0.41, 1.70) for worst (clozapine). Greater increases in glucose were predicted by higher baseline-weight (p=0.0015) and male-gender (p=0.0082). Non-Caucasian ethnicity was associated with greater increases in total-cholesterol (p=0.040). Improvements in symptom severity were associated with increases in weight (ρ=0.36, p=0.0021), BMI (ρ=0.84, p<0.0001), total-cholesterol (ρ=0.31, p=0.047), and LDL-cholesterol (ρ=0.42, p=0.013), and decreases in HDL-cholesterol (ρ= -0.35, p=0.035).

**Interpretation:** There are marked differences between antipsychotics in terms of metabolic side-effects, with olanzapine and clozapine exhibiting the worst profiles and aripiprazole, brexpiprazole, cariprazine, lurasidone, and ziprasidone the most benign profiles. Higher baseline weight, male gender, and non-Caucasian ethnicity are predictors of vulnerability to antipsychotic-induced metabolic change, and improvements in psychopathology are associated with metabolic disturbance. Treatment guidelines should be updated to reflect our findings. However, choice of antipsychotic should be made on an individual basis, considering the clinical circumstances and preferences of patients, carers, and clinicians.

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**INTRODUCTION**

Antipsychotics form the mainstay of treatment for patients with schizophrenia, but many, especially the second-generation antipsychotics, are associated with weight gain, lipid disturbance, and glucose dysregulation, thereby contributing to the development of metabolic syndrome.1 Indeed, it has been estimated that approximately one third of people with schizophrenia have metabolic syndrome, with rates as high as 69% in those with chronic illness.2 The prevalence of obesity, type 2 diabetes mellitus (T2DM), and hypercholesterolaemia in schizophrenia is estimated to be between 3-5 times higher compared with the general population.3 Compared with the general population, people with schizophrenia are both twice as likely to have a diagnosis and die as a consequence of cardiovascular disease (CVD).4 The mortality gap between people with schizophrenia and the general population is growing,5 suggesting a need for improved understanding of the factors underlying CVD in this group. While studies have previously examined change in weight with different antipsychotics,6 there has not yet been a study that comprehensively examines antipsychotic-induced metabolic change (i.e. glucose, cholesterol, and triglyceride alterations) using network meta-analysis (NMA). Thus, the relative degree to which metabolic alterations occur in acute-treatment with different antipsychotics remains unclear. Furthermore, it is unknown what physiological or demographic factors predict antipsychotic-associated metabolic dysregulation. Previous studies assessing comparative efficacies of different antipsychotics have used separate NMAs to respectively examine symptom change and change in weight.6 However, to date there has not been a meta-analysis that synthesises metabolic and symptom-change data. Thus, it is unclear if there is an association between antipsychotic-induced metabolic dysregulation and symptom-change in patients, as suggested by some, but not all previous longitudinal studies.7-9 As such, we have performed a NMA of trials comparing antipsychotics in treatment of schizophrenia, aiming to determine the relative effects of different agents on body-weight, body mass index (BMI), and metabolic measures (fasting-glucose, total-cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, and triglycerides). We have also performed bivariate meta-analyses and meta-regression analyses of placebo-controlled data to determine if baseline demographic and physiological factors predict magnitude of antipsychotic-induced metabolic change, and if there is a relationship between metabolic change and change in psychotic symptom severity during antipsychotic treatment.

**METHODS**

**Selection Procedures**

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)10 extension statement for NMA (appendix, p2), and the study registered on PROSPERO (CRD42019125322, appendix p5). We searched Medline, EMBASE and PsychINFO from inception until June 30, 2019. Our search strategy is described fully in the appendix (p5), but in brief we searched for: (antipsychotic OR [generic/branded antipsychotic names]) AND (schizo\* OR psychos\*) AND (random\* or ‘double blind’). We included randomised double-blind trials comparing antipsychotics licensed for schizophrenia-treatment in adults with acute exacerbation of schizophrenia/related disorder (schizoaffective/schizophreniform/delusional-disorders). We defined acute treatment as 6-weeks’ duration.6 If 6-week data were not available, data closest to 6-weeks were selected. Clinical trials registry data relating to papers identified in the literature review were included.

**Data Extraction and Processing**

Pairs of independent investigators (LV/KB/AA/GH/YM/TP) screened references and extracted study-level data, with discrepancies adjudicated by TP. We extracted outcome data (expressed as mean and standard deviation/standard error/confidence intervals) for change in body-weight (kilograms), BMI (kg/m2), fasting-glucose, total-cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides (all mmol/L) from initiation to end of treatment-trial for drug- and placebo-groups separately. Only continuous data were collected, not binary outcomes. We did not employ dose-limits owing to lack of evidence that dose influences metabolic dysregulation.11 For multi-arm studies reporting several doses of an antipsychotic, a summary value for a given metabolic parameter for all doses was calculated using formulae from the Cochrane Handbook (<http://handbook-5-1.cochrane.org/> and appendix p5).12 Since paliperidone is the active metabolite of risperidone,13 data for these drugs were combined as previously described.14 We also extracted publication-year; total-symptom-change (mean/variance, measured using Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS)); baseline-weight/baseline-metabolic parameter level; study-duration; antipsychotic; study population (first episode psychosis (FEP), multi-episode schizophrenia, treatment-resistant schizophrenia, older adults); age; gender (%male); and ethnicity (%non-Caucasian). Authors were contacted to request unreported data.

**Analysis**

**Pairwise meta-analysis**

All analyses were carried out in R (v3.5.1).15 For pairwise comparisons informed by ≥10 studies we synthesised data in a meta-analysis using a random-effects model in ‘metafor’ (v2.1-0). We investigated heterogeneity of treatment-effects visually by inspecting forest-plots, alongside monitoring of (standard deviation of random effects) and the I2 statistic. To visualize heterogeneity, prediction intervals were included in forest-plots. Small study effects and publication bias (SSE-PB) were assessed by visual inspection of contour-enhanced funnel-plots and via Egger’s test.

**Assessment of the transitivity assumption**

Transitivity is the key underlying assumption of NMA.16 In order to assess this assumption, we examined distribution of possible effect-modifiers across treatment comparisons. Potential effect-modifiers included age, gender, ethnicity, and body-weight.17-19

**Network meta-analysis**

We fitted random effects frequentist NMAs, where we assumed a common random-effects standard deviation ( for all comparisons in the network. We fitted our models in R using ‘netmeta’ (v1.0-1).20,21 Metabolic change for each parameter and each treatment comparison was estimated as mean difference (MD) with 95% confidence intervals (CI). Following recent recommendations, we avoided dichotomising results as statistically significant or not, and, instead presented results with confidence intervals to allow clinicians to gauge the range of likely effects.22,23 Placebo was used as the reference treatment in all forest-plots. We created league tables to display relative degree of metabolic disturbance for all comparisons among antipsychotics. We used P-scores to rank antipsychotics based on degree of metabolic dysregulation.24 P-scores range from 0 to 1, a higher P-score indicating greater degree of metabolic disturbance. To provide an overview of results, we generated a heat-map summarising ranking of disturbance across all metabolic parameters for all antipsychotics. Since increased HDL-cholesterol reduces CVD-risk,25 P-scores for this parameter were reversed to aid interpretation.

**Assessment of heterogeneity and inconsistency in the network**

We assessed network heterogeneity using  and I2 statistic. To visualize heterogeneity, we used prediction intervals in all forest-plots. We evaluated presence of network consistency using a ‘global’ (design-by-treatment inconsistency model) and a ‘local’ method (back-calculation).26,27

**Risk of bias in network analysis**

We assessed risk of bias of individual studies using the Cochrane Collaboration’s Tool for Assessing Risk of Bias,28 classifying risk of bias as high/moderate/low (appendix p5). We incorporated results into the ‘Confidence in Network Meta-Analysis’ (CINeMA)29,30 application (<https://cinema.ispm.unibe.ch/>) to evaluate credibility of findings from each NMA. CINeMA grades confidence in results of each treatment comparison as high/moderate/low/very low (appendix p19).

**Sensitivity analysis**

We hypothesized that inclusion of different study populations may contribute to heterogeneity and inconsistency. Thus, we evaluated sensitivity of our findings by repeating each NMA after excluding studies examining FEP, treatment-resistant schizophrenia, and older adults.

**Meta-regression: baseline predictors of antipsychotic-associated metabolic alterations**

In the general population, body-weight, age, gender, and ethnicity influence metabolic function.17-19 Therefore, we investigated if these covariates, as well as treatment factors, were related to change in metabolic parameters. Using the ‘metafor’ package (v2.0.0),31 we performed meta-regressions using placebo-controlled data aiming to examine the relationship between antipsychotic-associated metabolic change and baseline body-weight, baseline level of a given parameter (e.g. baseline-glucose if examining glucose change), age, gender (%male), and ethnicity (%non-Caucasian). In these meta-regressions, if a study had multiple active arms, estimates for each arm were merged, as described in the ‘Data Extraction and Processing’ section.12

**Assessing the relationship between alterations in metabolic parameters and psychopathology**

# The relationship between metabolic change and psychopathology change is uncertain. To examine whether these two outcomes are associated, we performed additional bivariate meta-analyses using placebo-controlled data. We meta-analysed the MD for change in weight/BMI/metabolic parameter and SMD for change in total-symptoms (assessed using PANSS or BPRS). Given that within-study correlations between the outcomes were not reported, we employed a model proposed by Riley and colleagues which overcomes this problem, using the package ‘metamisc’ (v0.2.0).32

**Role of the funding source**

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**RESULTS**

Of 6512 citations retrieved, 100 studies met inclusion criteria, examining the following: amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, flupenthixol, fluphenazine, haloperidol, iloperidone, lurasidone, olanzapine, quetiapine, risperidone, paliperidone, sertindole, ziprasidone, and zotepine (appendix pp20-21 show search and study characteristics). The overall sample included 25,952 participants (21,124 antipsychotic-treated, 4,828 placebo-treated). Average age was 35.03 years, 57.50% of participants were male, and 36.44% non-Caucasian. Treatment-duration ranged from 2-13 weeks (median 6-weeks). Risk of bias was high for 16% of data sets (appendix p34).

Age and gender of participants were similarly distributed across treatment-comparisons (appendix p36). There were however some differences noted for ethnicity and baseline-weight across treatment-comparisons, but overall we deemed the sample similar enough to synthesise jointly. There were 3 pairwise comparisons with ≥10 studies, all for weight change. The results of the meta-analyses and assessment of between-study heterogeneity and SSE-PB are described in the appendix pp37-40. We found evidence of SSE-PB for the comparison of change in body-weight with placebo and olanzapine: the corresponding contour enhanced funnel plot demonstrated absence of studies published with statistically insignificant (p>0.10) outcomes, and Egger’s regression test suggested funnel plot asymmetry (z=2.50, p=0.01). Network graphs are shown in Figure 1. Forest-plots for mean change in metabolic parameter for antipsychotics with placebo as the reference treatment are shown in Figure 2, and league tables comparing antipsychotics for each parameter in the appendix pp41-46. P-score ranking of antipsychotics for all metabolic parameters are shown collectively in a heatmap in Figure 3 and individually in the appendix pp47-49. Local assessments of inconsistency are shown in the appendix pp50-61. CINeMA confidence ratings are shown in the appendix pp62-87 and are used to colour-code forest-plots in Figure 2.

For change in weight, 83 studies compared 18 different antipsychotics with placebo (18,750 and 4,210 patients, respectively). We did not find evidence of weight gain with ziprasidone, haloperidol, fluphenazine, aripiprazole, lurasidone, cariprazine, amisulpride, or flupenthixol when compared with placebo. There was however evidence of weight gain (MD relative to placebo/kg, 95%CI) with brexpiprazole (0.88, 0.06-1.69); asenapine (1.17, 0.47-1.86); risperidone/paliperidone (1.28, 0.98-1.59); quetiapine (1.56, 1.09-2.04); iloperidone (1.77, 0.41-3.13); sertindole (2.37, 1.12-3.62); olanzapine (2.73, 2.38-3.07); zotepine (2.80, 1.09-4.53); and clozapine (3.01, 1.78-4.24) (Figure 2 and appendix p41). Ranking based on degree of weight gain identified haloperidol as the best and clozapine the worst (Figure 3 and Appendix p47).  was 0.59kg, considered small in the context of the observed antipsychotic-associated changes, and I2 71.3% (moderate-substantial). The global Q score for inconsistency was 97.41 (p<0.0001), and significant hot-spots of inconsistency identified in 5 of 154 treatment comparisons, including some disagreements between direct and indirect evidence (appendix p50). Certainty of evidence was low/very low in 91% of comparisons (appendix p62). Considering increased heterogeneity and inconsistency, we performed a post-hoc analysis excluding studies at high risk of bias. Estimated treatment effects were broadly similar, and heterogeneity and inconsistency assessments did not materially change (appendix pp88-92).

For change in BMI, 22 studies compared 9 different antipsychotics with placebo (4196 and 900 patients, respectively). Compared with placebo, there was no evidence of change in BMI observed with haloperidol or aripiprazole. There was, however, strong evidence for an increase in BMI (MD relative to placebo (kg/m2), 95%CI) with lurasidone (0.24, 0.08-0.41), risperidone/paliperidone (0.56, 0.42-0.70), quetiapine (0.70, 0.44-0.96), sertindole (0.76, 0.24-1.29), clozapine (1.02, 0.27-1.78), and olanzapine (1.07, 0.90-1.25) (Figure 2 and Appendix page 42). Ranking based on degree of associated BMI alteration identified haloperidol as the best and olanzapine the worst (Figure 3 and Appendix page 47).  was 0.32kg/m2, considered moderate in the context of the observed antipsychotic-associated changes, and I2 31.4% (low). Inspection of prediction intervals also confirmed that heterogeneity was limited, since for most treatment comparisons prediction intervals and CIs led to similar conclusions. The global Q score for inconsistency was 8.93 (p=0.54), and the back-calculation method did not provide evidence of network inconsistency (Appendix page 53). Thus, we deemed that there was no evidence of important heterogeneity or inconsistency in this NMA. Certainty of evidence was low/very low in 50% of comparisons (appendix p69).

For change in total-cholesterol, 36 studies compared 14 different antipsychotics with placebo (11,762 and 2,998 patients, respectively). Compared with placebo, there was no evidence of change in total-cholesterol observed with iloperidone, cariprazine, sertindole, ziprasidone, lurasidone, brexpiprazole, aripiprazole, risperidone/paliperidone, haloperidol, and amisulpride. There were, however, increases in total-cholesterol (MD relative to placebo (mmol/L), 95%CI) with quetiapine (0.31mmol/L, 0.19-0.42), olanzapine (0.40, 0.31-0.49), and clozapine (0.56, 0.26-0.86) (Figure 2 and appendix p43). Ranking based on degree of associated total-cholesterol alteration identified cariprazine as the best and clozapine the worst (Figure 3 and appendix p47).  was 0.08mmol/L, considered small in the context of the observed antipsychotic-associated changes, and I2 45.1% (moderate). Conclusions drawn from prediction intervals and CIs agreed. The global Q score for inconsistency was 35.55 (p=0.017). However, out of 91 treatment comparisons, we only identified a single hot-spot of inconsistency showing disagreement between indirect and direct evidence (appendix p54). Thus, overall we concluded that heterogeneity and inconsistency were not a source of concern in this NMA. Certainty of evidence was low in 71% of comparisons (appendix p71).

For change in LDL-cholesterol, 24 studies compared 9 different antipsychotics with placebo (7,439 and 2,419 patients, respectively). Compared with placebo, there was not strong evidence of change in LDL-cholesterol with ziprasidone, lurasidone, risperidone/paliperidone, aripiprazole, and brexpiprazole. We did, however, observe a decrease in LDL-cholesterol (MD relative to placebo (mmol/L), 95%CI) with cariprazine (-0.13, -0.21 to -0.05). We also observed increases in LDL cholesterol with quetiapine (0.17, 0.06-0.28) and olanzapine (0.20, 0.14-0.26) (Figure 2 and appendix p44). Ranking based on degree of associated LDL-cholesterol alteration defined cariprazine as the best and olanzapine the worst (Figure 3 and appendix p48).  was 0.03mmol/L, considered small in the context of observed antipsychotic-associated changes. Prediction intervals did not change conclusions when compared with CIs, while I2 was 16.2% (low). The global Q score for inconsistency was 4.46 (p=0.92), and although there were some disagreements between direct and indirect evidence (appendix p56), overall we concluded that there was no evidence of important heterogeneity or inconsistency in the network. Certainty of evidence was low in 53% of comparisons (appendix p73).

For change in HDL-cholesterol, 22 studies compared 10 different antipsychotics with placebo (7,073 and 2,189 patients, respectively). Compared with placebo, there was not strong evidence of change in HDL cholesterol observed with amisulpride, olanzapine, quetiapine, risperidone/paliperidone, lurasidone, cariprazine, or ziprasidone. There was, however, evidence of increases in HDL-cholesterol (MD relative to placebo (mmol/L), 95%CI) with aripiprazole (0.04, 0.00-0.08) and brexpiprazole (0.05, 0.00-0.10) (Figure 2 and appendix p44). Ranking based on degree of associated HDL-cholesterol alteration defined brexpiprazole as the best and amisulpride the worst (Figure 3 and appendix p48).  was 0.03mmol/L, considered medium/large in the context of the observed antipsychotic-associated changes, and I2 52.3% (moderate). The global Q score for inconsistency was 18.96 (p=0.025), and out of 45 treatment comparisons, we identified 2 hot-spots of inconsistency, although in both cases, direct and indirect evidence pointed in the same direction (appendix p57). Certainty of evidence was low/very low in 100% of comparisons (appendix p75).

For change in triglycerides, 34 studies compared 15 different antipsychotics with placebo (10,965 and 3021 patients, respectively). Compared with placebo, there was no strong evidence of change in triglyceride levels with brexpiprazole, lurasidone, sertindole, cariprazine, ziprasidone, aripiprazole, risperidone/paliperidone, amisulpride, haloperidol, and iloperidone. There was, however, evidence regarding increases in triglycerides (MD relative to placebo (mmol/L), 95%CI) with quetiapine (0.32mmol/L, 0.21-0.44), olanzapine (0.46, 0.37-0.55), zotepine (0.92, 0.25-1.59), and clozapine (0.98, 0.48-1.49) (Figure 2 and appendix p45). Ranking based on degree of associated triglyceride alteration identified brexpiprazole as the best and clozapine the worst (Figure 3 and appendix p48).  was 0.07mmol/L, considered small in the context of the observed antipsychotic-associated changes, and I2 42.6% (moderate). The global Q score for inconsistency was 45.07 (p<0.0001), but out of 105 treatment comparisons, we only identified 4 hot-spots of inconsistency showing disagreement between indirect and direct evidence (appendix p58). Certainty of evidence was low/very low in 92% of comparisons (appendix p77).

For change in fasting-glucose, 37 studies compared 16 different antipsychotics with placebo (10,681 and 3032 patients, respectively). Compared with placebo, there was no strong evidence change in glucose levels with amisulpride, asenapine, sertindole, ziprasidone, brexpiprazole, quetiapine, risperidone and paliperidone, aripiprazole, haloperidol, cariprazine, and iloperidone. There was, however, evidence of reductions in glucose (MD relative to placebo (mmol/L), 95%CI) with lurasidone (-0.29mmol/L, -0.55 to -0.03), and increases in glucose with olanzapine (0.20, 0.04-0.37), zotepine (0.99, 0.17-1.81), and clozapine (1.05, 0.41-1.70) (Figure 2 and appendix p46). Ranking based on degree of associated glucose alteration defined lurasidone as the best and clozapine the worst (Figure 3 and appendix p48).  was 0.18mmol/L, considered moderate in the context of the observed antipsychotic-associated changes, and I2 statistic 62.7% (moderate). The global Q score for inconsistency was 55.58 (p<0.0001), but out of 103 treatment comparisons only one significant hot-spot of inconsistency was identified with disagreement between indirect and direct evidence (appendix p60). Certainty of evidence was low/very low in 86% of comparisons (appendix p82).

The sensitivity of our findings for all 7 NMA outcomes were evaluated by repeating analyses following exclusion of studies examining patients with FEP (4 studies), treatment resistant schizophrenia (5 studies), and older adults (2 studies). The findings essentially remained the same in all sensitivity analyses (appendix pp88-97), indicating that the inclusion of these studies did not have a major influence on results. Assessments of heterogeneity and inconsistency were also broadly similar, except for LDL cholesterol where the global test of inconsistency worsened (Q=22.67, p=0.030) and triglycerides where the global test of inconsistency improved (Q=4.53, p=0.98), although local tests of inconsistency were materially unchanged (appendix p93).

Greater antipsychotic-induced increases in fasting-glucose levels were associated with higher baseline body-weight (study number (k)=20, z=3.18, estimate=0.01 kg-1 (0.00, 0.02), p=0.0015, figure 4A) and larger proportion of male participants (k=25, z=2.64, estimate=0.01 (0.00, 0.02), p=0.0082, figure 4B). Greater antipsychotic-induced increases in total-cholesterol were associated with larger proportion of non-Caucasian participants (k=22, z=2.05, estimate=0.003 (mmol/L)-1 (0.00, 0.01), p=0.040). We did not find strong evidence of an association between change in weight, BMI, LDL-cholesterol, HDL-cholesterol and triglycerides with any baseline variables.

Greater improvement in total-symptom severity was strongly associated with greater increases in body-weight (ρ=0.36 (df=61), p=0.0021, Figure 5A), BMI (ρ=0.84 (df=15), p<0.0001, Figure 5B), total-cholesterol (ρ=0.31 (df=29), p=0.047), and LDL-cholesterol (ρ=0.42 (df=28), p=0.013, Figure 5C). Greater improvement in total-symptom severity was however associated with greater reductions in HDL-cholesterol (ρ= -0.36 (df=25), p=0.035, Figure 5D).  We did not find evidence of an association between symptom-change and triglyceride or glucose changes.

**DISCUSSION**

Our main finding is that antipsychotics differ markedly in their effects on body-weight, BMI, total/LDL/HDL-cholesterol, triglycerides, and glucose. As expected,6 clozapine and olanzapine are, across virtually all parameters, associated with the largest degree of metabolic dysregulation. However, for several antipsychotics we did not find evidence of an effect versus placebo in terms of lipid or glucose measures. Interestingly, some of the drugs were shown to perform better than placebo on some metabolic measures: for instance, when compared with placebo, lurasidone led to reductions in glucose, cariprazine with reductions in LDL-cholesterol, and aripiprazole and brexpiprazole with increases in HDL-cholesterol. Our meta-analysis is the first to examine predictors of antipsychotic-induced metabolic change. We found that baseline body-weight, male gender, and non-Caucasian ethnicity predict greater vulnerability to antipsychotic-induced metabolic dysregulation, suggesting overlap between risk-factors for metabolic disease in the general population and in antipsychotic-induced metabolic disease. We did not however observe a relationship between baseline weight and magnitude of antipsychotic-induced weight gain, as observed in some but not all previous studies;33 the discrepancies between our results with some of those previously documented may be a consequence of the large sample size utilised in our study, and the restriction of our analyses to randomised controlled trials of acute treatment (with previous studies examining weight gain over prolonged time-periods of up to 3-years).33 We also showed that improvements in total-symptom severity are associated with increases in weight, BMI, total-cholesterol and LDL-cholesterol levels, and decreases in HDL cholesterol levels, suggesting that the most efficacious antipsychotics are associated with greatest metabolic disturbance. An alternative explanation is that metabolic side effects of antipsychotics are similar and that our findings reflect medication compliance, with poor medication concordance in some subjects resulting in a reduction in drug efficacy but also fewer metabolic side effects*.* If this hypothesis were correct, it would suggest that previous trial reports of relatively reduced metabolic side-effects of some antipsychotic treatments such as aripiprazole were not due to the pharmacological properties of the drug, rather the fact that patients did not take the treatment. However, when we examined data examining metabolic changes with aripiprazole where concordance was assured via use of long acting injectable formulation, glucose and lipid alterations with aripiprazole-treatment were no different from placebo-treatment, generally in keeping with our NMA findings.34 Furthermore, degree of metabolic dysregulation has been shown to be markedly different between antipsychotics in preclinical studies.35 Our results are also in line with the outcomes of previous studies suggesting that more efficacious antipsychotics such as olanzapine and clozapine are generally associated with weight gain,6 and for both BMI and weight, our findings agree with the results from previous cohort studies regarding magnitude and direction of association.7-9 Our findings do not mean that metabolic disturbance is a requirement for efficacy, but do highlight that those drugs that are most efficacious tend to have the broadest pharmacology, and metabolic effects may be due to off-target actions.

We employed strict inclusion criteria to obtain a homogenous sample. There was no evidence of inconsistency for NMAs examining change in BMI, LDL-cholesterol, and HDL-cholesterol, supporting the robustness of these outcomes. However, there were some concerns regarding inconsistency in the NMAs of triglycerides and glucose, and more important concerns for the NMA of weight. These NMAs showed evidence of global inconsistency, although only a small number of local ‘hot spots’ of inconsistency. Inconsistency may have been secondary to imbalances in the distribution of some effect-modifiers observed across comparisons, and SSE-PB that were noted in pairwise meta-analyses. Only a small proportion of studies (16%) showed no evidence of bias, and confidence in the evidence of the comparisons across all parameters was low/very low for 50-100% of treatment comparisons. Of note, the most recent and largest NMA examining comparative treatment-efficacy of different antipsychotics identified the same issue, with confidence of outcomes for 75% of treatment-comparisons regarded as low/very low.6 However, our sensitivity analyses excluding patients with FEP, treatment-resistant psychosis, older adults, and low quality studies found similar results to the overall findings, and measures of inconsistency were largely unchanged, supporting the inclusion of these data in primary analyses.

In the general population it has been estimated that that for every kilogram increase in body-weight, CVD risk increases by 3.1%,36 and for every kg/m2 increase in BMI, risk of heart failure increases by 5-7%37 and risk of T2DM increases by 8.4%.38 Furthermore, a 1mmol/L increase in triglyceride levels corresponds to a 32-76% increased risk of CVD.39 Thus, ~6-weeks of treatment with antipsychotics such as olanzapine and clozapine, that increase body-weight by approximately 3kg, BMI by approximately 1kg/m2, and triglycerides by approximately 1mmol/L, may lead to important increases in CVD-risk. Hypertriglyceridemia accompanies development of T2DM,40 and we observed increases in fasting-glucose of 1mmol/L with clozapine. At the onset of psychotic illness and prior to antipsychotic prescription, patients with schizophrenia have impaired glucose/lipid regulation.41-43 Thus, certain antipsychotics, within a few weeks, may worsen metabolic homeostasis in an already vulnerable cohort. This reinforces international recommendations that metabolic monitoring should accompany antipsychotic prescription.38 In contrast, aripiprazole was the only antipsychotic to demonstrate across all parameters either no evidence of change or improvement in metabolic parameter levels compared with placebo. Brexpiprazole, cariprazine, and lurasidone also showed improvements in some metabolic parameters compared with placebo. The metabolic effects of ziprasidone showed no clear difference compared with placebo for all parameters assessed. Given the risks of cardiovascular and other morbidity associated with metabolic dysregulation, these data should be used by clinicians and patients as one factor in the choice of an antipsychotic*.* This is particularly pertinent for people with risk factors such as increased body-weight, male gender, and non-Caucasian ethnicity, that we found predicted greater metabolic dysregulation. However, it is important to consider other side-effects such as extrapyramidal side-effects, 6,13 and that there are differences in efficacy between drugs,6 which should also be factored into treatment-choice.

Our findings should also be considered in the context of population-based studies showing that patients with schizophrenia who receive antipsychotic treatment, especially clozapine, have lower all-cause and cardiac mortality rates compared with patients who do not receive antipsychotic treatment.44 Our observation that symptomatic improvement accompanies metabolic dysregulation may provide some insight into why, paradoxically, cardiovascular mortality improves with treatments that lead to worse metabolic outcomes. Improvements in mental state may result in improved self-care and engagement with physical health services, which may offset the metabolic risk of a drug. This may be partially driven by the fact that clozapine and olanzapine are amongst the most effective antipsychotic drugs and are also the drugs associated with highest risk of metabolic dysregulation.6 It is unclear if the association between symptom improvement and metabolic dysregulation reflects an intrinsic therapeutic link. One possible explanation is that the antipsychotic receptor binding profiles implicated in metabolic dysregulation, such as serotonin 5-HT2A, histamine H1, and muscarinic M3 receptors,13 may also play a therapeutic role alongside D2 dopamine receptor blockade.38 In addition to serotonin, histamine, and muscarinic activity, peripheral dopaminergic signalling may play a role in defining the metabolic profiles associated with different antipsychotics. This could go some way to explaining the different lipid and glucose outcomes associated with dopamine receptor antagonists compared with partial agonists. However, both the central and peripheral mechanisms that underlie the effects of antipsychotic drugs on metabolic parameters are poorly understood. Future pre-clinical work should explore if peripheral receptor binding profiles of different antipsychotics explain their respective metabolic signatures, and whether this can be manipulated to mitigate the metabolic side-effects of treatment.

Strengths of our analysis include the large sample size (almost 26,000 participants), and methodological rigour (restriction to double-blind randomised controlled trials to control for illness and other non-drug related effects). However, some limitations should be acknowledged. Despite attempts made to contact authors, we were unable to obtain metabolic data for several trials, especially if the study was performed over 15 years ago. Thus, our findings are mostly restricted to RCTs of recently licensed antipsychotics; further work is required to define the metabolic profiles of older drugs which will better inform prescribing practice. We restricted our analyses to randomised controlled trials so that prescriber and biases were controlled for to give the best estimates of drug specific effects. However, as randomised controlled trials are generally relatively short, this means the duration of treatment in the studies included was in the range 2-13 weeks. Thus, it remains unclear if there is further metabolic change over a longer time period. As such, future NMAs should examine antipsychotic-induced metabolic dysregulation in patients receiving long-term maintenance therapy. Studies often failed to report on lifestyle and treatment factors that may influence metabolic outcomes, including physical comorbidity, alcohol use, smoking, diet, exercise, and co-prescription of psychiatric (e.g. mood stabilisers) or physical health medications (e.g. statins/anti-glycaemic agents) that may have influenced metabolic parameters. However, randomisation of participants should have distributed study participants with these confounders equally between groups. Our meta-regression analyses were based on study-level data and require replication with individual patient data. Finally, studies included in the meta-analysis often failed to report on relative proportions of different non-Caucasian ethnic groups, therefore we were unable to examine in greater detail the influence of different ethnicities on metabolic outcomes, something that should be explored in future studies.

In conclusion, there are marked differences between antipsychotics in their metabolic side-effects, with olanzapine and clozapine showing the worst side-effect profiles. Aripiprazole, brexpiprazole, cariprazine, lurasidone, and ziprasidone are associated with the best metabolic outcomes and these drugs can be considered safer options in those at higher risk of developing metabolic complications. However, clinical decisions to preferentially use antipsychotics with fewer metabolic side effects should consider that clinical improvement is associated with development of these side effects. We identified higher baseline-weight, male gender, and non-Caucasian ethnicity as potential risk factors for antipsychotic-induced metabolic disturbance. Treatment guidelines should be updated to reflect differences in metabolic risk, but the choice of the treatment intervention should be made on an individual patient basis, considering the clinical circumstances and preferences of patients, carers, and clinicians.

**LEGENDS**

**Figure 1.** Network graphs for all outcomes. The thickness of connecting lines corresponds to the number of trials comparing the treatments.

**Figure 2.** Forest-plots for mean differences of antipsychotic drugs compared with placebo. MD = mean difference. CI = 95% confidence interval. PI = 95% prediction interval. Green, blue, yellow and red colours indicate the confidence in the evidence for a given comparison: green = high, blue = moderate, yellow = low, red = very low. Confidence of outcomes was graded using CINeMA. Grey lines immediately below each coloured line indicate the prediction interval corresponding to that antipsychotic-placebo comparison. Full results for all treatment comparisons are shown in the appendix pp41-46.

**Figure 3.** Heat map of antipsychotic drugs ranked according to associated degree of alteration in body-weight, Body Mass Index (BMI) and metabolic parameters. Numbers reflect P-scores which rank antipsychotics on a continuous scale from 0 to 1. A higher P-score indicates greater degree of disturbance. The P-scores are reversed for HDL-cholesterol, where increased levels are considered beneficial. Grey squares indicate that data are not available.

**Figure 4.** 'Bubble-plots’ for meta-regressions on the effect of baseline predictors on antipsychotic-induced changes in fasting-glucose. Each bubble corresponds to a study. The size of the bubbles is proportional to sample size. The drawn line corresponds to the meta-regression estimate, and corresponding 95% CI.

**Figure 5.** 'Bubble-plots’ for the associations between change in symptom severity and change in metabolic parameters. Each bubble corresponds to a study.The size of the bubbles is proportional to sample size. The drawn line corresponds to the meta-regression estimate, and corresponding 95% CI.

**Contributors**

TP formulated the research questions and performed the literature search. TP, LV, YM, GH, AA, and KB selected the articles and extracted outcome data. TP and RM performed the statistical analyses. TP, RM, SN, OE, AC, and OH wrote the report. TP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Declaration of interests**

OH declares that he has received investigator-initiated research funding from and/or participated in advisory/ speaker meetings organised by Astra-Zeneca, Autifony, BMS, Eli Lilly, Heptares, Jansenn, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand and Roche. Neither Professor Howes nor his family have been employed by or have holdings/ a financial stake in any biomedical company. YM reports grants from Japan Society for the Promotion of Science, grants from Astellas Foundation for Research on Metabolic Disorders, grants from Japanese Society of Clinical Neuropsychopharmacology, grants from Mochida Memorial Foundation for Medical and Pharmaceutical Research, personal fees from Sumitomo Dainippon Pharma, personal fees from Bracket, personal fees from Medavante-Prophase outside the submitted work. TP, RM, LV, KB, SN, AA, GH, OE and AC declare no conflicts of interest.

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**REFERENCES**

1. Howes OD, Bhatnagar A, Gaughran FP, Amiel SA, Murray RM, Pilowsky LS. A prospective study of impairment in glucose control caused by clozapine without changes in insulin resistance. *Am J Psychiat.* 2004;161(2):361-363.

2. Vancampfort D, Stubbs B, Mitchell AJ, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry.* 2015;14(3):339-347.

3. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis. *Schizophr Bull.* 2013;39(2):306-318.

4. Correll. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls (vol 16, pg 163, 2014). *World Psychiatry.* 2018;17(1):120-120.

5. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry.* 2007;64(10):1123-1131.

6. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet.* 2019.

7. Hermes E, Nasrallah H, Davis V, et al. The association between weight change and symptom reduction in the CATIE schizophrenia trial. *Schizophrenia Research.* 2011;128(1-3):166-170.

8. Raben AT, Marshe VS, Chintoh A, Gorbovskaya I, Muller DJ, Hahn MK. The Complex Relationship between Antipsychotic-Induced Weight Gain and Therapeutic Benefits: A Systematic Review and Implications for Treatment. *Front Neurosci-Switz.* 2018;11.

9. Umbricht DS, Pollack S, Kane JM. Clozapine and weight gain. *J Clin Psychiatry.* 1994;55 Suppl B:157-160.

10. Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Journal of Clinical Epidemiology.* 2009;62(10):1006-1012.

11. Simon V, van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. *J Clin Psychiatry.* 2009;70(7):1041-1050.

12. Higgins PT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). 2011.

13. Kaar SJ, Natesan S, McCutcheon R, Howes OD. Antipsychotics: Mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. *Neuropharmacology.* 2019:107704.

14. Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet.* 2011;378(9799):1306-1315.

15. R Core Team. R: A language and environment for statistical computing. 2017; <https://www.R-project.org/>. Accessed February 19, 2018.

16. Efthimiou O, Debray TP, van Valkenhoef G, et al. GetReal in network meta-analysis: a review of the methodology. *Res Synth Methods.* 2016;7(3):236-263.

17. Hildrum B, Mykletun A, Hole T, Midthjell K, Dahl AA. Age-specific prevalence of the metabolic syndrome defined by the International Diabetes Federation and the National Cholesterol Education Program: the Norwegian HUNT 2 study. *Bmc Public Health.* 2007;7:220.

18. Pradhan AD. Sex differences in the metabolic syndrome: implications for cardiovascular health in women. *Clin Chem.* 2014;60(1):44-52.

19. Liu J, Hanley AJG, Young TK, Harris SB, Zinman B. Characteristics and prevalence of the metabolic syndrome among three ethnic groups in Canada. *Int J Obesity.* 2006;30(4):669-676.

20. Rucker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods.* 2012;3(4):312-324.

21. Rücker G, Krahn U, König J, Efthimiou O, Schwarzer G. netmeta: Network Meta-Analysis using Frequentist Methods. <https://github.com/guido-s/netmeta>. 2019.

22. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature.* 2019;567(7748):305-307.

23. Efthimiou O, White IR. The dark side of the force: multiplicity issues in network meta-analysis and how to address them. *Res Synth Methods.* 2019.

24. Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *Bmc Medical Research Methodology.* 2015;15.

25. Stone. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (vol 129, pg S1, 2014). *Circulation.* 2014;129(25):S46-S48.

26. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods.* 2012;3(2):98-110.

27. Konig J, Krahn U, Binder H. Visualizing the flow of evidence in network meta-analysis and characterizing mixed treatment comparisons. *Statistics in Medicine.* 2013;32(30):5414-5429.

28. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj-Brit Med J.* 2011;343.

29. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS One.* 2014;9(7):e99682.

30. Nikolakopoulou A, Higgins JP, Papakonstantinou T, et al. Assessing Confidence in the Results of Network Meta-Analysis (Cinema). *bioRxiv: pre-print.* 2019.

31. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *J Stat Softw.* 2010;36(3):1-48.

32. Riley RD, Thompson JR, Abrams KR. An alternative model for bivariate random-effects meta-analysis when the within-study correlations are unknown. *Biostatistics.* 2008;9(1):172-186.

33. Manu P, Dima L, Shulman M, Vancampfort D, De Hert M, Correll CU. Weight gain and obesity in schizophrenia: epidemiology, pathobiology, and management. *Acta Psychiatr Scand.* 2015;132(2):97-108.

34. Nasrallah HA, Newcomer JW, Risinger R, et al. Effect of aripiprazole lauroxil on metabolic and endocrine profiles and related safety considerations among patients with acute schizophrenia. *Journal of Clinical Psychiatry.* 2016;77(11):1519-1525.

35. Boyda HN, Tse L, Procyshyn RM, Honer WG, Barr AM. Preclinical models of antipsychotic drug-induced metabolic side effects. *Trends Pharmacol Sci.* 2010;31(10):484-496.

36. Willett WC, Manson JE, Stampfer MJ, et al. Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. *JAMA.* 1995;273(6):461-465.

37. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med.* 2002;347(5):305-313.

38. Cooper SJ, Reynolds GP, Barnes TRE, et al. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. *Journal of Psychopharmacology.* 2016;30(8):717-748.

39. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol.* 1998;81(4a):7b-12b.

40. Tirosh A, Shai I, Bitzur R, et al. Changes in Triglyceride Levels Over Time and Risk of Type 2 Diabetes in Young Men. *Diabetes Care.* 2008;31(10):2032-2037.

41. Pillinger T, Beck K, Gobjila C, Donocik JG, Jauhar S, Howes OD. Impaired Glucose Homeostasis in First-Episode Schizophrenia: A Systematic Review and Meta-analysis. *JAMA Psychiatry.* 2017;74(3):261-269.

42. Pillinger T, D'Ambrosio E, McCutcheon R, O DH. Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models. *Mol Psychiatry.* 2018.

43. Pillinger T, Beck K, Stubbs B, Howes OD. Cholesterol and triglyceride levels in first-episode psychosis: systematic review and meta-analysis. *Br J Psychiatry.* 2017;211(6):339-349.

44. Tiihonen J, Lonnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet.* 2009;374(9690):620-627.