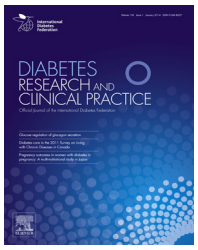
Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



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

Bridget Paravattil [a,*], *Kyle J. Wilby* [a], *Ricky Turgeon* [b]

[a] *College of Pharmacy, Qatar University, PO Box 2713, Doha, Qatar*
[b] *University of British Columbia Hospital, 2211 Westbrook Mall, Vancouver, Canada*

ARTICLE INFO

Article history:
Received 24 September 2015
Received in revised form
14 January 2016
Accepted 8 February 2016
Available online 17 February 2016

Keywords:
Topiramate
Type 2 diabetes mellitus
Weight loss
Obesity

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.

© 2016 Elsevier Ireland Ltd. All rights reserved.

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

* *Corresponding author*. Tel.: +974 4403 5586; fax: +974 4403 5551.
E-mail addresses: bridgetj@qu.edu.qa, bridgetp214@gmail.com (B. Paravattil).
http://dx.doi.org/10.1016/j.diabres.2016.02.002
0168-8227/© 2016 Elsevier Ireland Ltd. All rights reserved.

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].

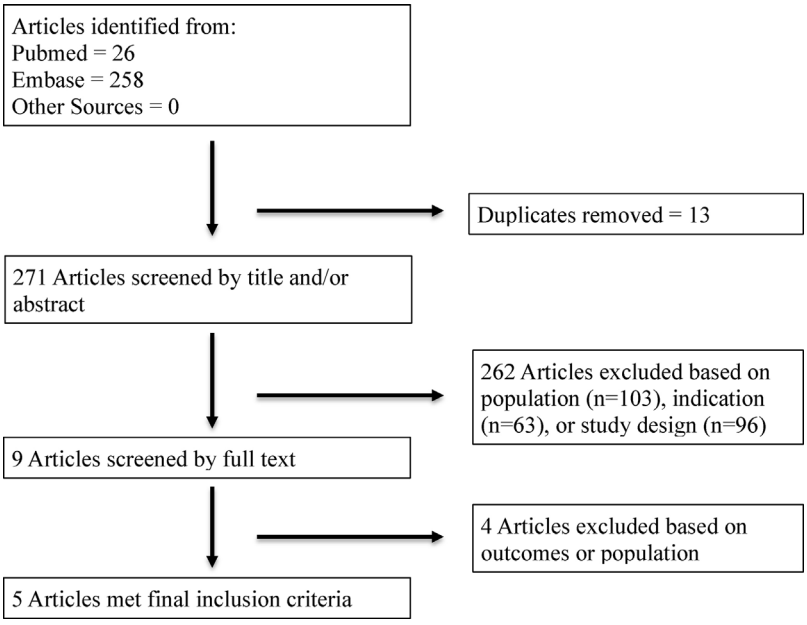


Fig. 1 – Literature search flow diagram.

Table 1 – Study characteristics.

Study	Population	Topiramate (mg) patients (*n*)	Placebo patients (*n*)	Primary outcome
Eliasson [15]	T2DM controlled by diet or SU × 6 months HbA1c 6.5–10.0% (48–86 mmol/mol) BMI 27–50 kg/m Stable weight × 2 months (±4 kg)	TP 192 *n* = 19	PB ± SF *n* = 19	mean weight change (kg) at week 44: TP −7.24 ± 4.26 PB 0.01 ± 2.54 $p < 0.0001$
Rosenstock [17]	T2DM treated with diet + exercise ± metformin BMI 27–50 kg/m HbA1c 6.5–11.0% (48–97 mmol/mol) FPG 7–13 mmol/l	TP CR 175 *n* = 54	PB + lifestyle program ± metformin *n* = 57	Mean weight loss (kg) at week 16: TP −6.0 ± 5.2 PB −2.5 ± 3.1 $p < 0.001$
Stenlof [18]	T2DM naïve to DM medications BMI 27–50 kg/m HbA1c <10.0% (86 mmol/mol) FPG 7–13 mmol/l	TP 96 *n* = 180 TP 192 *n* = 180	PB + lifestyle program *n* = 181	Weight loss (%) at week 40: TP 96 mg 6.6 TP 192 mg 9.1 PB 2.5% $p < 0.001$
Toplak [19]	18–75 years T2DM treated with only metformin × 4 months BMI 27–50 kg/m HbA1c <11.0% (97 mmol/mol) FPG 7–13 mmol/l	TP 96 *n* = 219 TP 192 *n* = 213	PB + lifestyle program *n* = 208	Weight loss (%) at week 24: TP 96 mg 4.5 TP 192 mg 6.5 PB 1.7 $p < 0.001$
Moradi [16]	Age 18–75 years T2DM, DM treatment unspecified BMI 27–50 kg/m A1C < 11.0% (97 mmol/mol) FPG 7–13 mmol/l Stable weight × 3 months (±3 kg)	TP 150 *n* = 39	PB + lifestyle program *n* = 30	Mean weight change (kg) at week 29: TP 1.83 ± 0.50 PB 5.18 ± 0.99 $p = 0.523$

BMI, body mass index; CR, controlled release; DM, diabetes; FPG, fasting plasma glucose; PB, placebo; SU, sulfonylurea; T2DM, type 2 diabetes; TP–topiramate.

3.2. *Risk of bias*

Risk of bias results was variable between studies as seen in Table 2. Two trials described adequate methods for sequence generation and blinding, while only 1 trial provided enough information to assess allocation concealment [17]. Two trials did not sufficiently address incomplete outcome data (drop-outs not all accounted for) [16,19], while all studies reported pre-defined outcomes. All studies were not free from other biases, which were largely based on imbalances in relevant baseline characteristics (HbA1c and fasting glucose) and definitions of modified intention to treat groups

Table 2 – Risk of bias assessments.

Study	Sequence generation	Allocation concealment	Blinding	Addressed incomplete outcome data	Selective outcome reporting	Free of other bias	Risk of bias
Eliasson [15]	Unclear	Unclear	Unclear	Yes	Yes	No	Unclear
Moradi [16]	Unclear	Unclear	Yes	No	Yes	No	High-unclear
Rosenstock [17]	Yes	Yes	Yes	Yes	Yes	No	Low
Stenlof [18]	Unclear	Unclear	Unclear	Yes	Yes	No	High-unclear
Toplak [19]	Yes	Unclear	Unclear	No	Yes	No	High

3.3. *Primary efficacy outcome*

3.3.1. *Weight change*

Three trials provided sufficient data on weight change for 200 study participants (Fig. 2). Topiramate produced a statistically significant reduction in weight compared to placebo using a fixed-effects model (mean difference −3.4 kg, 95% CI −3.8 to −3.0) [15–17]. Although there was high heterogeneity between studies (I^2 = 67%), removal of the smallest trial, which also had the largest effect size, reduced I^2 to 0%. All 3 trials individually demonstrated a statistically significantly favorable effect of topiramate, and use of a random-effects model did not attenuate this difference.

3.4. *Secondary efficacy outcomes*

3.4.1. *Change in body mass index*

Conforming with the primary outcome, for the 3 trials that provided sufficient data, BMI among 200 subjects was statistically significantly lower with topiramate than placebo using a fixed-effects model (mean difference −1.4 kg/m^2, 95% CI −1.8 to −1.0) [13–15]. As with the primary outcome, the large effect size in the smallest trial explained the high heterogeneity (I^2 = 50%). All 3 trials individually demonstrated a statistically significantly favorable effect of topiramate, and use of a random-effects model did not attenuate this difference.

3.4.2. *Change in hemoglobin A1c*

Three trials including a total of 436 subjects provided sufficient data on change in HbA1c for meta-analysis [15,17,19]. Topiramate produced a statistically significant reduction in HbA1c compared to placebo using a fixed-effects model (mean difference −0.45%, 95% CI −0.6 to −0.3). As with the primary outcome, the large effect size in the smallest trial explained the high heterogeneity (I^2 = 50%). All 3 trials individually demonstrated a statistically significantly favorable effect of topiramate, and use of a random-effects model did not attenuate this difference.

3.5. *Safety outcomes*

3.5.1. *Serious adverse events (SAE)*

Four trials provided sufficient data for serious adverse events (SAEs) (Fig. 3) [15,17–19]. For patients on topiramate treatment, 55 patients of 860 (6.4%) experienced a SAE, as compared to 17 patients of 464 (3.7%) on placebo. Using a fixed-effects model (I^2 = 0%), the risk of SAEs for 1324 subjects was higher with topiramate compared to placebo (RR 1.69, 95% CI 1.00–2.87, p = 0.05). SAEs reported include hepatic failure and other

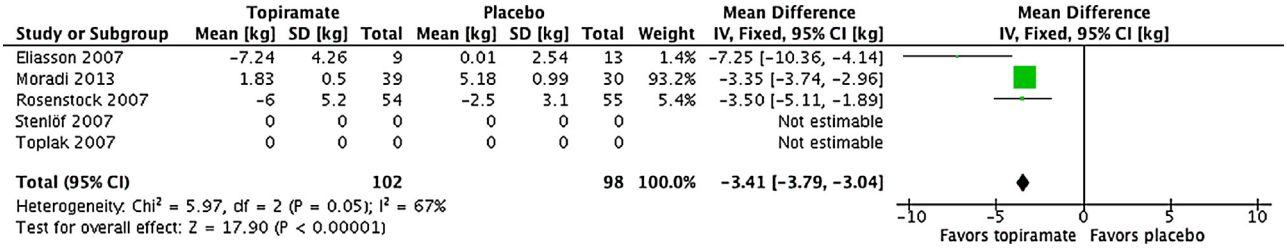


Fig. 2 – Primary outcome: mean difference in weight loss with topiramate versus placebo.

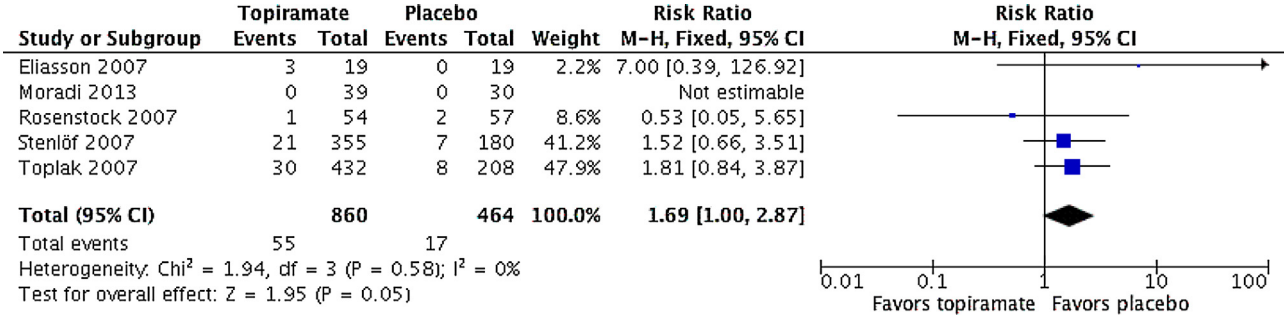


Fig. 3 – Secondary outcome: risk of serious adverse events (SAEs) with topiramate versus placebo.

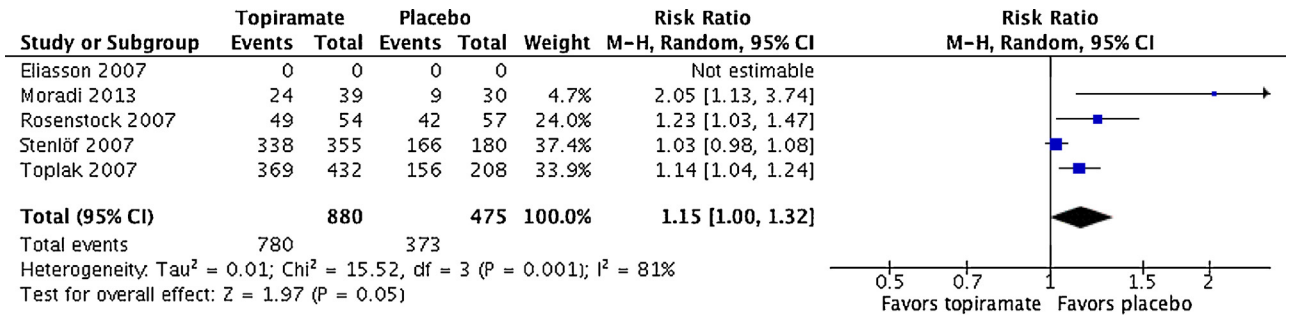


Fig. 4 – Secondary outcome: risk of adverse events with topiramate versus placebo.

increases in liver enzymes, injuries and falls, renal calculi, and viral infection with leukopenia.

3.5.2. *Total adverse events*

Four trials provided sufficient data for adverse events (Fig. 4) [16–19]. Adverse events experienced among topiramate users were 780 of 880 (88.6%) as compared to 373 of 475 (78.5%) for the placebo group. Using a random-effects model for the high heterogeneity not explained by any single trial ($I^2 = 81\%$), the risk of adverse events among 1355 subjects was higher with topiramate compared to placebo (RR 1.15, 95% CI 1.00–1.32, $p = 0.05$).

4. Discussion

This systematic review with meta-analysis showed topiramate decreased weight by a mean difference of 3.4 kg compared to placebo and other control agents, similar to its effects on non-diabetic individuals [12–14]. Other efficacy outcomes of change in BMI and HbA1c were also significantly reduced in topiramate groups. However, adverse events and serious adverse events occurred more commonly in topiramate users. Trials generally had high or unclear risk of bias in at least one domain, which would be expected to overstate benefits and attenuate harms in favor of topiramate.

The primary outcome showed weight reduction was significantly in favor of topiramate, however results must be interpreted within limitations of our data. Specifically, the two largest randomized controlled trials (Stenlof and Toplak) were not included in this outcome. This finding is therefore not a reflection of all identified studies from the systematic review. However, it is noted that these studies report findings in line with our meta-analyzed results by using percentage of weight change as the outcome measure. While a precise result cannot be known, we suspect that results would remain in favor of topiramate with the addition of these two studies.

Before recommendations can be made regarding the place of topiramate in practice, comprehensive risk-benefit analyses must be completed. The findings from our study show topiramate reduces weight in type 2 diabetic patients and may have minor reductions on BMI and HbA1c. To date, no evidence exists that the reductions observed in these surrogate markers translate into clinically meaningful reductions in hard endpoints such as the micro- and macrovascular complications of diabetes. Additionally, any proposed benefit from topiramate therapy must be interpreted against association risks. Our results demonstrate a high incidence of adverse events when these outcomes were meta-analyzed. Translating our data into clinically meaningful terms, we found numbers needed to harm for any adverse event to be 9 and for a serious adverse event to be 37. It is likely that these risks are unacceptable for clinicians and patients alike, especially with the lack of efficacy outcome data.

Although we found topiramate monotherapy reduces weight in type 2 diabetes patients, it should be used cautiously in practice at this time due to the limitations of the data identified and lack of clinically meaningful endpoints. Risks and benefits must be carefully weighed prior to topiramate initiation. The weight reduction observed, along with reductions in BMI and HbA1c, warrant further study to determine if long-term, clinically meaningful benefits can be found among obese, type 2 diabetes patients. Future studies should assess both monotherapy and combination agents over multiple years with endpoints relating to weight loss, HbA1c, and vascular events.

Conflicts of interest

None.

REFERENCES

[1] Kakkar AK, Dahiya N. Drug treatment of obesity: current status and future prospects. Eur J Intern Med 2015;26:89–94.
[2] Merlotti C, Morabito A, Ceriani V, Pontiroli AE. Prevention of type 2 diabetes in obese at-risk subjects: a systematic review and meta-analysis. Acta Diabetol 2014;51:853–63.
[3] Kyrou I, Kumar S. Weight management in overweight and obese patients with type 2 diabetes mellitus. Br J Diabetes Vasc Dis 2010;10:274–83.
[4] Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care 2007;30:1374–83.
[5] Klein S, Sheard NF, Pi-Sunyer X, Daly A, Wylie-Rosett J, Kulkami K, et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the

American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. Diabetes Care 2004;27:2067–73.
[6] Leong KS, Wilding JP. Obesity and diabetes. Best Pract Res Clin Endocrinol Metab 1999;13:221–37.
[7] Aldekhail NM, Logue J, McLoone P, Morrison DS. Effect of orlistat on glycaemic control in overwieght and obese patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Obes Rev 2015. http://dx.doi.org/10.1111/obr.12318.
[8] Wharton S. Current perspectives on long-term pharmacotherapy for obesity. Can J Diabetes 2015. http://dx.doi.org/10.1016/j.jcjd.2015.07.005. pii: S1499-2671(15)00553-5.
[9] Yanovski SZ, Yanovski JA. NAltrexone extended-release plus bupropion extended-release for treatment of obesity. JAMA 2015;313:1213–4.
[10] Fujioka K. Current and emerging medications for overweight or obesity in people with comorbidities. Diabetes Obes Metab 2015.
[11] Pucci A, Finer N. New medications for treatment of obesity: metabolic and cardiovascular effects. Can J Cardiol 2015;31:142–52.
[12] Harshman H, Kovach F. Clinical inquiries: is immediate-release topiramate an effective treatment for adult obesity? J Fam Pract 2014;63:745–6.
[13] Kramer CK, Leitao CB, Pinto LC, Canani LH, Azevedo MJ, Gross JL. Efficacy and safety of topiramate on weight loss: a meta-analysis of randomized controlled trials. Obes Rev 2011;12:e338–47.
[14] Domecq JP, Prutsky G, Leppin A, Sonbol MB, Altayar O, Undavalli C, et al. Clinical review: drugs commonly associated with weight change: a systematic review and meta-analysis. J Clin Endocrinol Metab 2015;100:363–70.
[15] Eliasson B, Gudbjornsdottir S, Cederholm J, Liang Y, Vercruysse F, Smith U. Weight loss and metabolic effects of topiramate in overweight and obese type 2 diabetic patients: randomized double-blind placebo-controlled trial. Int J Obes (Lond) 2007;31:1140–7.
[16] Moradi S, Kerman SR, Mollabashi M. The effect of topiramate on weight loss in patients with type 2 diabetes. J Res Med Sci 2013;18:297–302.
[17] Rosenstock J, Hollander P, Gadde KM, Sun X, Strauss R, Leung A. A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of topiramate controlled release in the treatment of obese type 2 diabetic patients. Diabetes Care 2007;30:1480–6.
[18] Stenlof K, Rossner S, Vercruysse F, Kumar A, Fitchet M, Sjostrom L. Topiramate in the treatment of obese subjects with drug-naive type 2 diabetes. Diabetes Obes Metab 2007;9:360–8.
[19] Toplak H, Hamann A, Moore R, Masson E, Gorska M, Vercruysse F, et al. Efficacy and safety of topiramate in combination with metformin in the treatment of obese subjects with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Int J Obes (Lond) 2007;31:138–46.