doi: 10.1111/j.1467-789X.2010.00846.x

Obesity Management

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

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Received 6 October 2010; revised 20 November 2010; accepted 22 November 2010

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Summary

Topiramate was associated with weight loss in clinical trials. We summarize the evidence on the efficacy and safety of topiramate in the treatment of overweight/obesity. The databases Medline, Embase, and Cochrane were searched. Randomized controlled studies with at least 16 weeks of duration that report the effect of topiramate on weight loss and adverse events were eligible for inclusion. Ten studies were included (3320 individuals). Patients treated with topiramate lost an average of 5.34 kg (95% confidence interval [95%CI] −6.12 to −4.56) of additional weight as compared with placebo. According to meta-regression analysis, treatment duration and dosage were associated with the efficacy of topiramate treatment. Evaluating trials using topiramate 96–200 mg day^{-1}, the weight loss was higher in trials with >28 weeks of duration (−6.58 kg [95%CI −7.48 to −5.68]) than in trials with ≤28 weeks (−4.11 kg [95%CI −4.92 to −3.30]). Data of 6620 individuals were available for adverse events evaluation and those more frequently observed were paraesthesia, taste impairment and psychomotor disturbances. The odds ratio for adverse events leading to topiramate withdrawal was 1.94 (95%CI 1.64–2.29) compared with the control group. In conclusion, topiramate might be a useful adjunctive therapeutic tool in the treatment of obesity as long as proper warnings about side effects are considered.

Keywords: Adverse events, obesity, topiramate.

obesity reviews (2011) **12**, e338–e347

Introduction

The prevalence of obesity is relentlessly increasing worldwide. Reports from all continents suggest a growing prevalence of overweight/obesity over the past 20 years (1–3). Estimates of the prevalence of overweight (body mass index [BMI] ≥ 25 kg m^{-2}) in the US population from 2007 to 2008 reached the substantial percentage of 68% (1). A changing perception of excess weight was recently reported by a UK survey study in which fewer overweight/obese individuals defined themselves as overweight in 2007 as compared with 1999 (4), suggesting that people are assuming a nihilistic position against the treatment of obesity. However, obesity is associated with several health risk conditions such as type 2 diabetes mellitus, hypertension, dyslipidemia, coronary heart disease, arthritis, some types of cancer (5), and therefore an effective treatment strategy for weight loss is imperative.

Disclosure Statement: The authors have nothing to disclose

Funding: This study was supported in part by Projeto de Núcleos de Excelência do Ministério de Ciência e Tecnologia, Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPQ 576627-2008-9), and Fundo de Incentivo a Pesquisa of Hospital de Clínicas de Porto Alegre (GPPG 09023). C.K.K is a recipient of a grant from Projeto Nacional de Pós-Doutorado no País (PNPD 03021/09-2). The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Non-pharmacological treatment of obesity can be effective, but the long-term success rate is low and regaining lost weight is a major problem (6). Drug therapy may be an important adjunctive treatment for obesity; the current guidelines recommend that anti-obesity pharmacotherapy can be considered for those with a BMI greater than 30 kg m^{-2}, or a BMI of 27–30 kg m^{-2} if they have comorbid conditions (7–9). Pharmacologic options include sibutramine, orlistat, phentermine, and diethylpropion. Both phentermine and diethylpropion have potential for abuse and are only approved for short-term use while sibutramine and orlistat result in modest weight loss (8,10). Moreover, recently the European Medicine Agency recommended that the marketing authorizations for sibutramine-containing medicines be suspended throughout Europe due to the preliminary results of the Sibutramine cardiovascular outcomes study (SCOUT) study showing that sibutramine is associated with more cardiovascular problems than placebo (11,12) which was followed by the sibutramine withdrawn from US market. In this sense, it might be important to review the current evidence about topiramate in the treatment of overweight/obesity.

Topiramate has been used for epilepsy and migraine treatment since the 1990s (13) and it was associated with weight loss which promptly led to the evaluation of its efficacy as an anti-obesity agent (14,15). Conversely, topiramate is not an approved drug for the treatment of obesity. Data from individual trials might not be sufficient to support clinical decision, and a robust evidence of its safety is lacking. Therefore, the aim of the present study was to assess the benefits and harms of topiramate in the treatment of obesity by a systematic review and meta-analysis of randomized controlled trials.

Methods

Data sources and searches

To identify randomized controlled studies that report the effect of topiramate on weight loss, we searched the electronic databases (beginning in 1950 to April 2010) Medline, Embase, and Cochrane as well as the Cochrane Controlled Trials Register and ClinicalTrials.gov registry for the following medical subject readings (MeSH) topiramate OR topamax AND (randomized controlled trial [pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ('clinical trial'[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ('latin square'[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh : noexp] OR comparative study[mh] OR evaluation studies[mh] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]). The reference list of retrieved articles was also checked. In this initial search, all randomized controlled studies were retrieved. All potentially eligible studies were considered for review, regardless of the primary outcome or language.

Study selection

Studies were considered eligible for inclusion if they fulfilled the following inclusion criteria: presented original data of randomized controlled trial assessing the effect of topiramate on weight loss, examined the effect of topiramate on weight loss after a minimum of 16 weeks' treatment, reported means (or differences between means) and standard deviations (SD) of weight at baseline and after the intervention and/or proportion of participants who have lost greater than 5% and 10% of baseline weight. When studies report more than one intervention group (i.e. different dosages of topiramate), each intervention group was considered as an individual report for statistical analysis.

Data extraction and quality assessment

Data were extracted independently by two investigators (C.K.K and L.C.P) with an agreement value of k = 95% and disagreements were resolved by a third author (C.B.L). Randomized controlled trials risk of bias was evaluated according to PRISMA recommendation (16). Extracted data include the first author's name, year of publication, number of participants, age, gender, health status of participants, trial design and duration, intervention dosages, and assessment of weight change as mean (SD) as well as the number of participants who lost more than 5% and 10% of baseline weight. For trials performed only on diabetic individuals, data from haemoglobin A1c were extracted as the mean change (SD). In addition, each trial included in the weight loss analyses was examined to determine whether it reported data on adverse events. Adverse events were recorded as the number of events.

Data synthesis and analyses

Absolute changes in weight in both topiramate and control groups were reported as differences between arithmetic means before and after interventions. To identify the potential effect of topiramate on clinically significant weight loss (weight loss ≥5% and ≥10%) as well as the effect of topiramate in causing adverse events, an overall odds ratio (OR) was calculated.

The Cochran's 2 *x*-test (Q test) was used to evaluate heterogeneity between studies and a threshold *P* value 0.1 was considered statistically significant; the I^2 test was also conducted to evaluate the magnitude of the heterogeneity

between studies (17). The pooled estimates of the mean differences in weight (kg) between placebo and intervention groups as well as pooled OR estimates (weight loss ≥5% and 10%, and adverse events) were calculated using the random effects model (DerSimonian–Laird method). We used risk estimates obtained with random-effect meta-analysis instead of fixed-effect models because we found significant heterogeneity between studies in preliminary models. Furthermore, this approach has a more conservative assessment of the average effect size. We used meta-regression analyses to investigate potential sources of heterogeneity between trials. The factors investigated (covariates) were topiramate dosage, treatment duration, presence of type 2 diabetes mellitus and baseline age. Covariates were chosen based on biological relevance before the meta-analysis was undertaken. We performed a sensitivity analysis based on meta-regression analysis results. When weight loss was defined as the outcome, the sensitivity analysis was performed: (i) Including only studies that evaluated topiramate at dosages of 96–200 mg day^{-1}, and treatment duration ≤28 weeks; (ii) Including only studies that evaluated topiramate at dosages of 96–200 mg day^{-1}, and treatment duration >28 weeks and (iii) Including only studies of diabetic individuals. When adverse event was defined as the outcome, the sensitivity analysis was performed stratifying studies by topiramate dosage: (i) Up to 96 mg day^{-1}; (ii) Between 96 to 200 mg day^{-1} and (iii) Above 200 mg.

We assessed the possibility of publication bias using a funnel plot of each trial's effect size against the standard error. Funnel plot asymmetry was evaluated by Begg's and Egger's tests, and a significant publication bias was considered if the *P* value was <0.1 (18).

All statistical analyses were performed using Stata 11.0 software (Stata, College Station, TX, USA).

Results

Literature search results and studies characteristics

We identified 2029 studies in the database searches (Fig. 1). Of them, 2000 were excluded based on title and abstract leaving 29 studies for further evaluation. A total of 10 studies fulfilled our inclusion criteria and were included, providing data from 3320 individuals.

Table 1 shows the characteristics of the included studies. The trials were published between 2003 and 2007, and varied in sample size. The length of the trials varied from 16 to 60 weeks. Topiramate dosage varied from 64 mg day^{-1} to 400 mg day^{-1}. One of them was a weight loss maintenance study that evaluated the topiramate effect on weight after a low-calorie diet run-in (15). Six studies had more than one study group (they compared topiramate in different dosages with placebo) and we considered each dosage arm as a separate report. Thus, a total of 19 reports were available for analysis. Four studies evaluated only patients with type 2 diabetes.

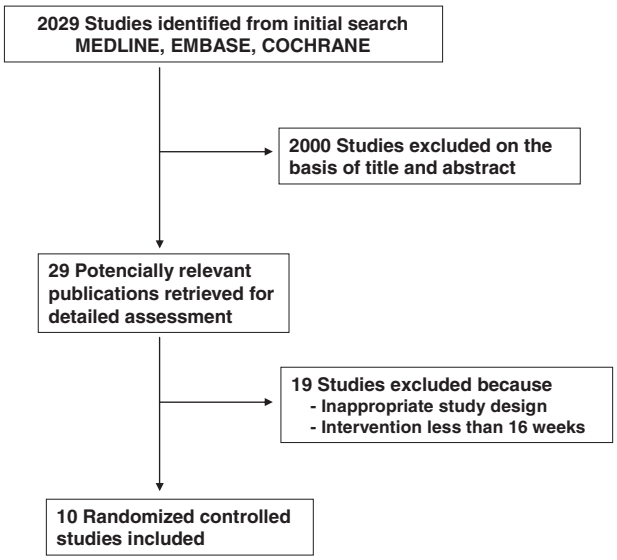

Figure 1 Flow diagram of literature search to identify randomized placebo-controlled trials of topiramate for weight loss.

Ninety per cent of studies fulfilled all Cochrane risk of bias tool components (19) and 100% fulfilled the randomization and blindness criteria (Table 2). Two trials were stopped early by the sponsor (20,21), for which the reasons were not described in the paper. Additionally, funnel plots and the Egger regression test suggested no significant asymmetry (Fig. 2). The trim-and-fill computation using the symmetry estimator L_0 revealed that there were no missing trials, also indicating that no publication bias was present (22).

Analyses of weight loss efficacy

In the pooled analysis of 19 included reports, patients treated with topiramate lost an average of 5.34 kg (95%CI −6.12 to −4.56 kg) of additional weight compared with placebo. All studies reported a significant additional weight reduction in the topiramate group compared with the placebo group regardless of dosage and duration of treatment (Fig. 3). A significant heterogeneity between the individual efficacy estimates was evident when compared with the magnitude of weight reduction (I^2 = 75.5%, P < 0.001).

In an analysis considering weight loss ≥5%, the chance of significant weight loss was higher in the topiramate treatment group than the placebo: pooled OR 6.02 (95%CI 4.81 to 7.53) (I^2 31.1%, P = 0.11), and the number needed to treat (NNT) was 2.63. The same was true for weight loss ≥10%: OR 7.16 (95%CI 5.48 to 9.36) (I^2 17.8%, P = 0.25), and NNT = 3.7.

Table 1 Summary of randomized controlled trials of topiramate for weight loss

Source	Inclusion criteria	Patients (*n*)	Topiramate dosage (mg)	Treatment duration (week)	Mean age (year); men (%)	Weight loss (mean ± SD) (kg)	≥5% weight/total (*n*/total *n*)
Bray GA, 2003 (14)	BMI ≥ 30 kg m^{-2} or ≥27 kg m^{-2} and hypertension/ dyslipidemia	101	64	24	44.3 (14·8%)	TP: –6.0 ± 4.9 Control: –3.9 ± 4.9	TP: 28/53 Control:14/48
		96	96			TP: –6.8 ± 4.9 Control: –3.9 ± 4.9	TP:29/48 Control: 14/48
		97	192			TP: –8.3 ± 4.9 Control: –3.9 ± 4.9	TP:35/49 Control: 14/48
		92	384			TP: –8.9 ± 4.9 Control: –3.9 ± 4.9	TP:27/44 Control: 14/48
Astrup A, 2004 (15)	BMI ≥ 30 kg m^{-2} and previous diet (run in 8 weeks)	190	96	44	43.8 (24%)	TP: –15.65 ± 6.96 Control: –8.58 ± 9.65	TP:92/93 Control: 68/97
		195	192			TP: –16.36 ± 8.92 Control: –8.58 ± 9.65	TP:95/98 Control: 68/97
Wilding J, 2004 (34)	BMI ≥ 30 kg m^{-2} or ≥27 kg m^{-2} and hypertension/ dyslipidemia	426	96	60	44.5 (18%)	TP: –7.3 ± 7.46 Control: –1.7 ± 7.35	TP:115/214 Control: 38/212
		426	192			TP: –9.3 ± 12.3 Control: –1.7 ± 7.35	TP:130/214 Control: 38/212
		421	256			TP: –10 ± 10.65 Control: –1.7 ± 7.35	TP:140/209 Control: 38/212
Tonstad S, 2005 (21)	BMI ≥ 27 kg m^{-2} and hypertension	105	96	28	50 (28%)	TP: –5.9 ± 5.21 Control: –1.9 ± 3.37	TP:23/49 Control: 10/56
		109	192			TP: –6.5 ± 4.85 Control: –1.9 ± 3.37	TP:34/53 Control: 10/56
Rosenstock J, 2007 (35)	BMI ≥ 27 kg m^{-2} and type 2 diabetes on diet and/or metformin	85	175	16	52.7 (32%)	TP: –6.0 ± 5.2 Control: –2.5 ± 3.1	TP:20/39 Control: 9/46
Stenlof K, 2007 (20)	BMI ≥ 27 kg m^{-2} and type 2 diabetes drug naive	152	96	40	53 (39%)	TP: –7.87 ± 5.2 Control: –2.7 ± 2.7	TP:42/74 Control: 19/78
		155	192			TP: –10.2 ± 7.1 Control: –2.7 ± 2.7	TP:60/77 Control: 19/78
Tremblay A, 2007 (36)	Men, BMI ≥ 27 kg m^{-2}, waist ≥ 100 cm and dyslipidemia	46	up to 400	24	43 (100%)	TP: –5.6 ± 3.56 Control: –1.1 ± 1.29	Not available
McElroy SL, 2007 (37)	BMI ≥ 30 kg m^{-2} and binge eating disorder	281	300	16	45 (15·8%)	TP: –4.5 ± 5.1 Control: 2 ± 3.2	Not available
Toplak H, 2007(38)	BMI ≥ 27 kg m^{-2} and type 2 diabetes on metformin	160	96	24	53 (41%)	TP: –5.0 ± 4 Control: –1.8 ± 3.7	TP:43/85 Control: 14/75
		161	192			TP: –7.0 ± 5.1 Control: –1.8 ± 3.7	TP:56/86 Control: 14/75
Eliasson B, 2007 (39)	BMI ≥ 27 kg m^{-2} and type 2 diabetes on diet and/or sulphonylurea	22	192	44	60 (75%)	TP: –7.24 ± 4.26 Control: 0.01 ± 2.54	Not available

BMI, body mass index; SD, standard deviation; TP, topiramate.

In an exploratory attempt to identify the sources of heterogeneity between trials when the absolute weight loss was taken into account, we undertook a meta-regression analysis considering as covariates the topiramate dosage, treatment duration, presence of type 2 diabetes, and baseline age. The weight loss effect of topiramate increases with both duration of treatment and dosage (Fig. 4). The presence of type 2 diabetes and older age was not associated with topiramate effect. The covariates topiramate dosage, treatment duration, presence of type 2 diabetes, and baseline age explained 75% of the between-studies variance ($P = 0.0012$). Figure 5 shows that treatment duration was associated with weight reduction in topiramate dosage of 96 mg and 96–200 mg.

Based on the meta-regression results, sensitivity analyses were performed including trials using topiramate at dosages of 96 to 200 mg day^{-1} with duration of treatment ≤28 and >28 weeks. In trials with ≤28 weeks, topiramate

Table 2 Studies risk of bias assessment

Source	Concealment of randomization	Stopped early	Patients blinded	Health care providers blinded	Data collectors blinded	Outcome assessors blinded
Bray GA, 2003 (14)	Yes	No	Yes	Yes	Yes	Yes
Astrup A, 2004 (15)	Yes	No	Yes	Yes	Yes	Yes
Wilding J, 2004 (34)	Yes	No	Yes	Yes	Yes	Yes
Tonstad S, 2005 (21)	Yes	Yes	Yes	Yes	Yes	Yes
Rosenstock J, 2007 (35)	Yes	No	Yes	Yes	Yes	Yes
Stenlof K, 2007 (20)	Yes	Yes	Yes	Yes	Yes	Yes
Tremblay A, 2007 (36)	Yes	No	Yes	Yes	Yes	Yes
McElroy SL, 2007 (37)	Yes	No	Yes	Yes	Yes	Yes
Toplak H, 2007 (38)	Yes	No	Yes	Yes	Yes	Yes
Eliasson B, 2007 (39)	Yes	No	Yes	Yes	Yes	Yes

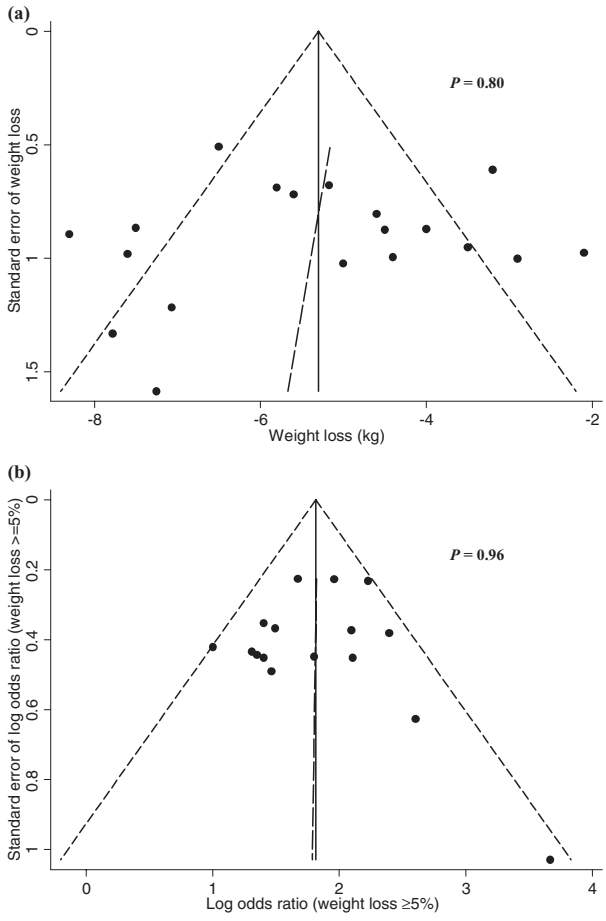

Figure 2 Funnel plots of weight loss with Egger regression line. (a) Weight loss (kg), (b) Weight loss greater than 5% (OR).

group had a significant weight loss of 4.11 kg (95%CI −4.92 to −3.30 kg). This approach reduced the heterogeneity between the individual efficacy estimates ($I^2 = 43.5\%$, $P = 0.10$). When only trials with >28 weeks of duration were included, topiramate was even more effective: the weight loss achieved was 6.58 kg (95%CI −7.48 to −5.68 kg; $I^2 = 35.6\%$, $P = 0.15$).

Although the meta-regression did not demonstrate that the presence of type 2 diabetes mellitus is an important factor in topiramate effect on weight loss, we performed another sensitivity analysis including only trials in diabetic individuals because diabetes is an important cardiovascular risk factor and frequently associated with obesity. Topiramate-treated diabetic patients lost an average of 5.25 kg (95%CI −6.66 to −3.85 kg) of additional weight compared with placebo ($I^2 = 78.3\%$, $P < 0.001$). The effect of topiramate on haemoglobin A1c reduction was described in four reports; diabetic patients treated with topiramate had an average reduction in haemoglobin A1c of 0.43% (95%CI −0.57 to −0.25%) ($I^2 = 15.6\%$, $P = 0.31$).

Analyses of drug safety

Data of 6620 individuals were available for adverse events (safety population). The assessment of adverse events by the trials was essentially obtained by individual's reports (either spontaneously or in response to general, non-direct questions). In a pooled meta-analysis for adverse events, it was demonstrated that the group treated with topiramate was at increased risk for paraesthesia than the group treated with placebo: pooled OR 8.70 (95%CI 6.90–11.0; I^2 58.5 $P < 0.001$). Other side effects more frequently observed were taste , perversion psychomotor disturbances and hypoesthesia (Table 3). Nevertheless, the risk of adverse events leading to treatment withdrawal was approximately twofold compared with placebo (OR 1.94 95%CI 1.64–2.29; I^2 0 $P = 0.87$) corresponding to a number needed to harm (NNH) of 13.7. None of the trials reported cardiovascular events or any other major adverse events.

A meta-regression analysis considering as covariates the topiramate dosage, treatment duration, presence of type 2 diabetes and baseline age showed that only topiramate

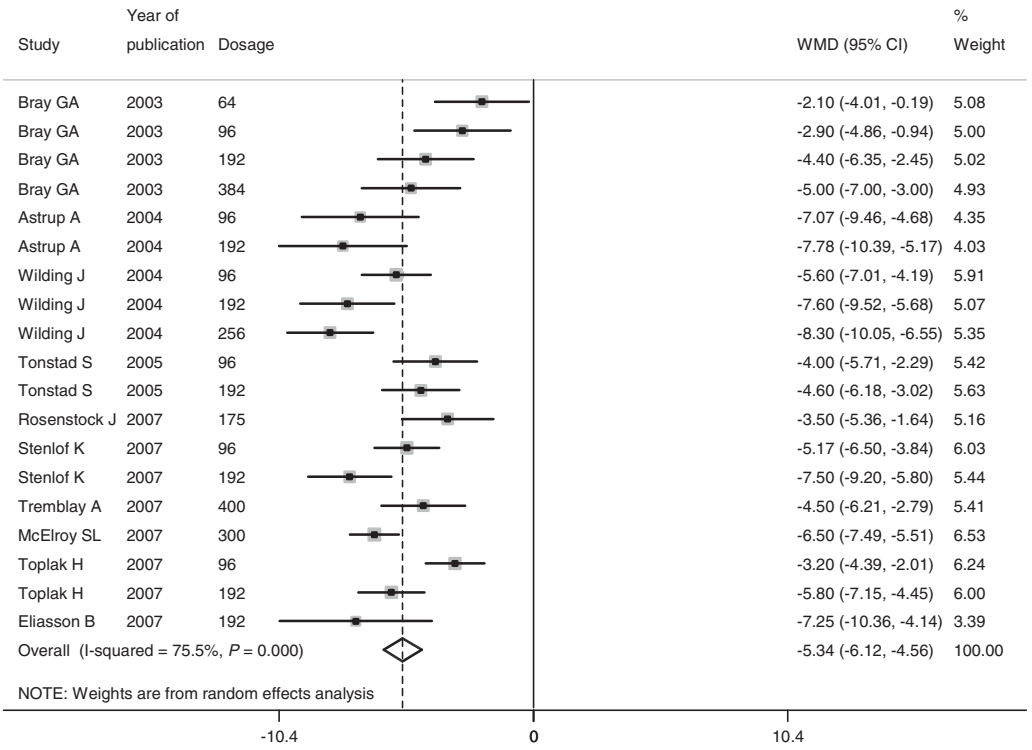

Figure 3 Meta-analysis of topiramate effect on weight loss (kg). WMD, Weighted mean difference.

dosage is associated with adverse events leading to withdrawal ($P = 0.02$). Based on the meta-regression results, sensitivity analyses were performed including trials using topiramate at dosages of (i) up to 96 mg day^{-1}; (ii) between 96 to 200 mg day^{-1} and (iii) above 200 mg day^{-1}. The odds for treatment withdrawal was increased in the subgroup with higher dosages (up to 96 mg day^{-1}: OR 1.60 95%CI 1.23–2.1, topiramate 96–200 mg day^{-1}: OR 2.18 95%CI 1.70–2.80, topiramate above 200 mg: OR 2.19 95%CI 1.40–3.38). The same pattern was observed when the most common adverse events were evaluated as follow: paresthesia (up to 96 mg day^{-1}: OR 6.41 95%CI 4.50–9.17, topiramate 96–200 mg day^{-1}: OR 10.30 95%CI 7.50–14.30, topiramate above 200 mg: OR 11.60 95%CI 8.50–15.60); taste perversion (up to 96 mg day^{-1}: OR 6.20 95%CI 2.60–15.00, topiramate 96–200 mg day^{-1}: OR 10.00 95%CI 4.71–21.50, topiramate above 200 mg: OR 13.30 95%CI 5.95–30.0); psychomotor impairment (up to 96 mg day^{-1}: OR 5.81 95%CI 1.70–20.00, topiramate 96–200 mg day^{-1}: OR 6.91 95%CI 1.81–26.30, topiramate above 200 mg: OR 12.20 95%CI 3.30–44.1); hypoesthesia (up to 96 mg day^{-1}: OR 3.70 95%CI 1.72–7.99, topiramate 96–200 mg day^{-1}: OR 5.84 95%CI 2.88–11.90, topiramate above 200 mg: OR 2.96 95%CI 0.30–29.0); anorexia (up to 96 mg day^{-1}: OR 2.88 95%CI 1.83–4.54, topiramate 96–200 mg day^{-1}: OR 3.75 95%CI 2.37–5.94, topiramate above 200 mg: OR 3.50 95%CI 1.98–6.14); concentration difficulty (up to 96 mg day^{-1}: OR 2.60 95%CI 1.66–3.90, topiramate 96–200 mg day^{-1}: OR 3.80 95%CI 2.48–5.80, topiramate above 200 mg: OR 4.06 95%CI 2.43–6.77); nervousness (up to 96 mg day^{-1}: OR 2.76 95%CI 1.31–5.80, topiramate 96–200 mg day^{-1}: OR 3.16 95%CI 1.40–7.12, topiramate above 200 mg: OR 2.93 95%CI 1.30–6.70); visual disturb (up to 96 mg day^{-1}: OR 1.78 95%CI 0.93–3.42, topiramate 96–200 mg day^{-1}: OR 2.71 95%CI 1.47–5.00, topiramate above 200 mg: OR 3.65 95%CI 1.50–8.60); dry month (up to 96 mg day^{-1}: OR 2.02 95%CI 1.20–3.40, topiramate 96–200 mg day^{-1}: OR 3.27 95%CI 2.10–5.01, topiramate above 200 mg: OR 1.42 95%CI 0.88–2.30); memory impairment (up to 96 mg day^{-1}: OR 1.83 95%CI 1.30–2.64, topiramate 96–200 mg day^{-1}: OR 2.31 95%CI 1.30–4.04, topiramate above 200 mg: OR 2.20 95%CI 1.50–3.30).

Discussion

The results of the present meta-analysis of 10 randomized clinical trials allow us to conclude that the topiramate-treated group had significant additional weight loss (~5.34 kg) compared with placebo-treated group. Topiramate treatment increased the chance of clinically significant weight loss (≥5 and 10%) by more than sixfold. The main limitation of its use was the increased chance of peripheral

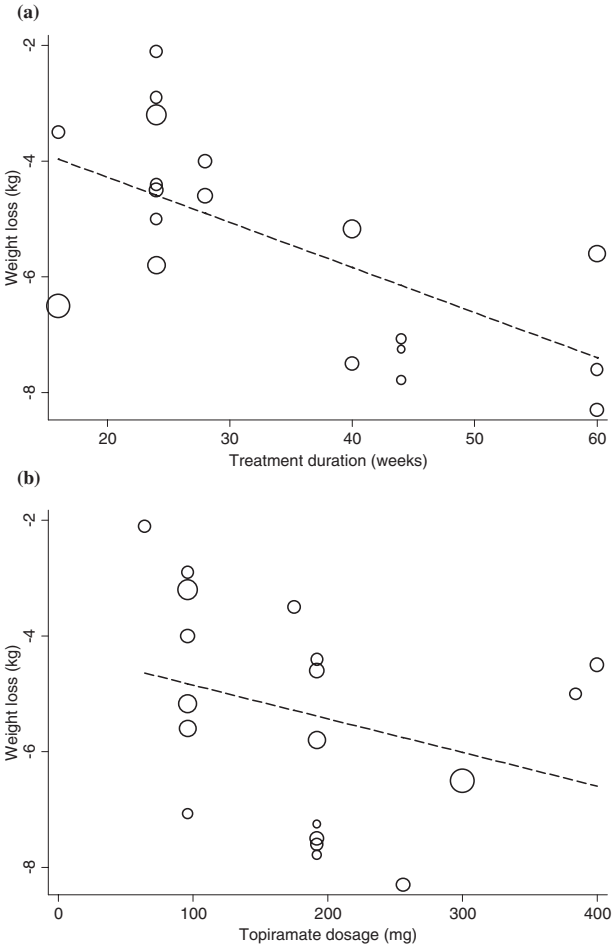

Figure 4 Bubble plot with fitted meta-regression line. (a) Treatment duration (weeks), (b) Topiramate dosage (mg).

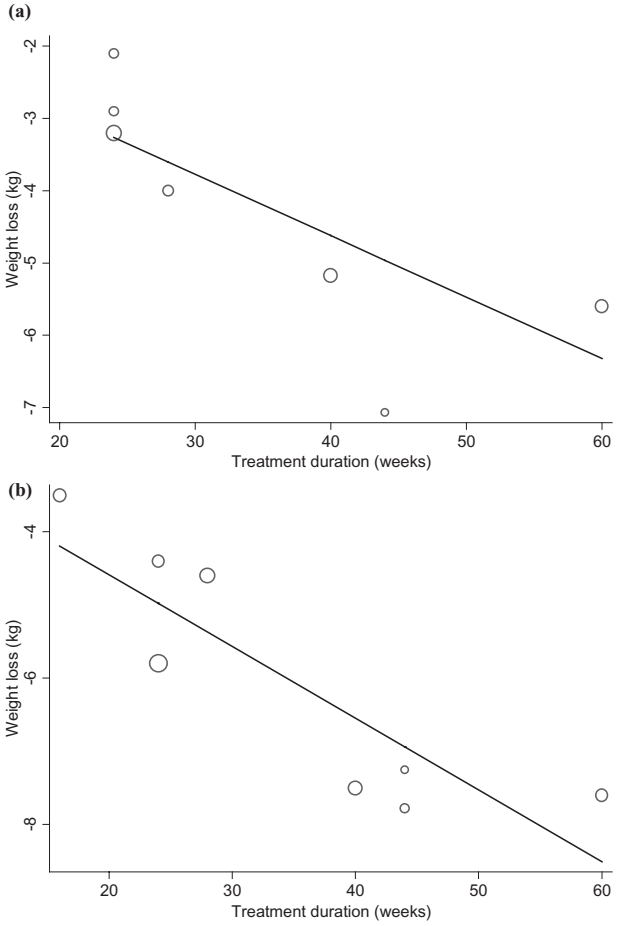

Figure 5 Bubble plot with fitted meta-regression line. (a) Topiramate dosage up to 96 mg day^{-1}. (b) Topiramate dosage 96 to 200 mg day^{-1}.

nerve symptoms (i.e. paraesthesia and hypoesthesia), changes in taste and psychomotor impairment; neither cardiovascular nor other major adverse events were observed. The topiramate dosage higher than 96 mg day^{-1} was associated with the higher rate of treatment discontinuation because of side effects.

The choice of medications for weight loss rests on the efficacy and the individual tolerance to the side effects. Although the current evidence lack trials with direct comparisons between different drugs, and the present meta-analysis was not designed to answer this question, the effect of topiramate on weight loss is comparable or even better than the effect of the other anti-obesity drugs. A meta-analysis of 16 orlistat trials and 10 sibutramine trials showed that patients given orlistat lost an average of 2.9 kg (95%CI 2.5–3.2 kg) of additional weight while patients taking sibutramine lost 4.2 kg (95%CI 3.6–4.7 kg) of additional weight than those taking placebo (7). Moreover, in a meta-analysis of four trials (23), the use of rimonabant led to additional weight loss of 4.7 kg (95%CI 4.1–5.3) as compared with placebo. The NNT of sibutramine to achieve a 5% and 10% of weight loss is 3.12 and 5.55, respectively (7,24), for orlistat the corresponding NNT is 7 and 9 (25), and for topiramate 2.63 and 3.7. Regarding the withdrawn because of adverse effect, the odds ratio and NNH for sibutramine were 2.2 and 12 (7,24), for orlistat 2.00 and 25 (25), and for topiramate 1.96 and 13.7, respectively. The weight loss induced by topiramate increased with longer treatment duration as demonstrated by the sensitivity analysis: the additional weight loss was 4.11 kg (95%CI −4.92 to −3.30 kg) at 28 weeks and 6.58 kg (95%CI −7.48 to −5.68 kg) in the studies with >28 weeks duration. Although sibutramine treatment also increased weight loss after 24 weeks of treatment as observed in the STORM study (24), the weight loss effect of topiramate after 28 weeks is unique because the effect of the majority of other anti-obesity drugs reaches a plateau at 6 months of treatment (7). This is an important aspect when treating a chronic disease such as obesity.

Another interesting finding was that our meta-analysis showed a similar placebo-subtracted weight reduction in

Table 3 Meta-analysis of adverse events

Adverse event	No. of reports describing the event	No. of participants reporting the even/total no. of participants		Pooled OR	95%CI	I^2	*P* value (heterogeneity)
		Intervention group	Control group				
Any event leading to topiramate withdrawal	12	446/2628	245/2525	1.94	1.64–2.29	0	0.87
Paraesthesia	17	1442/3035	289/3027	8.70	6.90–11.0	58.5	<0.001
Taste perversion	16	277/2981	30/2970	8.61	5.35–13.87	25.9	0.16
Psychomotor impairment	7	61/1264	6/1266	7.82	3.71–16.46	0	0.98
Hypoesthesia	9	109/1146	20/1133	4.51	2.76–7.40	0	0.52
Anorexia	11	215/2056	69/2034	3.33	2.51–4.41	0	0.99
Concentration difficulty	16	292/2981	91/2970	3.30	2.55–4.27	4.5	0.40
Nervousness	7	74/1265	26/1266	2.93	1.89–4.63	0	0.97
Visual disturb	5	88/1315	37/1326	2.48	1.66–3.70	0	0.69
Dry month	12	193/2676	88/2670	2.21	1.62–3.02	20.1	0.25
Memory impairment	15	276/2603	142/2611	2.05	1.63–2.58	8.9	0.35
Mood problems	11	116/1942	59/1992	2.00	1.44–2.77	0	0.82
Cough	9	139/1697	86/1682	1.58	1.20–2.11	0	0.47
Depression	15	213/2778	141/2770	1.55	1.24–1.94	0	0.83
Nausea	9	161/1716	109/1704	1.52	1.17–1.96	0	0.90
Constipation	12	156/2106	92/2099	1.71	1.31–2.25	0	0.60
Dyspepsia	7	50/791	29/773	1.71	1.06–2.76	0	0.91
Abdominal pain	9	129/1618	92/1618	1.37	0.98–1.92	14.9	0.31
Dizziness	14	291/2477	221/2465	1.35	1.11–1.63	2.4	0.42
Fatigue	16	529/2843	413/2825	1.34	1.16–1.55	0.3	0.45
Back pain	6	77/737	58/716	1.32	0.92–1.90	0	0.84
Insomnia	12	120/2091	90/2091	1.31	0.98–1.74	0	0.63
Somnolence	11	136/1874	107/1877	1.27	0.98–1.67	0	0.61
Upper respiratory tract infection	11	716/2375	609/2367	1.26	1.10–1.43	0	0.66
Diarrhea	11	214/2071	171/2056	1.26	1.02–1.56	0	0.70
Migraine	7	127/1342	113/1330	1.11	0.84–1.47	0	0.52

CI, confidence interval; No., number; OR, odds ration.

diabetic patients compared with individuals without diabetes. There are reports suggesting that patients with type 2 diabetes usually lose less weight than non-diabetic patients (26). These findings imply that topiramate might play a potential role in the treatment of obesity associated with type 2 diabetes mellitus.

The topiramate group was more likely to have unpleasant symptoms such as paraesthesias, hypoesthesia and changes in taste, but no major adverse events were found. The odds ratio for side effects was increased when topiramate was prescribed in higher dosage as demonstrated by our sensitivity analyses. However, because adverse events were analyzed as intention-to-treat after a short period of treatment, side effects that are intermittent and prone to vanish after weeks of treatment could not be properly evaluated. On the other hand, it is worthy to notice that other side effects that required a long-term topiramate treatment (i.e. renal stones) might have been underestimated because the longest follow-up was 60 weeks. In addition, despite being infrequently reported as visual disturbs in our meta-analysis, the occurrence of topiramate-associated acute glaucoma is well described in the literature (27,28) and because its potential unfavourable prognosis if not promptly detected, this association should be taken into account. In this sense, proper warnings about the potential side effects are needed for topiramate prescription.

The mechanism of weight loss promoted by topiramate is not well known. Topiramate is a weak carbonic anhydrase inhibitor, and also enhances gamma-aminobutyric acid-mediated chloride fluxes (29), blockade of kainite-induced fluxes (30) and state-dependent blockade of sodium (31).Those pathways have no obvious relationship to appetite or weight loss, although animal models suggest that topiramate central action might reduce the food intake (32). Moreover, in rodents' models, topiramate showed an effect in lipoprotein lipase in adipose tissue and muscle (33).

Our literature search was extensive; we tested for and found no evidence of publication bias. The quality of original studies was checked according to PRISMA statement and most of the studies fulfilled all components. We are aware that publication bias and the quality issues of individual studies may still exist despite our best efforts to conduct a comprehensive search and despite the lack of statistical evidence of existence of bias. Moreover, several

unanswered questions remained about topiramate prescription as an anti-obesity agent such as direct comparisons with currently approved drugs for obesity, optimal treatment duration and efficacy of topiramate combination with other anti-obesity drugs.

In summary, our findings suggest that topiramate's prescription as an anti-obesity agent is associated with substantial weight loss. Although unpleasant side effects were a limitation of its use and proper warnings about side effects are needed for topiramate prescription, topiramate treatment was not associated with major harmful events. These findings suggest that topiramate might be a useful adjunctive therapeutic tool in the treatment of obesity, especially in patients who have other indications, such as seizure disorders, in addition to obesity.

Author contributors

Dr Kramer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kramer CK; Acquisition of data: Kramer CK, Pinto LC; Analysis and interpretation of data: Kramer CK, Leitão CB, Canani LH, Azevedo MJ, Gross JL; Drafting of the manuscript: Kramer CK; Critical revision of the manuscript for important intellectual content: Kramer CK, Leitão CB, Azevedo MJ, Canani LH, Gross JL; Statistical analysis: Kramer CK; Obtained funding: Leitão CB, Azevedo Jobim MJ, Canani LH, Gross JL.

Ethical approval

Not required.

Conflict of Interest Statement

No conflict of interest was declared.

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