Amantadine for olanzapine-induced weight gain: a systematic review and meta-analysis of randomized placebo-controlled trials

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Abstract:

Objective: The objective of this study was to conduct a systematic review and meta-analysis of randomized placebo-controlled trials of amantadine for the treatment of olanzapine-induced weight gain.

Methods: Studies were identified using online searches of PUBMED/MEDLINE and Cochrane database (CENTRAL), along with websites recording trial information such as ClinicalTrials.gov, Controlled-trials.com, and Clinicalstudyresults.org. Study eligibility criteria included randomized, double-blind clinical trials comparing amantadine with placebo for olanzapine-induced weight gain with body weight as an outcome measure and study duration of at least 12 weeks. The methodological quality of included trials was assessed using the Jadad Scale. Separate meta-analyses were undertaken for each outcome (body weight and frequency of weight loss >7%) and treatment effects were expressed as weighted mean differences (WMD) and Mantel–Haenszel odds ratio for continuous and categorical outcomes, respectively.

Results: A systematic review of literature revealed six studies that had assessed amantadine for olanzapine-induced weight gain. Of these, two studies ($n = 144$) met the review inclusion criteria and were included in the final analysis. Meta-analysis was performed to see the effect size of the treatment on body weight and frequency of body weight loss >7%. For body weight change, WMD was -1.85 [95% confidence interval (CI) -3.31 to -0.39] kg with amantadine as compared with placebo; the overall effect was statistically significant ($p = 0.01$). For frequency of body weight loss >7%, Mantel–Haenszel odds ratio for weight loss was 3.72 (95% CI 1.19 – 11.62), favoring amantadine as compared with placebo, and the overall effect was significant ($p = 0.02$).

Conclusions: Existing data is limited to two studies, which support the efficacy of amantadine for olanzapine-induced weight gain and a significant proportion of patients might lose weight with amantadine compared with placebo.

Keywords: amantadine, olanzapine, meta-analysis, systematic review, weight gain

Introduction

Body weight gain and metabolic alterations are clinically relevant side effects of atypical antipsychotics, specifically olanzapine and clozapine, which is evident at approximately 10 weeks of treatment [Allison *et al.* 1999; Sussman, 2001; Komossa *et al.* 2010] and appears to be dose related [Simon *et al.* 2009]. Olanzapine, in particular, is linked to clinically significant body weight gain ranging from 0.9 kg/month to up to 6–10 kg or more after 1 year of treatment [Nemeroff, 1997].

In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, 30% of olanzapine-treated patients gained >7% of their baseline body weight [Lieberman *et al.* 2005]. Therefore, effective pharmacological and nonpharmacological strategies are urgently required for optimal body weight control during olanzapine treatment [Faulkner *et al.* 2007]. Several medications such as amantadine, nizatidine, ranitidine, famotidine, topiramate, fenfluramine, reboxetine, fluoxetine, fluvoxamine, sibutramine, dextroamphetamine, d-fenfluramine,

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Figure 1. PRISMA 2009 flow diagram.

orlistat, phenylpropanolamine, rosiglitazone, and metformin have been trialed and have been reported to effectively prevent and reduce antipsychotic-induced body weight gain [Faulkner and Cohn, 2006; Baptista *et al.* 2008; Maayan *et al.* 2010].

Although the mechanism for olanzapine-induced weight gain is not known, appetite stimulation and insulin resistance are possible factors associated [Henderson *et al.* 2005; Kluge *et al.* 2007]. Appetite stimulation has been suggested to involve serotonin 5HT_{2C} and histamine H₁ receptor antagonism, resulting in food craving and binge eating [Stahl, 1998]. Amantadine is an antiviral agent effective against influenza A infection [Jefferson *et al.* 2006] as well as an antiparkinsonian drug used for the treatment of extrapyramidal side effects associated with antipsychotic drugs [Silver and Geraisy, 1996]. It has been studied for weight reducing effects in those with antipsychotic-induced weight gain, based on its ability to modify dopamine and serotonin neurotransmission. In an animal study, there was dose-dependent appetite loss following administration of amantadine through

the lateral hypothalamus, possibly through release of dopamine and serotonin in the nucleus accumbens and lateral hypothalamus [Baptista *et al.* 1997], although it failed to prevent sulpiride-induced weight gain completely. As the weight gain pattern is different for olanzapine as compared with other atypical antipsychotics and it is one of the most commonly used antipsychotics, we conducted a systematic review and meta-analysis with an objective to determine the effects of amantadine for reducing or preventing weight gain associated with olanzapine.

Methods

In our systematic review and meta-analysis, we adhered to the recent update of preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [Moher *et al.* 2009]. The flow of studies is summarized in Figure 1.

Data sources and search strategy

Studies were identified using online searches of PUBMED/MEDLINE and the Cochrane

database (CENTRAL). Also, websites recording trial information such as ClinicalTrials.gov, Controlled-trials.com, and Clinicalstudyresults.org were searched for relevant studies. Searches were conducted using combination of terms 'atypical antipsychotics', 'olanzapine', 'body weight gain', 'obesity' and 'amantadine'. We inspected reference list of all identified studies, including existing reviews for relevant citations. The search was restricted to publications in the English language.

Study selection: inclusion criteria

One reviewer (SKP) initially evaluated the abstracts from the literature search. The following criterion was used to identify the studies:

1. randomized, double-blind clinical trials comparing amantadine with placebo for olanzapine-induced weight gain;
2. outcome measures include body weight;
3. study duration of at least 12 weeks.

Data extraction

Two reviewers (SKP and PSVNS) decided, independently, whether individual studies met the inclusion criteria. We used a standardized form, and extracted data which included patient and study characteristics, outcome measures and study results.

Assessment of methodological quality of studies

The methodological quality of included trials in this review was assessed using the Jadad scale [Jadad *et al.* 1996]. It includes three items:

1. Was the study described as randomized?
2. Was the study described as double-blind?
3. Was there a description of withdrawals and drop outs?

Scoring was done as follows: one point for positive answer and one point deducted if either the randomization or the blinding/masking procedures are inadequate. Cut-off of two points on the Jadad scale was considered.

Quantitative data synthesis

Meta-analyses were undertaken to estimate overall treatment effects where the trials were considered to be similar enough to combine using RevMan 5 version. This decision was based on assessing similarity of trial characteristics as well

as results. Separate meta-analyses were undertaken for each outcome (body weight and frequency of weight loss >7%). Treatment effects were expressed as weighted mean differences (WMD) for continuous outcomes with 95% confidence intervals (CIs). For categorical outcome, Mantel-Haenszel odds ratio (with 95% CI) was obtained. Homogeneity among studies was tested using Cochran's Q test and I^2 statistic, in which greater than 50% indicates a moderate amount of heterogeneity [Higgins *et al.* 2003]. If significant statistical heterogeneity was detected (Cochran Q test $p < 0.1$ or I^2 value >50%), random effects estimates were calculated. Otherwise, a fixed-effect model was used for analysis.

Results

Studies included

The combined search strategies identified six papers on the use of amantadine in olanzapine-induced weight gain after removing duplications. Three studies [Floris *et al.* 2001; Gracious *et al.* 2002; Bahk *et al.* 2004] were excluded as they were open-label studies or case series. The Eli Lilly study was excluded as it was not placebo-controlled [ClinicalTrials.gov Identifier: NCT00401973]. Finally, two studies [Deberdt *et al.* 2005; Graham *et al.* 2005] met the review inclusion criteria (total 144 subjects) and were included in the final analysis. Characteristics of included studies are summarized in Table 1. In the study by Deberdt and colleagues, 16-week values were included in the meta-analysis [Deberdt *et al.* 2005].

Study quality

Both of the studies [Deberdt *et al.* 2005; Graham *et al.* 2005] were described as randomized and were double blind. Dropout rates were mentioned in both of the studies, and it varied from 11.2% to 14.2%. Concealment of allocation was not adequately reported in both the studies. Therefore, as it was unclear how randomization sequences were kept concealed, it is likely that the studies are prone to at least a moderate degree of bias [Juni *et al.* 2001].

Meta-analysis

Forest plots for meta-analyses for body weight and frequency of weight loss >7% are presented in Figures 2 and 3. For body weight change, the test for heterogeneity was not significant ($p = 0.20$,

Table 1. Characteristics of included studies

Study	Methods	Participants	Intervention	Outcome
Deberdt <i>et al.</i> [2005]	Allocation: randomized Blinding: double Duration: 16 weeks (+8 weeks)	Diagnosis: schizophrenia, schizoaffective, schizophreniform and bipolar I disorder N = 125	1. Olanzapine 5–20 mg plus amantadine 100–300 mg daily. N = 60 2. Olanzapine 5–20 mg plus placebo. N = 65	Body weight, BMI, BPRS, MADRS, lipid profile, leptins, insulin, fructosamine, prolactin
Graham <i>et al.</i> [2005]	Allocation: randomized Blinding: double Duration: 12 weeks	Diagnosis: schizophrenia, schizoaffective and bipolar disorder N = 21	1. Olanzapine 5–30 plus amantadine up to 300 mg daily. N = 12 2. Olanzapine 5–30 mg plus placebo. N = 9	Body weight, BMI, PANSS, glucose, insulin, prolactin, lipid profile

BMI, body mass index; BPRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Syndrome Scale

Figure 2. Forest plot showing body weight change (kg) at 12 weeks in randomized controlled trials comparing amantadine and placebo for olanzapine-induced weight gain ($N = 144$). **Figure 3.** Forest plot showing the frequency of weight loss (>7%) at 12 weeks in randomized controlled trials comparing amantadine and placebo for olanzapine-induced weight gain ($N = 144$).

$I^2 = 40\%$); therefore, a fixed-effects model was used. Weighted mean difference for body weight change was -1.85 (95% CI -3.31 to -0.39) kg with amantadine as compared with placebo; the overall effect was statistically significant ($p = 0.01$).

For, frequency of body weight loss >7% ($N = 144$), the test for heterogeneity was not significant ($p = 0.45$, $I^2 = 0\%$) and the fixed-effects model was used. The Mantel-Haenszel odds ratio for weight loss was 3.72 (95% CI 1.19 – 11.62), favoring amantadine as compared with placebo, and the overall effect was significant ($p = 0.02$).

Discussion

Existing data shows that the weight mitigating effect of amantadine at doses of 100–300 mg per day was statistically significant as compared with placebo in patients with olanzapine-induced weight gain, although the results are based on a small sample ($N = 144$). In these studies, amantadine was well tolerated with some adverse effects, such as insomnia and upper abdominal discomfort were significantly higher than placebo. There is no evidence of worsening of symptoms after the addition of amantadine. Nevertheless, these data may not be sufficient to recommend routine use

of amantadine for the treatment of olanzapine-induced weight gain.

It is interesting to note that odds of significant weight loss (>7% initial body weight) was higher in those receiving amantadine (odds ratio [OR] 3.72, 95% CI 1.19–11.62) as compared with the placebo group. It appears that a subset of patients might have benefited from treatment with amantadine. In a recent *post hoc* analysis of studies evaluating weight-reducing agents (nizatidine, amantadine and sibutramine) as adjunctive treatment to olanzapine therapy, it was observed that these medications do not benefit all patients, but might have therapeutic potential for some patients [Stauffer *et al.* 2009]. In future, prospective studies are required for identification of these subsets of patients who will benefit from such treatments.

Furthermore, the search for genetic mechanisms underlying the drug response in antipsychotic-induced metabolic dysfunction is important. Preliminary results have shown that leptin tended to increase after placebo whereas there was a small nonsignificant reduction after metformin, in spite of similar weight gain suggests a beneficial effect of this antidiabetic agent in olanzapine-induced weight gain [Baptista *et al.* 2007]. In another study by Fernandez and colleagues, specific genetic polymorphism of leptin gene showed a blunted response to metformin in clozapine-treated patients [Fernández *et al.* 2010]. Such pharmacogenetic studies will identify specific subsets of patients who will benefit from treatment with anti-obesity medications during antipsychotic treatment.

Our review is limited by the number of studies included for meta-analysis. Fewer studies did not allow us to conduct tests for publication bias. Also, sensitivity analysis was not performed in our study. Heterogeneity was absent for body weight change and frequency of weight loss; therefore, a fixed effects model was used. In both of the studies, subjects had gained weight following olanzapine treatment; in the study by Graham and colleagues, a minimum weight gain of 5 lbs was required [Graham *et al.* 2005]; whereas, in the study by Derberdt and colleagues, subjects gained 5% or more of their baseline weight [Derberdt *et al.* 2005]. It has been observed that reversal of weight gain is a less effective strategy than the prevention of weight gain, therefore medications to counter weight gain need to be

started early in the course of treatment [Hasnain *et al.* 2010]. Both of the studies did not address the possibility of prevention of weight gain with the addition of amantadine along with initiation of olanzapine treatment. Therefore, in future studies prevention of weight gain needs to be assessed.

We also suggest that all future studies should respect standards of measuring outcomes and of reporting data in order to enhance the comparability of study results. Also, binary outcomes (number of patients losing >7% initial body weight) should be reported as they are easier to interpret and clinically relevant. Such outcome measures may reveal significantly different results, as observed in our meta-analysis. Details regarding the allocation sequence and allocation concealment should be clearly described in all of the studies to prevent bias.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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