Glucagon-like peptide-1 receptor-agonists for antipsychotic-associated cardio-metabolic risk factors: a systematic review and individual participant data meta-analysis

Authors:
Dan Siskind[*1,2]
Margaret Hahn[3,4]
Christoph U. Correll[5,6,7]
Anders Fink-Jensen[8,9]
Anthony W. Russell[2,10]
Nikolaj Bak[11]
Brian V. Broberg[11]
Julie Larsen[8,12]
Pelle L. Ishøy[11]
Tina Vilsbøll[9,13]
Filip K. Knop[9,13,14]
Steve Kisely[1,2]
Bjørn H. Ebdrup[9,11]

1 Metro South Addiction and Mental Health Service, Brisbane, Australia
2. University of Queensland, School of Medicine, Brisbane, Australia
3. Centre for Addiction and Mental Health, Toronto, ON, Canada
4. University of Toronto, Department of Psychiatry, Toronto, ON, Canada
5 The Zucker Hillside Hospital, Department of Psychiatry, Northwell Health, Glen Oaks, NY, USA
6 Hofstra Northwell School of Medicine, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA
7 Charité Universitätsmedizin, Department of Child and Adolescent Psychiatry, Berlin, Germany
8. Psychiatric Centre Copenhagen, Rigshospitalet, Mental Health Services - Capital Region of Denmark, Copenhagen, Denmark
9. Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
10. Princess Alexandra Hospital, Brisbane, Australia
11. Centre for Neuropsychiatric Schizophrenia Research & Centre for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Mental Health Centre Glostrup, University of Copenhagen, Copenhagen, Denmark
12. Novo Nordisk A/S, Research and Development, Søborg, Denmark

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13. Clinical Metabolic Physiology, Steno Diabetes Center Copenhagen, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark
14. Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

* Corresponding Author
c/- MIRT
Level 2 Mental Health
228 Logan Rd
Woolloongabba, Qld, 4102
Australia
Ph +61-7-3317-1040
Email d.siskind@uq.edu.au

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Abstract (Current 215. Max 250)

Objective: Patients with schizophrenia have higher cardio-metabolic risk, partially from antipsychotic-induced weight-gain. Glucagon-like-peptide-1 receptor-agonists (GLP-1RAs) may reduce antipsychotic-associated weight-gain, however, safety and efficacy in schizophrenia has not been systematically reviewed.

Materials and Methods: We systematically searched PubMed/EMBASE/PsycINFO/Cochrane, using the search terms "(antipsychotic and GLP-1RA)". Individual participant data from studies randomizing patients to GLP-1RA or control were meta-analysed. Primary outcome was difference in body weight between GLP-1RA and control; secondary outcomes included cardio-metabolic parameters and adverse drug reactions (ADRs). Multiple linear regression was conducted including sex, age, psychosis severity, metabolic parameter, ADRs, and GLP-1RA-agent.

Results: Three studies (exenatide once-weekly=2; liraglutide once-daily=1) provided participant-level data (n=164, age=40.0±11.1years, weight=105.8±20.8kg). After 16.2±4.0 weeks of treatment, weight loss was 3.71 kg (95% CI=2.44-4.99 kg) greater for GLP-1RA vs. control ($p<0.001$), number-needed-to-treat ≥5% weight-loss=3.8 (95%CI=2.6-7.2). Waist, BMI, HbA1c, fasting-glucose and visceral-adiposity were each significantly lower with GLP-1RA. Sex, age, psychosis severity, nausea, any ADR, and GLP-1RA-agent did not significantly impact outcomes. Weight loss with GLP-1RAs was greater for clozapine-/olanzapine-treated patients (n=141) than other antipsychotics (n=27) (4.70kg, 95%CI=3.13-6.27 vs 1.5kg 95%CI=-1.47-4.47) ($p<0.001$). Nausea was more common with GLP-1RAs than control (53.6% vs 27.5%, $p=0.002$, number-needed-to-harm=3.8).

Conclusion: GLP-1RAs are effective and tolerable for antipsychotic-associated weight-gain, particularly clozapine-/olanzapine-treated patients. With few included

patients, further studies are required before making routine use recommendations for GLP-1RAs.

Keywords: GLP-1RAs, Obesity, Weight Loss, Antipsychotics, Schizophrenia, Cardiovascular Risk

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Background

The life expectancy for patients with schizophrenia is over 14-20 years shorter than for the general population[1, 2], with 35% of excess deaths attributable to cardiovascular disease and diabetes[3]. Patients with schizophrenia are at increased risk of developing cardio-metabolic disease, mediated by or coincident with obesity, for several reasons including a genetic predisposition for developing diabetes, reduced physical activity, poor diet and the use of antipsychotic medications[4, 5].

Although the underlying mechanisms have not been fully elucidated, it is well-established that antipsychotic medications can lead to obesity with clozapine and olanzapine having the greatest propensity for weight gain[6]. Among patients with schizophrenia, about half of those on clozapine and a third of those on olanzapine have metabolic syndrome [7].

Body weight gain is associated with poorer quality of life[8], reduced social engagement[9], and is the most distressing side-effect reported to mental health helplines[10]. Weight gain also reinforces patients' negative views of themselves and may compromise adherence with treatment[10]. Furthermore, being overweight or obese increases the risk of all-cause mortality with an association between weight and higher mortality risk[11, 12].

The current evidence for interventions addressing antipsychotic-associated obesity is limited. Physical activity interventions are compromised by low rates of uptake and acceptability[13], while many pharmacological treatments can result in unacceptable adverse events[14]. For instance, sibutramine was withdrawn because of cardiovascular risks[15], while in the case of rimonabant it was removed because of increased risk of depression, anxiety and suicide[16]. Orlistat is associated with poor adherence due to steatorrhoea [17]. Finally, there is only modest (and heterogeneous) weight loss following the addition of metformin[18, 19] or topiramate[20] for obese and overweight patients on antipsychotics and/or those at risk for antipsychotic weight gain[14].

As a result of these limitations, there has been increasing interest in glucagon-like peptide-1 receptor agonists (GLP-1RAs) to counteract the weight gain associated with antipsychotic treatment in general [21] and clozapine and olanzapine treatment in particular [22, 23]. Glucagon-like peptide-1 (GLP-1) is an endogenous peptide, synthesised in the intestinal mucosa[24], which stimulates insulin secretion and decreases glucagon secretion in a glucose-dependent manner. It also delays gastric emptying and lowers food intake by promoting satiety[25].

GLP-1RAs have well-established glucose and weight lowering properties in patients with[23] and without[26] type 2 diabetes (T2DM). GLP-1RA treatment is also associated with a lower risk of major adverse cardiovascular endpoints (composite endpoint including cardiovascular-related mortality, non-fatal myocardial infarction, and non-fatal stroke)[27]. In addition to daily injections, several GLP-1RAs are now available as weekly injections, which may improve adherence among patients with schizophrenia.

To our knowledge prior to conducting the comprehensive systematic review, at least three individual trials investigating the effect of GLP-1RAs (exenatide once-weekly or liraglutide once-daily) on antipsychotic-associated obesity[28-30] had been published. A meta-analysis of participant-level data has the potential to identify whether the effects of GLP-1RAs vary for different antipsychotics and also examine the influence of more clinically relevant participant-related factors than is possible in a meta-analysis of study-level data.

Aims of the Study

We aimed to test the hypotheses that:

- GLP-1RAs would be superior to the control conditions for weight loss, as well as all other anthropometric and cardiometabolic outcomes.

- Patients treated with clozapine or olanzapine, would experience greater weight loss with GLP-1RAs.

Material and Methods

Protocol and registration. This study was registered with PROSPERO (CRD42017079791)[31]. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for the background, search strategy, methods, results, discussion and conclusions[32]. Ethical approval was not required as all the included data had been previously published.

Search Strategy. The following databases were searched from inception to 24 October 2017: PubMed, PsycInfo, Embase, the Cochrane Schizophrenia Group's Trials Register. Hand searches of references listed in included studies and other key publications were also conducted. Studies were limited to humans. Search terms included terms for antipsychotics and GLP-1RAs. There were no language limitations. PubMed search terms are provided in Supplemental Table 1.

Eligibility criteria & Study selection. We included all randomised controlled trials of patients on antipsychotic medications who were overweight or obese where a GLP-1RA was compared to placebo or usual care. All studies were independently screened at the title and abstract level by two authors (DS and MH). Studies that met the inclusion criteria on title and abstract review, or that could not be excluded on the basis of information provided in the abstract were reviewed at full text level.

Data collection process. Authors of the included studies provided access to de-identified individual participant data. Key authors of the included studies are also co-authors of this meta-analysis. These data were collated and analysed with validation by the corresponding authors of the included studies. Quality assessment was conducted by an author not involved in the included studies (MH).

Outcomes. The primary outcome was the difference in endpoint weight adjusted for baseline weight and study between GLP-1RA arm and control arm. We analysed the following secondary outcomes in the same way: metabolic syndrome components (waist circumference, blood pressure (BP), high density lipoprotein (HDL), low density lipoprotein (LDL) cholesterol, triglycerides (TG), and fasting plasma glucose (FPG)), BMI, HbA1c, homeostatic model assessment (HoMA), insulin, visceral fat, and android-to-gynoid ratio (android adipose tissue surrounds the abdomen, chest, shoulder and nape of the neck, while gynoid adipose tissue surrounds the hips, breasts and thighs).

Psychosis severity for individual patients was based on published inter-scale linkage thresholds for the PANSS, BPRS and GCI[33, 34],

Study quality. We assessed study quality, using criteria adapted from the Cochrane Collaboration guidelines[32]: 1) selection bias (random sequence generation and allocation concealment); 2) performance bias; 3) detection bias; 4) attrition bias; 5) reporting bias, and; 6) other sources of potential bias including pharmaceutical company funding. Studies were deemed to be of low-quality if they had three or more elements with high risk of bias, while those of high-quality had four or more elements with a low risk of bias.

Statistical Analyses. We conducted a one-step meta-analysis on individual participant data, where data from all included studies were modelled simultaneously, while adjusting for clustering of patients within included studies[35]. The primary and secondary outcomes were analysed as differences in endpoint values between intervention and control, adjusted for baseline value and study as a random effect, using ANCOVA with Bonferroni correction on SPSS Version 24 for Mac OS. Where individual patient data were missing, we used the modified intention-to-treat model[29], where the last valid value after the baseline value was carried forward.

We performed multiple linear regressions with endpoint variable as the dependent variable, including the baseline variable, and, respectively, each of the following co-variables: demographics (age, sex), psychosis severity, metabolic variables (weight, BMI, waist circumference, HbA1c, fasting blood glucose, HDL, LDL, triglycerides, systolic blood pressure (SBP), diastolic blood pressure (DSP), HoMA, insulin) and treatment variables (treatment arm, nausea, any adverse drug reaction and GLP-1RA agent). If any covariates were significant, they were all included in a multiple linear regression, using backward elimination. Adjusted R^2 of the final model was calculated.

We conducted sensitivity analyses to explore the impact of the specific antipsychotic used (patients on clozapine and/or olanzapine versus patients on other antipsychotics) on treatment arm and endpoint metabolic variables, adjusted for the baseline variable and conducted a meta-analysis for each metabolic variable using RevMan 5.3. We also did a sensitivity analysis by excluding patients with T2DM.

Chi-Square tests were conducted on the proportion of patients in the GLP-1RAs and control groups who achieved ≥5% and ≥7% weight loss. Number-needed-to-treat was calculated for the proportion of patients with ≥5% or ≥7% weight loss by dividing 1 by the risk difference.

BMI was categorised into WHO Categories (Overweight 25-29.9, Obese Class I 30-34.9, Obese Class II 35-39.9, Obese Class III 40 and above)[36], and the proportion of GLP-1RA treated patients and controls, who shifted between categories from baseline to endpoint was analysed using a chi-square test.

FPG was categorise into ADA categories (normoglycaemic <5.6 mmol/l, impaired fasting plasma glucose 5.6-6.9 mmol/l, T2DM >6.9 mmol/l). Chi-Square tests between baseline and endpoint FPG categories were conducted for total participants, and those in the GLP-1RA and control arms.

Adverse Drug Reactions were compared between treatment and control groups using Chi-Square tests, with data available on nausea, diarrhoea, vomiting, other adverse drug reactions and any adverse drug reaction, and a number-needed-to-harm was calculated for ADRs that were significantly different between GLP-1RAs and Control by dividing 1 by the risk difference. A regression analysis for weight, adjusted for baseline weight, study and nausea, was conducted to assess any potential impact of nausea as a mediating factor in weight change.

Publication Bias. If the meta-analyses included 10 or more studies, we planned to test for publication bias using funnel plot asymmetry where low P values suggest publication bias [37].

Results

Study selection. Our search identified 56 unique articles. Of these, 43 were excluded at title and abstract level, leaving 13 articles for review at full text level. Three articles met inclusion criteria[28-30] with a total of 168 patients (GLP-1RA=84, Control=84). Reasons for exclusion at full text level are provided in *Supplementary Figure 1 PRISMA Diagram, and Supplementary Table 2 Table of Excluded Studies*.

Study characteristics. Studies were conducted in Denmark (n=2) and in Australia (n=1) (Table 1 Included Studies). Duration ranged from 12 to 24 weeks (mean 16.2 weeks, SD 4.0). Two studies used exenatide 2 mg s.c. once-weekly[28, 30] , and one study used liraglutide 1.8 mg s.c. once-daily[29], the standard maximum doses used for diabetes[38]. All studies examined GLP-1RA for people on antipsychotic medications, with no notable changes in antipsychotic doses among participants. One study was restricted to participants receiving clozapine and olanzapine[29], and another to clozapine alone[30]. The third study included a naturalistic patient sample treated with clozapine, olanzapine, aripiprazole, risperidone, paliperidone, quetiapine, ziprasidone, amisulpride and sertindole[28]. After initial publication, an erratum on corrected metabolic blood markers was published for the third study, and these data were used in the current meta-analysis [39]. Two studies were blinded and placebo-controlled[28, 29], while the third was open label[30]. All studies were of adults aged 18-65 (mean age= 40.0 years, SD 11.1), 58.3% were male, and the mean BMI of participants was 35.4 kg/m^2 (SD 5.7). All studies included patients with schizophrenia, while two also included schizoaffective disorder[28, 30]. One study also included patients with T2DM[30], while the other two specifically excluded T2DM[28, 29]. One study required patients to have impaired glucose tolerance[29]. All studies provided data on body weight, BMI, fasting glucose, HDL, triglycerides, systolic and diastolic blood pressure and HbA1c. Two studies provided data on insulin and HoMA[29, 30], and two on android/gynoid ratio and visceral adiposity[28, 29]. Two studies (n= 97 and n=28) showed significant effect on their primary outcome[29, 30], while the third one (n=43) was equivocal[28]. Baseline characteristics of the combined dataset are provided in Table 1 Included Studies. All studies were rated to be of high quality *(Supplementary Table 3 Risk of Bias)*.

Primary Outcome

The mean adjusted difference in endpoint body weight between intervention and control groups was 3.71 kg lower for the intervention groups (95% CI: 2.44kg to 4.99) (Table 3 Outcomes). This was a statistically significant difference for treatment arm ($p<0.001$), but not for study ($p=0.430$).

Secondary Outcomes

Reductions in waist circumference, BMI, HbA1c, FPG, LDL and visceral fat were all significantly different between treatment and control (p values <0.001 to 0.03). Lower LDL and diastolic blood pressure were associated with study effect (Table 3).

Linear Regression

Treatment arm and the baseline variable were statistically significant in the multiple linear regressions of endpoint body weight, BMI and HbA1c (Supplementary Appendix A). Treatment arm, the baseline variable and the additional metabolic variable(s) provided in brackets were statistically significant for endpoint waist circumference (baseline weight), endpoint FPG (baseline HbA1c), endpoint LDL (baseline triglycerides), endpoint triglycerides (baseline waist circumference) and endpoint visceral fat (baseline insulin).

The variables (in brackets) were significantly associated with the outcome however, treatment type was not associated with changes in the following variables: endpoint HDL (baseline HDL), endpoint SBP (baseline SBP and DBP), DBP (baseline DBP and android/gynoid ratio), HoMA (baseline insulin and visceral fat) insulin (baseline insulin and visceral fat) and android/gynoid ratio (baseline android/gynoid ratio and triglycerides).

Age, sex, psychosis severity, baseline SBP, nausea, any adverse drug reaction and GLP-1RA agent were not significant in any of the linear regressions of endpoint variables. Adjusted R^2 for the multiple linear regressions ranged from 0.284 for SBP to 0.958 for body weight (Supplementary Appendix A).

Sensitivity Analyses

For the sensitivity analysis by antipsychotic, patients on clozapine and/or olanzapine (n=141) had a statistically significant reduction in body weight with GLP-1RAs (4.70kg, 95% CI 3.13kg to 6.27), while those on other antipsychotics (n=27) did not have statistically significant change in body weight (1.5kg 95%CI=1.47-4.47). The difference between these two groups was statistically significant (p<0.001). This pattern of statistically significant change in metabolic variables among patients on clozapine and/or olanzapine, but not other antipsychotics, was also seen for waist circumference, BMI, FPG and visceral fat. Both patients on clozapine and/or olanzapine, and those on other antipsychotics had a statistically significant reduction in HbA1c. (Figure 1 Forest Plot of Standardised Mean Difference of Metabolic Variables by Antipsychotic & Supplementary Table 4 Mean Difference in Metabolic Variables by Antipsychotic). When patients only on clozapine were examined (n=113), they had a 4.90 kg greater weight loss (95%CI=3.16-6.64) with GLP-1RAs compared to controls. When patients only on olanzapine were examined (n=25), they had a 4.70 kg greater weight loss (95%CI=1.15-8.25) with GLP-1RAs compared to controls. The difference in comparative weight loss between clozapine and olanzapine was not statistically significant (p=0.845).

When patients with T2DM were excluded, reduction in body weight with GLP-1RAs remained statistically significant (3.85kg, 95% CI 2.54kg to 5.15).

Percentage Change in Body Weight

A significantly greater proportion of patients on GLP-1RA treatment than controls had a weight loss of ≥5% (36.9% vs 10.7% $p<0.001$) and ≥7% (19.0% vs 6.0% $p=0.010$). The number-needed-to-treat (NNT) to achieve ≥5% weight loss was 3.8 (95%CI=2.6 to 7.2), while for ≥7% the NNT was 7.7 (95%CI=4.4 to 31.8).

Shift in BMI category

Among patients on GLP-1RAs, 15 (17.9%) shifted down a BMI category, 69 (82.1%) remained in the same category and none increased a category, while among controls seven (8.4%) shifted down a category, 72 (86.7%) remained in the same category, and four (2.4%) increased a category (Ç^2 6.967, 2 degrees of freedom, $p=0.031$). (*Supplementary Table 5 BMI category shift)*

Shift in FPG category

Among those with impaired fasting glucose, 26 of 38 (68.4%) participants on GLP-1RAs had normal fasting plasma glucose at endpoint, while only 9 of 38 (23.7%) participants in the control arms normal fasting plasma glucose at endpoint. Changes in fasting blood plasma categories are provided in *Supplementary Table 6.*

Adverse Events

Patients on GLP-1RAs reported significantly more nausea compared to controls (53.6% vs 27.5%, $p=0.002$), with a number needed to harm of 3.8 (95%CI 2.4 to 9.7). Neither the presence of any adverse drug reaction (76.8%% vs 62.9% $p=0.073$), diarrhoea, vomiting, nor other adverse drug reactions were significantly different between the two groups *(Supplementary Table 7 Adverse Drug Reactions)*. Nausea did not significantly impact the regression model for weight.

Publication Bias. We were unable to assess publication bias, as no analyses included ten or more studies.

Discussion

This systematic review and patient-level meta-analysis suggests that GLP-1RAs can induce a clinically meaningful weight loss in patients with schizophrenia on antipsychotic medications who are overweight or obese. Patients in the intervention arm lost 3.7 kg more weight than controls. The NNT to achieve a weight loss of at least 5% (considered clinically meaningful) was 3.8, while for loss of at least 7%, the NNT was 7.7. GLP-1RA treatment was also associated with greater reductions in BMI, fasting glucose, HbA1c and visceral fat. Weight loss was greatest for those on clozapine and/or olanzapine compared to other antipsychotics. Age, sex, psychosis severity, nausea, any adverse drug reaction and GLP-1RA agent did not affect body weight or other metabolic variables.

In terms of adverse events, nausea was more common in the GLP-1RA group, but was not associated with greater weight loss, and thus unlikely to explain the findings. Antipsychotics, including clozapine and olanzapine, have antiemetic properties[40, 41] which may have mitigated this adverse event. In addition, GLP-1RAs are not hepatically metabolised by cytochrome P450, and as such unlikely to interfere with elimination of antipsychotics[42].

Our findings are consistent with data in non-psychiatrically ill patients with[23] and without type 2 diabetes[26]. There is increasingly acknowledgement of the role of GLP-1RAs as a efficacious pharmacological management strategy for the management of obesity, with suggestions that they are under-utilised in the general population [43].

Our finding of a reduction in visceral adiposity is also important, as this is an independent risk factor for cardiovascular disease[44], diabetes [45] and death [46]. This is particularly relevant in schizophrenia where antipsychotic use is both associated with increases in visceral fat and subsequent metabolic syndrome[47].

The improvements in fasting glucose and HbA1c associated with GLP-1RA treatment are also of clinical importance, given the high rates of glucose intolerance (55%) and impaired fasting glucose (21%) in patients on clozapine or other second-generation antipsychotics[48, 49]. Over one third of patients on clozapine develop type 2 diabetes[50]. In turn, there is a higher mortality among those with serious mental illness and type 2 diabetes than those diagnosed with either type 2 diabetes alone, or serious mental illness alone[51, 52]. This finding highlights the advantages of weight loss medications that are also approved anti-hyperglycaemic drugs with demonstrated reductions in cardiovascular mortality in patients with high risk T2DM[27].

Differences in endpoint weight between GLP-1RA treatment and control interventions were greater for patients on clozapine and/or olanzapine, which is consistent with pre-clinical findings on olanzapine's and clozapine's disruption of the GLP-1RA-pathway[22]. This result is important, as clozapine remains the only antipsychotic indicated for patients with treatment resistant schizophrenia, and has the best evidence for managing positive symptoms[53] and reducing hospitalisations[54] in this population. Weight gain can be both a barrier to commencement of clozapine and a reason for its discontinuation. Our finding of a body weight loss of almost 5kg more than in the control group among patients on clozapine was significantly greater than that reported for metformin in a recent meta-analysis of people on clozapine[55] (-3.1 kg 95%CI -4.9 to -1.4) (p=0.024). The potential superiority of GLP-1RAs over metformin is also supported by pre-clinical models. For instance, GLP-1RAs normalise glucose tolerance and decrease body weight in rats treated with clozapine, providing mechanistic justification of their therapeutic potential in this context[22]. By contrast, metformin only partially attenuates glucose dysregulation in animal models of antipsychotic metabolic abnormalities[56]. To date, there have been no head-to-head studies of GLP-1RAs versus metformin on body weight loss among overweight patients on antipsychotics.

We were not able to include data on non-alcoholic fatty liver disease (NAFLD). NAFLD is a precursor for the development of incident T2DM and metabolic syndrome [57] and has a mutual and bi-directional relationship with these disease entities [58], There is recent evidence for the efficacy of liraglutide for non-alcoholic steatohepatitis [59]. Future studies of GLP-1RAs should include measures of NAFLD.

A key strength of this study is the use of individual participant data. This approach allowed for consistent analytic techniques across studies, notably endpoint values adjusted for baseline values, as recommended by the European Medicines Agency[60]. It also allowed sensitivity analyses by specific variables, notably antipsychotic, age, sex and study duration, and for correlations between change in BMI and baseline BMI.

There are also limitations to this study. There were differences in study inclusion criteria. Although all studies used overweight or obesity as inclusion criteria, one study specifically recruited patients with pre-diabetes, while another also included patients with T2DM. Only one study included patients who were not on clozapine nor olanzapine, and these patients may have differed in baseline characteristics. This limits both the power and the certainty of differences in the effect of GLP-1RAs on patients who were not on clozapine or olanzapine. One study was not blinded, increasing the risk of bias, however sensitivity analysis by removal of this study did not markedly change the outcomes. It is unclear why diastolic blood pressure and HDL cholesterol were significantly different due to study effect, but this result may have been related in part to the pre-diabetes entry criteria of the one study of liraglutide[29]. None of the included studies could report whether the weight gain was specifically due to antipsychotic use. The included studies did not use easily comparable psychotic symptom rating scales, making psychotic symptoms impractical to assess as an outcome. Study durations were too short to evaluate comparative risks of major adverse cardiovascular endpoints. We were only able to include 168 patients from three studies, which limits our ability to draw firm conclusions or infer clinical recommendations. We do not have data for older participants, and as such these results can not be generalised to older adults on antipsychotic medications. Further studies are required in this population.

In conclusion, our findings suggest a promising role for GLP-1RA treatment for weight management in patients with schizophrenia treated with clozapine or olanzapine, however there is insufficient data to comment on the role of GLP-1RAs for those on other antipsychotics. GLP-1RA agents are also well-tolerated with nausea being the most common adverse drug reaction. The availability of a once-weekly injectable formulation may also offer advantages when compared to traditional weight loss or diabetic medications requiring daily administration. However, obviously, the availability of an oral formulation would increase the ease of use. While several weight loss agents have been withdrawn due to cardiac adverse effects , GLP-1RAs are associated with lowering of cardiovascular mortality[27]. Our findings also suggest ancillary improvements in glucose homeostasis and visceral adiposity. While our data suggest that individuals taking clozapine or olanzapine may benefit most from GLP-1RAs with a less compelling argument for the use of GLP-1RAs for patients on other antipsychotics, this conclusion should be tempered by the fact that only one study included patients on antipsychotics other than clozapine and olanzapine. Further randomised clinical trials of GLP-1RAs in overweight or obese antipsychotic-treated patients with schizophrenia are required, particularly head-to-head trials comparing metformin and GLP-1RAs.

Conflicts of Interest

DS, BB and PI have no interests to declare. SK has received speaker honoraria from Janssen. AFJ has received an unrestricted research grant from Novo Nordisk. AR has received speaker honoraria and travel grants from Astra Zenica, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk and Sanofi and has participated on advisory panels for MSD and Novo Nordisk. MKH has participated on an advisory board for Alkermes. TV has no conflicts of interest to declare. FKK has served on scientific advisory panels and/or Speaker's Bureaus for, served as a consultant to and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Gubra, MSD/Merck, Novo Nordisk, Sanofi and Zealand Pharma. BE has received lecture fees and/or is part of Advisory Boards of Bristol-Myers Squibb, Eli Lilly and Company, Janssen-Cilag, Otsuka Pharma Scandinavia and Takeda Pharmaceutical Company. CUC has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Angelini, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, Medavante, Medscape, Merck, Neurocrine, Otsuka, Pfizer, ROVI, Servier, Sunovion, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, ROVI and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a shareholder of LB Pharma. JRL and BVB became a full-time employee at Novo Nordisk after completion of the clinical studies included in the meta-analysis. NB became a full-time employee at Lundbeck after completion of the clinical studies included in the meta-analysis.

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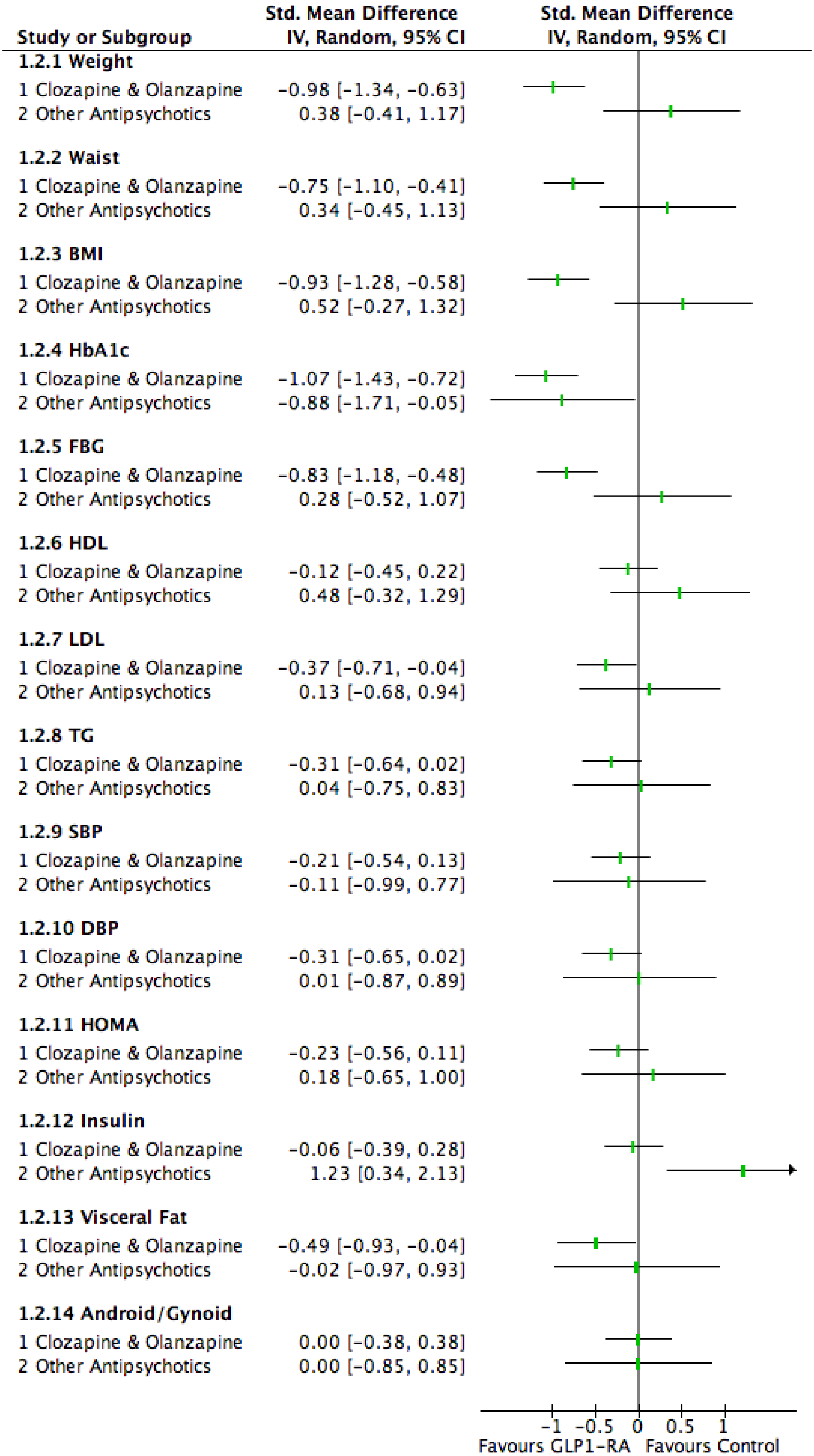
Figure 1. Forest Plot of Standardised Mean Difference of Metabolic Variables by Antipsychotic


Study or Subgroup
Std. Mean Difference IV, Random, 95% CI
Std. Mean Difference IV, Random, 95% CI
1.2.1 Weight
1 Clozapine & Olanzapine -0.98 [-1.34, -0.63]
2 Other Antipsychotics 0.38 [-0.41, 1.17]
1.2.2 Waist
1 Clozapine & Olanzapine -0.75 [-1.10, -0.41]
2 Other Antipsychotics 0.34 [-0.45, 1.13]
1.2.3 BMI
1 Clozapine & Olanzapine -0.93 [-1.28, -0.58]
2 Other Antipsychotics 0.52 [-0.27, 1.32]
1.2.4 HbA1c
1 Clozapine & Olanzapine -1.07 [-1.43, -0.72]
2 Other Antipsychotics -0.88 [-1.71, -0.05]
1.2.5 FBG
1 Clozapine & Olanzapine -0.83 [-1.18, -0.48]
2 Other Antipsychotics 0.28 [-0.52, 1.07]
1.2.6 HDL
1 Clozapine & Olanzapine -0.12 [-0.45, 0.22]
2 Other Antipsychotics 0.48 [-0.32, 1.29]
1.2.7 LDL
1 Clozapine & Olanzapine -0.37 [-0.71, -0.04]
2 Other Antipsychotics 0.13 [-0.68, 0.94]
1.2.8 TG
1 Clozapine & Olanzapine -0.31 [-0.64, 0.02]
2 Other Antipsychotics 0.04 [-0.75, 0.83]
1.2.9 SBP
1 Clozapine & Olanzapine -0.21 [-0.54, 0.13]
2 Other Antipsychotics -0.11 [-0.99, 0.77]
1.2.10 DBP
1 Clozapine & Olanzapine -0.31 [-0.65, 0.02]
2 Other Antipsychotics 0.01 [-0.87, 0.89]
1.2.11 HOMA
1 Clozapine & Olanzapine -0.23 [-0.56, 0.11]
2 Other Antipsychotics 0.18 [-0.65, 1.00]
1.2.12 Insulin
1 Clozapine & Olanzapine -0.06 [-0.39, 0.28]
2 Other Antipsychotics 1.23 [0.34, 2.13]
1.2.13 Visceral Fat
1 Clozapine & Olanzapine -0.49 [-0.93, -0.04]
2 Other Antipsychotics -0.02 [-0.97, 0.93]
1.2.14 Android/Gynoid
1 Clozapine & Olanzapine 0.00 [-0.38, 0.38]
2 Other Antipsychotics 0.00 [-0.85, 0.85]
-1
-0.5
0
0.5
1
Favours GLP1-RA
Favours Control

HbA1c - haemoglobin A1c
FPG - Fasting Plasma Glucose
HDL – High Density Lipoprotein Cholesterol
LDL – High Density Lipoprotein Cholesterol
TG – Triglycerides
SBP – Systolic blood pressure
DBP – Diastolic blood pressure
HOMA – Homeostatic Model Assessment

Table 1 Table of Included Randomized Studies

Author year	Location	Duration	Key Inclusion criteria	GLP-1-RA Agent	frequency	Control	Included antipsychotics	Number of Participants (GLP-1-RA / Control)	% completed (GLP-1-RA / Control)	Gender (male %) (GLP-1-RA / Control)	Age (mean (SD)) (GLP-1-RA / Control)
Ishoy et al 2017	Denmark	12 weeks	18-65 years old Schizophrenia and Schizoaffective disorder BMI >30 No T2DM	Exenatide 2mg s/c weekly	weekly	placebo	clozapine, olanzapine, aripiprazole, risperidone, paliperidone, quetiapine, ziprasidone, amisulpride and sertindole	23 / 20	95.7% / 90%	47.8% / 45.0%	37.1 (10.7) / 34.4 (10.6)
Larsen et al 2017	Denmark	16 weeks	18-65 years old Schizophrenia BMI >27 FPG 6.1 – 6.9mmol/L or OGTT >140mg/dl No T2DM	Liraglutide 1.8mg s/c daily	daily	placebo	Clozapine and olanzapine	47 / 50	95.7% / 100%	63.8% / 60.0%	42.1 (10.7) / 43.0 (10.5)
Siskind et al 2017	Australia	24 weeks	18-65 years old Schizophrenia and Schizoaffective	Exenatide 2mg s/c weekly	weekly	Usual care	Clozapine	14 / 14	100% / 100%	78.6% / 50.0%	39.9 (14.0) / 35.7 (8.2)

			disorder BMI 30-45 +/- T2DM								
TOTAL		Mean 16.2 weeks SD 4.0 weks						84 / 84	96.4% / 97.6%	61.9% / 54.8%	40.3 (11.4) / 39.7 (10.8)

s/c = sub cutaneous
BMI – Body Mass Index
FPG – Fasting Plasma Glucose
T2DM – Type 2 Diabetes Mellitus
OGTT – Oral Glucose Tolerance Test

Table 2 – Baseline Characteristics

	N	Mean	SD
Age	168	40.0	11.1
Weight (kg)	168	105.8	20.8
BMI kg/m^2	168	35.4	5.7
Waist Circumference (cm)	167	119.1	13.9
HbA1c (IFCC)	168	36.7	4.7
FPG (mmol/L)	168	5.7	0.7
HDL (mmol/L)	168	1.1	0.3
LDL (mmol/L)	166	3.0	1.0
TG (mmol/L)	168	2.4	1.4
SBP (mmHg)	167	125.5	12.0
DBP (mmHg)	167	82.6	9.6
HOMA	167	6.7	3.3
Insulin (pmol/L)	167	182.0	83.4
Visceral Fat (gm)	110	2061.4	914.2
Android Gynoid ratio	138	1.2	0.2
Sex (Male)	168	n=98	58.3%

HbA1c - haemoglobin A1c (NGSP=(0.09148*IFCC)+2.152).
IFCC - International Federation of Clinical Chemistry
NGSP - National Glycohemoglobin Standardization Program
FPG - Fasting Plasma Glucose (mg/dL = mmol/l*18)
HDL – High Density Lipoprotein Cholesterol (mg/dL = mmol/l*38.6)
LDL – High Density Lipoprotein Cholesterol (mg/dL = mmol/l*38.6)
TG – Triglycerides (mg/dL = mmol/l*88.5)
SBP – Systolic blood pressure
DBP – Diastolic blood pressure
HOMA – Homeostatic Model Assessment
Insulin (mU/L = pmol/L * 0.144)

Table 3 Outcome data

Variable*	N	Mean Difference GLP-1RA vs control	SE	Treatment effect		Study Effect	
				F value	p-value	F value	p-value
Weight (kg)	168	-3.71	0.65	33.19	<0.001	0.85	0.430
Waist (cm)	167	-3.00	0.68	19.24	<0.001	2.05	0.132
BMI (kg/m^2)	168	-1.19	0.22	30.25	<0.001	1.13	0.326
HbA1c (IFCC)	166	-3.25	0.66	24.54	<0.001	1.28	0.281
FPG (mmol/L)	166	-0.45	0.09	24.89	<0.001	1.54	0.218
HDL (mmol/L)	166	-0.01	0.02	0.33	0.566	2.92	0.034
LDL (mmol/L)	162	-0.17	0.08	4.82	0.030	3.10	0.048
TG (mmol/L)	166	-0.24	0.12	3.73	0.055	0.68	0.508
SBP (mmHg)	160	-1.89	1.61	1.39	0.241	0.94	0.392
DBP (mmHg)	160	-1.91	1.17	2.68	0.104	5.84	0.004
HOMA	163	-0.58	0.59	0.96	0.328	1.98	0.142
Insulin (pmol/L)	163	4.59	12.93	0.13	0.723	1.65	0.196
Android/gynoid ratio	131	-0.006	0.014	0.16	0.692	0.002	0.963
Visceral fat (gm)	97	-177.51	68.71	6.67	0.011	2.92	0.091

* ANCOVA endpoint value adjusted for baseline value and study.
HbA1c - haemoglobin A1c (NGSP=(0.09148*IFCC)+2.152).
IFCC - International Federation of Clinical Chemistry
NGSP - National Glycohemoglobin Standardization Program
FPG - Fasting Plasma Glucose (mg/dL = mmol/l*18)
HDL – High Density Lipoprotein Cholesterol (mg/dL = mmol/l*38.6)
LDL – High Density Lipoprotein Cholesterol (mg/dL = mmol/l*38.6)
TG – Triglycerides (mg/dL = mmol/l*88.5)
SBP – Systolic blood pressure
DBP – Diastolic blood pressure
HOMA – Homeostatic Model Assessment
Insulin (mU/L = pmol/L * 0.144)