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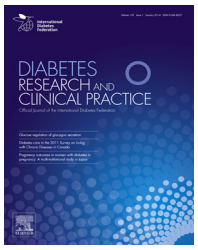

Topiramate monotherapy for weight reduction in patients with type 2 diabetes mellitus: A systematic review and meta-analysis

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ABSTRACT

Aims: To conduct a systematic review with meta-analysis to determine the efficacy and safety of topiramate as monotherapy for weight reduction in patients with type 2 diabetes mellitus.

Methods: We searched MEDLINE, Embase, and International Pharmaceutical Abstracts from inception to June 2015. We included randomized controlled trials that evaluated topiramate monotherapy versus control agents or placebo for weight loss in obese type 2 diabetes patients.

Results: Of the 284 studies identified, 5 studies fulfilled the inclusion criteria. Topiramate decreased weight by a mean difference of 3.4 kg (95% CI, −3.79 to −3.04) compared to placebo. Mean HbA1c reduction of −0.4% (95% CI, −0.58 to −0.32) and mean BMI reduction of −1.43 kg/m^2 (95% CI, −1.83 to −1.03) were both significantly observed with topiramate ($p < 0.00001$). Serious and total adverse events occurred more commonly among topiramate users, with a risk ratio for serious adverse events of 1.69 (95% CI, 1.00–2.87). All but one study had high risk of bias.

Conclusions: Topiramate monotherapy reduced weight in obese type 2 diabetes patients, but increased adverse events including serious adverse events. Given these safety concerns and the absence of data on clinically meaningful efficacy endpoints, clinicians should generally avoid use of topiramate alone for this indication.

1. Introduction

Obesity is an increasing global epidemic with strong links to the development of diabetes and cardiovascular disease [1,2]. Approximately 80% of diabetes patients are classified as being overweight or obese making the need to control this epidemic apparent [3]. Weight loss benefits among obese diabetes patients have shown to reduce cardiovascular risk and improve insulin resistance and glycemic control [4]. Currently, lifestyle modifications are the mainstay for weight reduction, however sustained reductions in weight are both difficult to achieve and maintain [5,6]. Therefore, pharmacological agents are being explored to assist patients achieve desired body weight goals.

Many weight loss agents have been released into the market with few proving adequate efficacy and/or safety. Orlistat has demonstrated promising weight reductions in numerous trials. A recent meta-analysis among obese type 2 diabetes patients, orlistat revealed a mean weight reduction of

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4.25 kg within one year [7]. These effects also extend to improvements in glycemic control. Despite its favorable effects, significant gastrointestinal intolerances have limited orlistat's use as a long term weight loss agent [8]. The combination of naltrexone and bupropion has demonstrated a 7% weight loss compared to placebo persisting up to 1 year. However, elevations in blood pressure and a black box warning of increased suicidal risk and serious neuropsychiatric events question this option as being viable for most obese patients [9]. Comparatively, phentermine and topiramate combination studies have shown to achieve greater weight loss reductions of approximately 10% when over a year among obese patients with various comorbidities [10,11]. This combination has been recommended for long term obesity treatment, however, abuse potential, high costs, and adverse effects associated with maintenance therapy may hinder its use [12].

Topiramate as monotherapy has been used as an off-label weight loss agent yet the mechanism for this welcomed side effect is not clearly understood [1,13]. A meta-analysis of drugs associated with weight change has revealed up to 4 kg reduction in body weight with the use of topiramate alone [14]. Another meta-analysis of 10 randomized controlled trials has shown favorable effects of topiramate averaging 5 kg weight reduction among obese patients [12,13]. Furthermore, this meta-analysis highlighted the potential role of topiramate possibly reducing weight among obese type 2 diabetes patients [13]. Despite this evidence, topiramate's role as monotherapy for weight reduction among patients with type 2 diabetes mellitus is not established. Therefore, the aim of this systematic review is to determine the efficacy and safety of topiramate as monotherapy for weight reduction in patients with type 2 diabetes mellitus.

2. Material and methods

2.1. Literature search

We conducted a literature search using the databases MEDLINE, Embase, and International Pharmaceutical Abstracts up to June 2015. The following search terms were combined: topiramate, Topamax, obesity, type 2 diabetes mellitus, weight reduction, and weight loss. The search was limited to studies reporting results in human subjects and English language. Clinicaltrials.gov was searched on June 14, 2015 for unpublished or ongoing studies. Reference lists of relevant articles were also screened. Attempts (via email) were made to contact authors of relevant papers to seek additional information regarding unpublished or ongoing studies.

2.2. Study selection

Two reviewers (BP, KW) independently screened all studies by title or abstract for eligibility. Studies were included if they reported results from randomized controlled studies in patients with type 2 diabetes mellitus receiving topiramate for a minimum of 16 weeks and included change in body weight as a study outcome. Studies were eligible regardless of differences in combination or background therapy. Abstracts and conference proceedings were excluded. Two reviewers (BP and KW) independently extracted information from each study in an electronic spreadsheet and resolved any discrepancies through discussion. Both reviewers (BP and KW) independently performed a risk of bias assessment using methods described in the *Cochrane Handbook*, which assessed each study for selection, performance, detection, attrition, reporting and miscellaneous biases. Studies were subsequently assigned a rating of low, high, or high-unclear risk based on these findings.

The primary endpoint for meta-analysis was weight change in kilograms. Secondary outcomes included change in body mass index (BMI), change in HbA1c, adverse events and serious adverse events.

2.3. Statistical analysis

We performed all statistical analyses using Review Manager Version 5.3. We present dichotomous data as relative risk (RR) with 95% confidence intervals (CIs). Whenever possible, we present data according to the group to which they were allocated, in accordance with the intention-to-treat (ITT) principle. For dichotomous outcomes, we assumed that patients lost to follow-up before the end of the trial had not experienced an event. For trials with multiple topiramate treatment arms utilizing different doses, we combined these arms into a single topiramate group.

We assessed for statistical heterogeneity with visual inspection of the forest plot and calculation of the I^2 statistic. We defined $I^2 < 25\%$ as low heterogeneity, 25–50% as moderate heterogeneity, and >50% as large heterogeneity. When meta-analysis was possible because of acceptable clinical and methodological heterogeneity, we calculated both fixed- and random-effects models, and described any discrepancies. We reported the fixed-effects model for all non-discrepant analyses. We set the threshold for a positive test for interaction at ≤ 0.10. We made no adjustments for multiple comparisons.

We intended to assess for publication bias by visual inspection of the funnel plot for any meta-analysis with at least 10 trials, as this test is considered to be of little value with fewer trials.

3. Results

3.1. Study characteristics

Initially 284 articles were identified during the database search (Fig. 1). Of those, 271 studies were screened and 5 randomized double blind placebo controlled studies enrolling 1399 patients fulfilled the criteria [15–19]. Study characteristics are given in Table 1. The included trials assessed topiramate monotherapy versus placebo or placebo in combination with lifestyle interventions and/or metformin or sulfonylurea therapy in type 2 diabetes patients. All included studies assessed weight loss outcomes. For the primary outcome, only 3 studies reported weight loss in kg [15–17]. Data from the other 2 trials were not reported and unattainable from the study authors and therefore excluded from the primary outcome analysis [18,19].