

## Efficacy and safety of topiramate on weight loss: a meta-analysis of randomized controlled trials

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### CRD summary

This generally well-conducted review found that topiramate may be a useful adjunctive treatment for obesity, and may play a role in the treatment of obesity in individuals with type 2 diabetes mellitus. The authors' conclusions are likely to be reliable.

### Authors' objectives

To assess the potential benefits and harms of topiramate in the treatment of obesity.

### Searching

MEDLINE, EMBASE, the Cochrane Library and ClinicalTrials.gov were searched up to April 2010 for relevant studies; search terms were reported. Reference lists of the retrieved articles were checked to identify additional references. There were no language restrictions.

### Study selection

Randomised controlled trials (RCTs) that assessed the effectiveness of topiramate (administered for at least 16 weeks) on weight loss were eligible for inclusion. Trials had to report weight measurements at baseline and post-intervention, and/or the proportion of participants who lost more than 5% or 10% of their baseline weight.

Participants in the included trials were of a mean age of 43 to 60 years; the proportion of men ranged from 14.8 to 100%. Participants presented with body mass index of over 27kg/m<sup>2</sup>. Some trials included participants with diabetes, hypertension, dyslipidaemia and binge-eating disorders. Two trials enrolled participants who were receiving dietary interventions. Topiramate dosage ranged from 64 to 400mg/day. The duration of treatment across the trials ranged from 16 to 60 weeks. The comparators were placebo treatments.

The authors did not state how many reviewers performed the study selection.

### Assessment of study quality

Two reviewers evaluated the methodological quality of included trials using concealment of randomisation, whether the trial was stopped early, and the blinding of participants, healthcare providers, data collectors and outcome assessors.

The kappa score was used to assess inter-reviewer agreement. Any disagreements were resolved by a third reviewer.

### Data extraction

Data were extracted by two independent reviewers to calculate odds ratios (ORs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, with 95% confidence intervals (CIs) for each estimate. Any disagreements were resolved by a third reviewer; kappa scores were calculated for inter-reviewer agreement.

### Methods of synthesis

Pooled odds ratios, mean differences and 95% confidence intervals for the summary estimates were calculated using a DerSimonian and Laird random-effects model. The Cochran's Q-statistic and I<sup>2</sup> were used to assess heterogeneity across the trials. Numbers needed to treat (NNT) for benefit and number needed to harm (NNH) were calculated.

Meta-regression analyses were conducted to investigate potential sources of heterogeneity across the trials including topiramate dosage, treatment duration, presence of type 2 diabetes mellitus, and baseline age.

For trials where weight loss was the defined outcome of interest, sensitivity analyses were performed on the administration of topiramate doses at 96 to 200mg/day, treatment duration (up to 28 weeks or over 28 weeks), and the trials of individuals with diabetes. For adverse events, sensitivity analyses were undertaken where trials were stratified on the basis of topiramate dosage.

Publication bias likelihood was evaluated using visual appraisal of funnel plots and the Begg and Egger tests.

### Results of the review

Ten RCTs (n=3,320 participants) were included in the review. The sample sizes ranged from 22 to 1,273 participants. All the included trials reported concealment of randomisation and blinding of health care providers, data collectors and outcome assessors. Two trials were stopped prematurely by the sponsors.

The participants treated with topiramate lost a mean of 5.34kg (95% CI -6.12 to -4.56) of additional weight compared with participants who received placebo, regardless of dose and duration of treatment. There was substantial heterogeneity present (I<sup>2</sup>=75.5%).

The likelihood of significant weight loss was higher in the topiramate group compared with placebo; higher proportions of participants who received topiramate achieved weight loss of 5% or more (OR 6.02, 95% CI 4.81 to 7.53; NNT 2.63; I<sup>2</sup>=31.1%) and 10% or more of baseline body weight (OR 7.16, 95% CI 5.48 to 9.36; NNT 3.7; I<sup>2</sup>=17.8%).

The results of meta-regression analyses found that the effect of topiramate on weight loss increased with treatment duration and dosage.

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Participants with diabetes who were treated with topiramate lost a mean of 5.25 kg (95% CI -6.66 to -3.85 kg; four trials) of additional weight compared with placebo-treated participants, but substantial heterogeneity was observed for this outcome ( $I^2=78.3\%$ ).

In the analysis of adverse events, participants treated with topiramate had an increased risk of paraesthesia (OR 8.70, 95% CI 6.90 to 11.0;  $I^2=58.5\%$ ) and of adverse events leading to withdrawal from treatment compared with placebo-treated participants (OR 1.94, 95% CI 1.64 to 2.29;  $I^2=0$ ; NNH 13.7 patients). There were higher risks of taste perversion (OR 8.61, 95% CI 5.35 to 13.87;  $I^2=25.9\%$ ), psychomotor impairment (OR 7.82, 95% CI 3.71 to 16.46;  $I^2=0$ ) and hypoaesthesia (OR 4.51, 95% CI 2.76 to 7.40;  $I^2=0$ ) and various other adverse events in the topiramate group.

There was no evidence of publication bias from the appraisal of funnel plots or the Egger's test.

### Authors' conclusions

Topiramate may be a useful adjunctive treatment for obesity, and may play a role in the treatment of obesity in individuals with type 2 diabetes mellitus. Although warnings about some side effects were required for prescribing topiramate, the treatment was not associated with major harmful events.

### CRD commentary

The review addressed a clearly defined question. Criteria for the inclusion of studies were stipulated. The restriction of the review to randomised controlled trials was appropriate for the assessment of effectiveness data, but relevant studies of adverse events may have been missed. Appropriate databases were searched without restriction for relevant studies; attempts were made to identify unpublished trials. Publication bias was assessed using standard methods and no evidence of bias was found. Steps were reported to minimise errors and bias for the assessment of methodological quality and data extraction, but not for study selection.

The included trials were reported to be adequately randomised and blinded, but it was not clear how many participants were lost to follow-up. There was some clinical heterogeneity across the trials in the dose of topiramate administered and co-morbidities of the included participants which may have some implications for the generalisability of the review findings. Substantial heterogeneity was observed in some meta-analyses, although the authors conducted appropriate meta-regression analyses to evaluate potential sources of heterogeneity.

The review was generally well conducted and the authors' conclusions are likely to be reliable.

### Implications of the review for practice and research

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that more research was required in direct comparisons with currently approved drugs for obesity and to determine the optimal treatment duration and efficacy of topiramate in combination with other anti-obesity drugs.

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### Bibliographic details

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