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# Effects and safety of use off label of the topiramate on weight loss

Efectos y seguridad de uso off label del topiramato en la pérdida de peso

Efeitos e segurança do uso off label do topiramato na perda de peso

## ABSTRACT

**Objective:** to conduct a survey in the national and international literature on the efficacy and safety of Topiramate in off-label use in weight loss. **Method:** This is an integrative review, in which the search for data was carried out in PUBMED, Embase and Cochrane, between the years 2016 to 2021, 10 researches were selected. **Results:** Topiramate can be a safe and effective therapeutic tool in the treatment of obesity, providing a reduction in body mass index, favoring glycemic control and blood pressure, both in adults and adolescents. Adverse effects associated with treatment mainly included dysgeusia, paresthesia and dry mouth. **Conclusion:** Topiramate used alone or in combination with metformin, phentermine, bupropion-naltrexone and Ispagula showed beneficial effects on weight loss.

**DESCRIPTORS:** Topiramate; Treatment; Obesity. Effects and safety; Weight Loss Drugs.

## RESUMEN

**Objetivo:** realizar una encuesta en la literatura nacional e internacional sobre la eficacia y seguridad del topiramato en uso sin receta en la pérdida de peso. **Método:** Se trata de una revisión integradora, en la que la búsqueda de datos se realizó en PUBMED, Embase y Cochrane, entre los años 2016 a 2021, se seleccionaron 10 investigaciones. **Resultados:** El topiramato puede ser una herramienta terapéutica segura y eficaz en el tratamiento de la obesidad, proporcionando una reducción del índice de masa corporal, favoreciendo el control glucémico y la presión arterial, tanto en adultos como en adolescentes. Los efectos adversos asociados con el tratamiento incluyeron principalmente disgeusia, parestesia y sequedad de boca. **Conclusión:** El topiramato usado solo o en combinación con metformina, fentermina, bupropión-naltrexona e Ispagula mostró efectos beneficiosos sobre la pérdida de peso.

**DESCRIPTORES:** topiramato; Tratamiento; Obesidad. Efectos y seguridad; Medicamentos para bajar de peso.

## RESUMO

**Objetivo:** realizar um levantamento na literatura nacional e internacional sobre a eficácia e a segurança do Topiramato no uso off-label na perda de peso. **Método:** Trata-se de uma revisão integrativa, na qual a busca dos dados, foi realizada no PUBMED, Embase e Cochrane, entre os anos de 2016 a 2021, foram selecionadas 10 pesquisas. **Resultados:** o Topiramato pode ser uma ferramenta terapéutica segura e eficaz no tratamento da obesidade, proporcionando redução do índice de massa corpórea, favorecendo o controle glicêmico e a pressão arterial, tanto em adultos, quanto em adolescentes. Os efeitos adversos associados ao tratamento incluíram principalmente disgeusia, parestesia e boca seca. **Conclusão:** o Topiramato utilizado de forma isolada ou em combinação com a metformina, a fentermina, bupropiona-naltrexona e a Ispagula mostrou efeitos vantajosos na perda de peso.

**DESCRIPTORIOS:** Topiramato; Tratamento; Obesidade. Efeitos e segurança; Fármacos para Perda de Peso.

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**INTRODUCTION**

**O**besity is a chronic disease of multifactorial origin characterized by excess body adiposity, which causes damage to health. Obesity is assuming epidemic proportions in almost every country. <sup>1</sup> According to projections by the World Health Organization (WHO), it is estimated that around 2.3 billion adults in the world are overweight and that 700 million of these are considered obese. <sup>2</sup> In Brazil, the proportion of obese individuals in 2017 was 18,9%, with greater representation among men (19,2%) than among women (18,7%). <sup>3-4</sup> Obesity can be classified into endogenous and exogenous. <sup>5</sup> The treatment of obesity includes nutritional, pharmacological and/or physical activity approaches, but these techniques and lifestyle changes have been shown to be ineffective (98% of recurrence) in morbidly obese individuals. <sup>6-8</sup>

For the pharmacological treatment of obesity, a study showed that the most used were Sibutramine (65%), followed by Orlistat (26.25%), Fluoxetine (3.75%), Duloxetine (2.5%) and Topiramate (2.5%), remembering that the last three are off-label medications (off the package insert) that is, they are marketed for the treatment of anxiety and depression. <sup>9</sup>

With regard to Topiramate, it is noteworthy that it is a medication indicated for the treatment of seizures, being considered a substituted sulfamate monosaccharide. It has currently been used in the management of migraine, migraine, neuropathic pain, depressive syndrome and obesity. In addition, Topiramate has been used off label in the treatment of weight loss. However, its mechanism of action as a cause of weight reduction is still unknown, it is known that it inhi-

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bits neurotransmitters, such as serotonin, noradrenaline, causing satiety to occur. <sup>9-10</sup>

The use of offlabel medication is an experimental treatment, without any scientific evidence of its effectiveness, which can pose risks to patients' lives. <sup>10</sup> However, what can be seen in the context of dispensing such drug classes is that the financial health of the pharmaceutical industries is the main beneficiary of the commercialization of these drugs. <sup>11-12</sup> Taking into account the impacts caused by obesity and the diversity of existing treatments, the interest in analyzing in the literature the efficacy and safety of Topiramate in the use of the label in weight loss emerged. Therefore, the general objective of this research was to carry out a survey in the national and international literature on the efficacy and safety of Topiramate in the use of the label in weight loss, and specifically it was the intention to identify the advantages and disadvantages of using Topiramate in weight loss, demonstrate the dosages and time of use of Topiramate in weight loss.

**METHODS**

It was an integrative review research, developed in the following phases: elaboration of the guiding question, literature search or sampling, data collection, critical analysis of the included studies, discussion of results and presentation of the integrative review. The research question was: what is the efficacy and safety of Topiramate in the use of the label in weight loss?

The search for research was carried out in PUBMED, Embase and Cochrane, by combining the following descriptors in English: Topiramate; Treatment; Obesity; Effects and safety; Weight

Loss Drugs (according to Medical Subject Headings - MESH). These descriptors were used in the databases mentioned with the Boolean connective “and”.

The study included primary research, experience reports published from January 2016 to March 2021, in Portuguese, English and Spanish, which studied the effects of topiramate on weight loss in obese patients. Duplicate researches, carried out in animals, that escaped the objective proposed by this study and review researches, with the exception of meta-analyses, were excluded.

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The collected data were submitted to a thorough reading for selection. The researches were characterized in a summary table and the results were distributed in a discursive way, making a comparison between the different findings through a standardization of the contents, which were grouped according to their similarity. Finally, the data were validated by two researchers.

## RESULTS

The results of this study were built

through the analysis and interpretation of 10 studies that responded to the proposed objectives, with greater emphasis on those published in 2020, with three selected. As for the methodology adopted by these studies, clinical trials stood out. Only one study evaluated Topiramate in isolation for weight loss.<sup>13</sup> Two studies evaluated the combination of Topiramate with metformin. Another five evaluated the combination of topiramate and phentermine.<sup>14-20</sup> Chart 1 shows the databases, country of origin, title, type of study, authors, journal and year of publication.

## DISCUSSION

Topiramate has an established role

Chart 1: Characterization of the results of selected surveys.

DATA BASE	COUNTRY	TITLE	STUDY TYPE	AUTHORS	JOURNAL AND PUBLICATION YEAR
PUBMED	U.S.A.	Health-related quality of life in two randomized controlled trials of phentermine/topiramate for obesity: What mediates improvement?	Randomized Clinical Trial	Kolotkin et al.	Qual Life Res/ 2016
PUBMED	Brazil	Safety assessment of combination therapies in the treatment of obesity: focus on naltrexone/bupropion extended release and phentermine-topiramate extended release	Clinical Review	Halpern e Mancini	Expert opin drug saf./2017
Embase	U.S.A.	An Innovative Disease-Drug-Trial Framework to Guide Binge Eating Disorder Drug Development: A Case Study for Topiramato.	Case study	Kalaria et al.	Clin Transl Sci/ 2019
PUBMED	U.S.A.	A randomized, double-blind, placebo-controlled, pharmacokinetic and pharmacodynamic study of a fixed-dose combination of phentermine/ topiramate in adolescents with obesity.	A randomized, double-blind, placebo-controlled trial	Hsia et al.	Diabetes Obes Metab/ 2020
PUBMED	Israel	The Mitigating Effect of Phentermine and Topiramate on Weight Regain After Roux-en-Y Gastric Bypass Surgery	Randomized Clinical Trial	Istfan et al.	Obesity (Silver Spring)/ 2020
Cochrane	China	Efficacy and safety of phentermine/topiramate in adults with overweight or obesity: A meta-analysis and systematic review	A systematic review and meta-analysis	Lei et al.	MedRxiv preprint/ 2020
Embase	Israel	A randomized, placebo controlled crossover trial of phentermine topiramate ER in patients with binge eating disorder and bulimia nervosa.	Randomized, placebo-controlled crossover trial	Safer et al.	First published/ 2020

PUBMED	China	Outcomes and safety of concomitant topiramate or metformin for antipsychotics-induced obesity: a randomized-controlled trial.	Randomized Clinical Trial	Wang et al.	Ann Gen Psychiatry/ 2020
PUBMED	India	Study on Efficacy of Topiramate: Impact on weight Loss in Obese patients.	Randomized Clinical Trial	Nithyakala e Sathyaprabha	Expert opin drug saf/ 2021
Expert opin drug saf/ 2021	Estados Unidos da América	Case Report: Off Label Utilization of Topiramate and Metformin in Patients With BMI $\geq$ 50 kg/m <sup>2</sup> Prior to Bariatric Surgery.	Case Report	Sari, Seip e Umashanker	Case Report: Pharmacological Weight Loss With Generics 2021
Source: PUBMED, Embase and Cochrane					

as an anticonvulsant, but it may have a role in the treatment of obesity, as most of the studies analyzed showed, as only in one of the studies was it possible to identify that the combination therapy of Topiramate and phentermine was not well tolerated, in which more than half of the patients stopped taking it due to adverse effects.<sup>16</sup>

Two studies agree that the use of topiramate as a first-line therapy for weight loss is limited due to its side effect profile, which includes cognitive dysfunction, paresthesia, taste perversion, metabolic acidosis and ocular toxicity that can occur as adverse effects. Thus, selection of the appropriate dose is necessary to maximize the benefit of reducing and limiting the risks associated with adverse effects.<sup>13,15</sup> Differently, a study that analyzed the combination of topiramate and phentermine in the weight loss of patients with bulimia nervosa, identified that this combination proved to be safe and effective, being well tolerated, without mentioning any disadvantages.<sup>20</sup> In another study, Topiramate was used in obese patients with binge eating disorder. In the control group, the dose-response relationship identified demonstrated that a daily dose of 125 mg of Topiramate was necessary to exhibit a marked reduction in weekly weight loss.<sup>13</sup>

In most of the studies analyzed, the main advantage of using Topiramate, either individually or in combination with phentermine or metformin, was the significant weight loss, which ranged from 5 to more than 10%, improving cardiovascular risk factors, inclu-

ding lowering systolic blood pressure and glucose levels.<sup>14,15,18-18</sup>

In a study carried out in the United States of America, with three patients, identified the association of topiramate with metformin, with the advantages of modifying the hunger impulse, including the reduction of cravings and an increase in the feeling of satiety. Medications can be used alone or in combination to facilitate preoperative weight loss.<sup>15</sup> Similar to the previous study, authors explored the efficacy and safety of topiramate and metformin in Chinese patients, and it was possible to verify that these two medications had effective effects in reducing obesity, significantly reducing body weight, BMI, the waist-hip ratio and good tolerance in psychiatric patients, with no disadvantages being observed in its use.<sup>14</sup>

Another study analyzed 1.196 electronic medical records of patients undergoing bariatric surgery between 2004 and 2015 and showed that phentermine and topiramate, used individually or in combination, can significantly reduce weight loss after bariatric surgery. There was no evidence of disadvantage in the use of these medications.<sup>18</sup>

In another study, it was possible to identify the same advantages of the combination of these two medications mentioned above and also brought direct benefits to the health-related quality of life of 88,2% of the 2.374 patients evaluated.<sup>15</sup> In a meta-analysis of randomized clinical trials, phentermine therapy combined with topiramate resulted in a 7,73 kg weight loss, reduced waist circumference, blood pressure, blood

sugar levels and lipid levels. Adverse effects associated with treatment mainly included dysgeusia, paraesthesia, dry mouth.<sup>19</sup>

In another meta-analysis, fixed-dose combinations of bupropion-naltrexone and titrated-dose combinations of phentermine and topiramate were evaluated in 2.410 patients, and it was possible to identify efficacy and safety, with the same adverse effects mentioned in the previous study.<sup>21</sup> Other authors evaluated the fixed-dose combination of immediate-release phentermine and extended-release topiramate in adolescents aged 12 to 17 years with obesity and found that the weight loss was statistically significant and the safety profile was tolerable. These data indicate that medium and high dose levels are appropriate and have long-term efficacy in adolescents.<sup>17</sup>

With a different approach from previous studies, Topiramate and Ispaghula were tested in obese patients for 6 months. The final dose of Topiramate 25 mg to 50 mg/day and Ispaghula 1,2 g to 3,6 g/day varied, making it possible to identify that Topiramate can be considered in the treatment of patients with obesity. When comparing the mean BMI results of ispaghula and topiramate, it was observed that topiramate is more effective in reducing weight in patients in Group 2 (test).<sup>22</sup>

## CONCLUSION

Topiramate has been found to be an effective adjuvant therapeutic tool in the treatment of obesity, as long as side

effects are considered. This medication showed significant effects on weight loss, reduction of BMI, reduction of weight gain after bariatric surgery, glycemic control and blood pressure, both in adults and adolescents. These advantages were observed in its use alone, as well as in combination with metformin

or phentermine. With regard to the recommended dosage, it was not possible to identify a consensus among the literature analyzed. However, the minimum dosage per day used was 50 mg and the maximum was 150 mg, for a minimum period of 3 months.

The disadvantages of using Topira-

mate to control obesity were related to the adverse effects of this medication, which can influence the tolerance of patients and, consequently, give up the treatment. Further long-term clinical and pharmacovigilance studies are needed to understand the long-term efficacy and safety of Topiramate. ■

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