Efficacy and acceptability of pharmacological interventions for the treatment of antipsychotic-related weight gain and metabolic abnormalities

A systematic review and network meta-analysis

Abstract

Antipsychotic treatment (AP) is associated with metabolic abnormalities including weight gain. Targeting AP-associated weight gain, several pharmacological interventions have been investigated. Nevertheless, there is barely evidence for comparative efficacy and acceptability of these interventions. In this study, we will systematically review evidence for weight loss reducing agents in AP-medicated patients and compare outcomes of interventions in terms of efficacy and acceptability. Only blinded, randomized controlled studies of adjunctive agents for weight loss reduction in AP-medicated patients will be included. Pooled data will be analysed using a network meta-analysis. The primary outcomes will be measured as the mean difference for weight change and as odds ratio for treatment discontinuations due to any cause. Further analyses will encompass an additive model to evaluate the influence of components such as lifestyle counselling, exercise and diet. Subgroup, meta-regression and sensitivity analyses will focus on the impact of factors such as age, sex, body mass index, AP dose and type of AP. Results will be published in a peer-reviewed journal.

Introduction

Although older reports are available, the study of weight gain related to antipsychotics has been particularly extensive in the past two decades. Almost all widely prescribed antipsychotics have been related to weight gain (1-4). This association is of particular clinical interest as it is connected to major health risks (5, 6). The mortality gap is a term established to described the reduced life expectancy in patients with severe mental illnesses compared to the general population (7, 8). There are various factors linked to this excess mortality; lifestyle aspects, such as smoking, unhealthy eating and lack of physical exercise seem to have a crucial impact (9, 10). The role of antipsychotics with their adverse weight and metabolic effects is also related to physical health risk factors (11). When dealing with antipsychotic-associated weight gain, various types of interventions including pharmacological agents have been investigated. Several of these agents have received considerable attention. Nevertheless, no head-to-head comparisons are available and these strategies are often off-label. Thus, there is the need to provide evidence about the comparative efficacy and acceptability of these pharmacological interventions as well as the confounding factors affecting treatment response.

Aim of this study is to systematically review evidence for pharmacologic interventions targeting cardiometabolic abnormalities in antipsychotic-treated patients and compare efficacy and acceptability of these interventions.

Methods

Search strategy

We will perform a systematic review and network meta-analysis (NMA). Our search will include MEDLINE, Embase and the US National Institutes of Health Trials Registry for double-blind, randomised clinical trials for the aforementioned agents.

Inclusion & exclusion criteria

Blinded, randomized studies comparing one adjunctive pharmacological agent with another or with placebo for weight gain and/or metabolic abnormalities will be included. Eligible population consists of adult antipsychotic-medicated patients. We will exclude trials studying patients with eating disorders as primary diagnoses or comorbidities and studies of children/adolescents. Studies of weight loss agents in antipsychotic-medicated healthy volunteers will be excluded, as these findings are less representative of real-life conditions.

Type of intervention

We are interested in comparing the following pharmacological interventions targeting weight gain and/or metabolic abnormalities in antipsychotic-medicated patients: amantadine, aripiprazole, α-lipoic acid,

betahistine, D-fenfluramine, famotidine, fluvoxamine, liraglutide, melatonin, metformin, naltrexone, nizatidine, omega-3 fatty acids, orlistat, reboxetine, sibutramine, topiramate and zonisamide.

Control

Placebo or active control with additional agents prescribed for weight gain and/or metabolic abnormalities.

Data extraction

Data will be extracted independently by three of the authors based on PRISMA guidelines statement (12).

Risk of bias assessment

The studies' risk of bias will be assessed in accordance to the Cochrane Handbook for Systematic Reviews of Interventions (13).

Statistical analysis

Primary outcomes are efficacy (weight change) and acceptability (treatment discontinuation due to any cause). Secondary outcomes include mean overall changes in body mass index, waist circumference, leptin serum levels, fasting glucose and insulin, lipids, insulin resistance index (HOMA-IR), glycosylated haemoglobin (HbA1c), diastolic and systolic blood pressure.

Effect measures

We will analyze the primary outcome using mean difference (MD) or standardised mean difference (SMD) depending on whether different measures are used to assess the same outcome. For acceptability of interventions we will use odds ratio (OR) for discontinuation rates. For secondary continuous outcomes we will either use MD or SMD.

Network meta-analysis

We will perform a random-effects NMA to compare pharmacological agents for the primary and secondary outcomes. NMA enables the integration of direct and indirect comparisons of the effects of agents prescribed for weight loss using a common comparator resulting to more precise treatment effect estimates compared with their pairwise meta-analysis counterparts. We will perform NMA using a graph-theoretical method; the methodology has been found equivalent to other frequentist approaches (14). Heterogeneity will be assumed common across different comparisons. We will assess the magnitude of heterogeneity by comparing it with derived empirical distributions (15, 16). To assess incoherence we will apply a local method comparing direct to indirect evidence in each comparison (17), and a design-by-

treatment interaction model which is a global method to assess incoherence, meaning that it infers about the presence of incoherence from any source in the entire network (18, 19).

Additive model

In some treatment arms in the network, patients received parallel to the medications lifestyle counselling, diet or exercise and others not. To evaluate the influence of individual components on the primary outcome‑the effects of the pharmacological interventions and that of lifestyle counselling, exercise and diet (each at a time) alone- we will implement an additive NMA model assuming that the effect of treatment combinations (drug plus lifestyle counselling, exercise or diet) is the sum of the effects of its components (20).

Subgroup, meta-regression and sensitivity analyses

We will examine the potentially differential effect of the various AP related to the weight gain in several subgroup analyses, meta-regressions and sensitivity analyses. If data for conducting a network meta-regression are not enough, we will conduct a meta-regression based on a pairwise meta-analysis of any treatment versus placebo to investigate several demographic characteristics such as age, percentage of sex in the study, the duration of the pharmacological intervention and baseline BMI. Further, we will conduct subgroup analysis for the groups of obese and non-obese patients based on a BMI cut-off≥ 30kg/m^2. Moreover, based on subgroup analysis, we will assess the role of daily AP dose using 500 chlorpromazine equivalents (CPZ) as cut-off for low- versus high-dose of AP (21). Moreover, we will control for the type of the AP related to the metabolic abnormalities; patients receiving olanzapine and/or clozapine will be classified as at high-risk for metabolic abnormalities, whereas patients receiving risperidone and/or quetiapine will be classified as at moderate-risk (21, 22). In additional subgroup analysis, we will examine the impact of co-medication with known adverse metabolic effects such as mood stabilizers, antidepressants and long-acting APs. A further subgroup analysis will be conducted for first-episode patients (FEP).

Dissemination plans

Results will be published in a peer-reviewed journal.

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