Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis

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CRD summary
The authors concluded that no treatment had sufficient evidence to recommend broad clinical usage. The review had some methodological weaknesses, but the authors’ conclusions were suitably cautious and appear appropriate.

Authors' objectives
To inform clinical practice by identifying the most effective pharmacological therapies to attenuate antipsychotic-related weight gain and metabolic abnormalities.

Searching
MEDLINE, EMBASE, Web of Science and PsycNET were searched for published articles. Search terms were reported. Reference lists of included and relevant studies and reviews were searched.

Study selection
Randomised placebo-controlled trials (RCTs), open-label and double-blind, in patients treated with weight reduction medications for antipsychotic-related weight gain were eligible for inclusion. Primary outcomes of interest were the effect of individual weight-loss agents on body weight or body mass index (BMI). Secondary outcomes of interest were change in waist circumference, 7% or more weight gain, changes in glucose, insulin, leptin, triglycerides, cholesterol, psychiatric symptoms and all-cause discontinuation.

The included RCTs studied adult or paediatric patients treated with a weight loss medication versus placebo. The included patients were diagnosed with schizophrenia, schizophrenic-form, schizoaffective disorder, depression, bipolar disorder or psychosis. The included weight-loss medications were: amantadine; dextroamphetamine; d-fenfluramine; famotidine; fluoxetine; fluvoxamine; metformin; nizatidine; orlistat; phenylpropanolamine; reboxetine; rosiglitazone; sibutramine; metformin plus sibutramine; and topiramate. The included baseline antipsychotics were predominantly second-generation; some first-generation drugs were included. Mean age of patients in the treatment arm was 11 years in paediatric patients and 36 years in adult patients; mean age of patients in the placebo arm was 12 years in paediatric patients and 37 years in adult patients. The mean weighted baseline BMI was approximately 27 in both the treatment group and the placebo group. Mean trial duration was 13.1 weeks (range six to 16 weeks). Most trials were conducted in adults.

The authors did not state how many authors undertook the selection process.

Assessment of study quality
The authors did not state if quality assessment was undertaken.

Data extraction
One author extracted data, which were checked by a second author and disagreements were reviewed and resolved. Pooled outcomes and standard deviations were used to calculate weighted mean differences (WMDs) or standardised mean differences (SMDs), with 95% confidence intervals (CIs); when standard deviations were not available or easily derived from other statistics, they were estimated. Authors of the included RCTs were contacted for missing data.

Methods of synthesis
Pooled SMDs or WMDs, together with 95% CIs, were calculated using Mantel-Hansel random-effects meta-analysis. Statistical heterogeneity was assessed using $I^2$ and $X^2$ statistics. Sensitivity analysis was undertaken according to prevention versus intervention trials, study duration, hospitalisation status and lifetime antipsychotic treatment duration. Subgroup analysis by drug was undertaken and presented by outcome. The number needed to treat (NNT) was calculated.
Results of the review
Thirty-two RCTs were included in the review (n=1,482): 30 RCTs in adults and two RCTs in children. The number of patients in each trial ranged from 14 to 125. There was no evidence of publication bias.

Primary outcomes: Overall, compared with placebo, pharmacological interventions were associated with greater weight loss (WMD -1.99kg, 95% CI -2.77 to -1.20, I²=86%; 29 RCTS, n=1,013). Compared with placebo, metformin had the greatest weight loss (WMD -2.94kg, 95% CI -4.89 to -0.99, I²=91%; seven RCTs, n=334), followed by d-fenfluramine (WMD -2.60kg, 95% CI -5.14 to -0.06; one RCT, n=16), sibutramine (WMD -2.56kg, 95% CI -3.91 to -1.22; I²=40%; two RCTs, n=55), topiramate (WMD -2.52kg, 95% CI -4.87 to -0.16; I²=75%; two RCTs, n=133) and reboxetine (WMD -1.90kg, 95% CI -3.07 to -0.72; I²=0%; two RCTs, n=79). Compared with placebo, there were no significant differences in weight loss with amantadine, dextroamphetamine, famotidine, fluoxetine, nizatidine, orlistat, fluvoxamine, metformin plus sibutramine and rosiglitazone.

Secondary outcomes: There was no significant difference between pharmacological agents compared with placebo for nausea, all-cause discontinuation and psychiatric symptoms. The findings were conflicting for the effects of different drugs on carbohydrate metabolism and blood lipids (findings reported in the review).

Sensitivity analysis: There were few differences in outcomes when analyses were conducted for type of trial, trial duration, hospitalisation status and lifetime antipsychotic treatment duration; the level of statistical heterogeneity remained generally high.

Authors’ conclusions
No treatment had sufficient evidence to recommend broad clinical usage.

CRD commentary
Inclusion criteria for the review were broadly defined. Several relevant sources were searched for published data; search dates were not reported. There was no attempt to locate unpublished studies, but there was no evidence of publication bias. The authors did not state whether language restrictions were imposed, so there was potential for language bias. The authors did not state how many reviewers performed study selection, which may have introduced selection bias into the review. The authors did not state whether quality assessment was undertaken, which made verifying the quality of the included studies difficult. Studies were combined using random-effects meta-analysis, but there appeared to be both clinical and statistical heterogeneity in the analyses and this raised doubts as to the appropriateness of pooling the results. The authors acknowledged certain review limitations, which included a lack of head-to-head comparisons of different drugs and the small number of studies for certain comparisons.

Overall, the review had some methodological weaknesses, but the authors’ conclusions were suitably cautious and appear appropriate.

Implications of the review for practice and research
Practice: The authors stated that although metformin outperformed other agents compared with placebo, the evidence was too limited to support regular clinical use.

Research: The authors stated that future research should consist of large studies that assessed a wide array of body composition and metabolic parameters, documented previous treatment history and weight change carefully, focused on moderators and mediators of the response and ideally included a pharmacological component. Studies were needed to document the time course and sustainability of weight loss over longer periods of time. Studies were needed in antipsychotic-naïve patients and in children and adolescents, who are at particular risk for weight gain and its long-term consequences. Studies should be conducted in patients with disorders other than schizophrenia for which antipsychotics were endorsed or frequently prescribed. The authors stated that antipsychotics with no or minimal cardiometabolic liability, as well as interventions that prevented or normalised adverse antipsychotic cardiometabolic effects, were needed.
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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.