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REVIEW

Analysis of the Effectiveness and Safety of the Fentermine and Topiramate Association in Obesity: A Systematic Review of the Literature

Análisis de la Eficacia y Seguridad de la Asociación de Fentermina y Topiramato en la Obesidad: Una Revisión Sistemática de la Literatura

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ABSTRACT

Introduction: obesity is a chronic disease that can manifest itself at any stage of life, with an increasing incidence and prevalence, which contributes to other health problems.
Objective: to determine the application of Phentermine and Topiramate in the treatment of obesity.
Methods: a search for clinical trials and randomized controlled trials was conducted. The search was carried out exhaustively in the search engines/databases PubMed, Cachrane Library, Scopus, Google Scholar and Web of Science.
Results: 21 studies were identified, of which 11 met the inclusion criteria. The evaluated research articles provided moderate evidence that the combination of Phentermine and Topiramate is effective and safe for the treatment of obesity. A gradual decrease in patients' body weight was observed from the start of treatment and up to 20 weeks thereafter. In addition, notable secondary outcomes, such as changes in blood pressure, triglyceride levels, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and glycosylated hemoglobin (A1C) were found from the start of treatment.
Conclusion: the doses of these drugs for chronic weight control in adults are 3,75 mg, 7,5 mg and 15 mg in the case of phentermine and 23 mg, 46 mg and 92 mg of topiramate, being the maximum recommended dose 15 mg/92 mg. If a 5 % weight loss is not achieved after 12 weeks with this dose, their use should be reconsidered.

Keywords: Obesity; Weight Loss; Chronic Disease; Phentermine; Topiramate.

RESUMEN

Introducción: la obesidad es una enfermedad crónica que puede manifestarse en cualquier etapa de la vida, con una incidencia y prevalencia en aumento, que contribuye con otros problemas de salud.
Objetivo: determinar la aplicación de la Fentermina y el Topiramato en el tratamiento de la obesidad.
Métodos: se realizó una búsqueda de información de tipo ensayos clínicos y ensayos controlados randomizados. La búsqueda se realizó de manera exhaustiva en los buscadores/bases de datos PubMed, Cachrane Library, Scopus, Google Académico y Web of Science.
Resultados: se identificaron 21 estudios, de las cuales 11 cumplieron con los criterios de inclusión. Los artículos de investigación evaluados proporcionaron evidencia moderada de que la combinación de Fentermina y Topiramato es efectiva y segura para el tratamiento de la obesidad. Se observó una disminución gradual en el peso corporal de los pacientes desde el inicio del tratamiento y hasta las 20 semanas posteriores. Además, se encontraron resultados secundarios notables, como cambios en la presión arterial, niveles de triglicéridos, colesterol de lipoproteínas de alta densidad (HDL), colesterol de lipoproteínas de baja densidad (LDL) y hemoglobina glicosilada (A1C) desde el inicio del tratamiento.
Conclusión: las dosis de estos medicamentos, para el control crónico del peso en adultos es de 3,75 mg, 7,5 mg y 15 mg en el caso de la fentermina y de 23 mg, 46 mg y 92 mg de topiramato, siendo la dosis máxima recomendada 15 mg/92 mg. si no se logra una pérdida de peso del 5 % después de 12 semanas con esta dosis, se debe reconsiderar su uso.

Palabras clave: Obesidad; Pérdida de Peso; Enfermedad Crónica; Fentermina; Topiramato.

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INTRODUCTION

Obesity is a chronic disease characterized by the excessive consumption of calories that the body stores as fat. It can manifest itself at any stage of life, and its prevalence progressively increases over the years, contributing to other health problems such as diabetes, heart disease, peripheral vascular disease, cerebrovascular accidents, sleep apnea, osteoarthritis, fatty liver, infertility, and even some types of cancer.[1] Its prevalence is so high that the World Health Organization (WHO) has called it "the epidemic of the 21st century", emphasizing that obesity should not only be managed as a chronic disease but also as a serious global public health problem.[1,2]

Body mass index (BMI) is an evaluative, easy, and inexpensive measurement that relates a person's weight and height to categorize their weight as underweight, healthy weight, overweight, or obese.[1,3,4,5] For this evaluation, we will divide the person's weight in kilograms by the square of their height in meters. In the adult population, the World Health Organization defines a BMI of 25kg/m2 or higher as overweight and a BMI of 30kg/m2 or higher as obese (figure 1).[2,6,7,8]

TABLA 1Clasificación del sobrepeso y la obesidad según el IMC, la circunferencia de la cintura y el riesgo de enfermedad asociado (1)

			Riesgo de enfermedaden relación con el peso normal y la circunferencia de la cintura	
			Hombres ≤102 cm (≤40 pulgadas)	> 102 cm (>40 pulgadas)
	IMC, kg/m2	clase de obesidad	Mujeres ≤88 cm (≤35 pulgadas)	> 88 cm (>35 pulgadas)
Bajo peso	<18,5	-	-	-
Normalb	18,5-24,9	-	-	-
Exceso de peso	25,0-29,9	-	Aumentó	Alto
Obesidad	30,0-34,9	I	Alto	Muy alto
	35,0-39,9	II	Muy alto	Muy alto
Obesidad extrema	≥40	III	Extremadamente alto	Extremadamente alto

NotaLos riesgos de comorbilidades y los puntos de corte para considerar una intervención terapéutica difieren en las poblaciones asiáticas y no asiáticas (3). Los miembros de raza negra y algunos grupos étnicos minoritarios también corren un mayor riesgo de padecer enfermedades crónicas con un IMC más bajo que la población blanca (6).

aRiesgo de enfermedad por diabetes tipo 2, hipertensión y enfermedades cardiovasculares.

bEl aumento de la circunferencia de la cintura también puede ser un marcador de mayor riesgo, incluso en personas con peso normal.

Figure 1. Classification of overweight and obesity according to BMI, waist circumference and associated disease risk

The imminent prevalence of overweight and obesity worldwide has given relevance to methods of losing weight through dietary adjustments and physical activity. However, the results are primarily short-term.[2] Pharmacological therapy has been a great complement to improve weight loss in people with obesity, overweight, and metabolic complications.[4]

For this reason, the Food and Drug Administration (FDA) has approved using several medications to complement and synergize the effectiveness of conventional weight loss methods. One of these medications is the combination of Phentermine and Topiramate, which has not only been shown to be effective in the treatment of overweight and obesity but also demonstrated an improvement in specific comorbidities such as blood pressure, cholesterol and triglyceride levels, and blood glucose.[5]

Phentermine is a drug used to help obese adolescents and adults who have not managed to lose enough weight with conventional methods such as diet and exercise and even as a complementary treatment in not-so-conventional methods such as bariatric surgery. This drug suppresses the appetite through interaction with biogenic amines, improving the release of dopamine and noradrenaline.[2,5]

Topiramate, on the other hand, is an anticonvulsant derived from D-fructose. Its mechanism of action has not been discovered with certainty. However, it is cataloged as a glutamate antagonist, as well as a carbonic anhydrase inhibitor; it also blocks sodium channels and increases GABA-mediated chlorine currents, activating hyperpolarizing K+ currents and inhibiting the activation of AMPA-type glutamic acid receptors. In general terms, it is an anticonvulsant, but it has also been used to treat alcohol dependence and compulsive eating disorders and as a prophylactic for migraines.[3,5,9]

The doses of these drugs for chronic weight control in adults are 3,75 mg, 7,5 mg, and 15 mg for phentermine, and 23 mg, 46 mg, and 92 mg for topiramate, with the maximum recommended dose being 15 mg/92 mg. If a 5 % weight loss is not achieved after 12 weeks with this dose, its use should be reconsidered.[6,7,8,9]

The result obtained was the change in weight from the start of treatment until at least 20 weeks after initiation. Secondary results were percentage changes in weight, as well as changes in blood pressure, triglyceride level, level of high-density lipoprotein (HDL) cholesterol, level of low-density lipoprotein (LDL) cholesterol, and glycosylated hemoglobin (A1C) from the start date (figure 2).[10]

There are several articles published to date that mention the adverse effects produced by the pharmacological treatment with the association of phentermine and topiramate, such as paraesthesias, constipation, diarrhea, nausea, dry mouth, depressed mood, agitation, suicidal ideation or self-injurious behavior. However, more adverse effects have been reported due to digestive intolerance to the medication than to neurological complications.

Multiple studies have shown a prevalence of cases in which the treatment has obtained safe and favorable results over those in which it has caused some complication or adverse effect.[8,11]

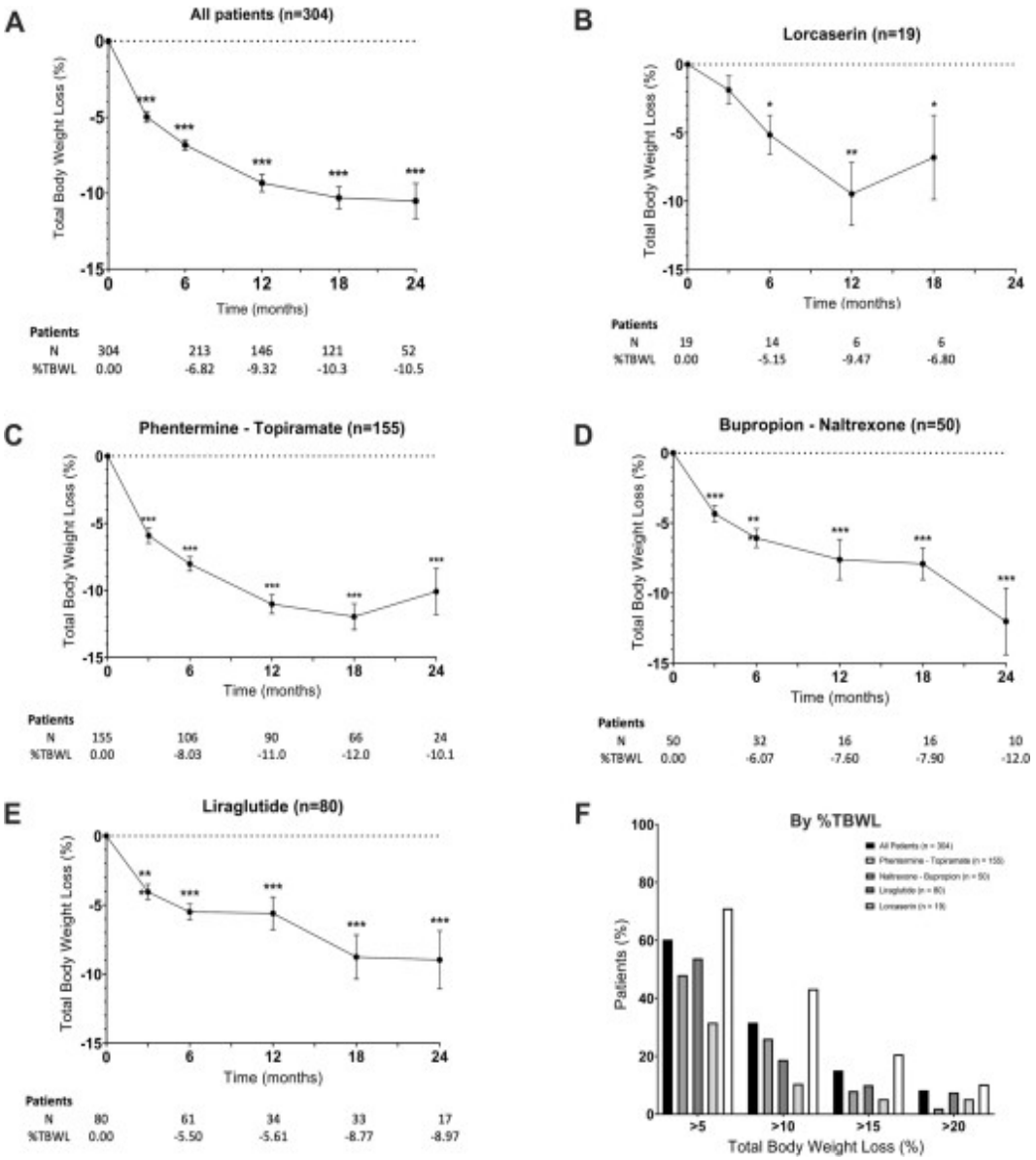


Figure 2. Weight loss results after starting anti-obesity medication. Change in body weight from baseline (% TBWL) at each visit over the course of 24 months. A) All, b) Lorcaserin c) Phentermine/topiramate-ER, d) Bupropion/naltrexone-SR, e) Liraglutide, and; f) Percentage of participants who at the last clinic visit had lost at least 5 %, 10 %, 15 % and 20 % of their total body weight.

METHOD

Study design

This study is configured as a systematic review that allows us to synthesize and critically and exhaustively analyze the available scientific evidence on the efficacy and safety of the association of Phentermine and Topiramate as a therapeutic option for the treatment of overweight and obese adolescents and adults, two increasingly prevalent health conditions that represent an essential challenge for public health.

Study population

Articles such as clinical trials and randomized controlled trials have been used in the association of Phentermine and Topiramate in treating obesity and overweight in adolescents and adults without restriction of time or sex.

Inclusion Criteria

- Scientific papers and publications evaluate the effectiveness and safety of the association of Phentermine and Topiramate in treating obesity and overweight in women and men.
- Publications in English and Spanish.
- Patients who are overweight and obese as diagnosed by BMI (body mass index). A BMI of 25 kg/m2 or higher is overweight, and a BMI of 30kg/m2 or higher is obese.
- Adolescent and adult patients with and without comorbidities who have undergone combination therapy with Phentermine and Topiramate.

Exclusion Criteria

- Children and pregnant women.
- Repeated publications.
- Patients with life-threatening morbidity or specific health conditions that could affect the evaluation of the treatment.
- Drug addicts.

Scope of the study

The scope of the study is university-based and carried out for the Universidad Abierta Interamericana as a final degree project.

Operational description of the variables

Table 1. Operational description of the variables

Variable	Definition	Type	Scale
Phentermine	Drug that acts as an appetite inhibitor by releasing noradrenaline and dopamine, being chemically similar to amphetamine.	Cualitativo	Nominal
Topiramate	It is an anticonvulsant derived from D-fructose. Its mechanism of action has not been discovered with certainty, however, it seems to act in several ways: inhibiting the action of carbonic anhydrase, blocking sodium channels, increasing GABA-mediated chlorine currents, activating hyperpolarizing K+ currents and inhibiting the activation of AMPA-type glutamic acid receptors. In general terms, its anticonvulsant action is more related to the prevention of epileptic seizures, but it has also been used to treat alcohol dependence and for the treatment of compulsive eating disorders and essential tremors.	Cualitativo	Nominal
Obesity	Obesity is a chronic disease characterized by the excessive consumption of calories that the body stores as fat. It can manifest itself at any stage of life and its prevalence increases progressively over the years, contributing to other health problems such as diabetes, heart disease and even some types of cancer.	Cualitativo	Ordinal

RESULTS

Our bibliographic and electronic search initially yielded 21 citations, of which the complete texts were obtained and investigated further. From the review of the full text, 10 studies were excluded for the following reasons: individual use of Phentermine in the treatment of overweight and obesity (n=5), treatment of childhood obesity (n=3), and no result of interest (n=2). Of the remaining studies that met our inclusion criteria, 8 were randomized controlled trials, and 3 were clinical trials.

Pharmacological treatment for overweight and obesity has been a topic of study and debate in medicine for many years due to the initial option of the usual methods such as exercise and healthy eating. However, multiple studies have shown the efficacy and safety of the combination of Phentermine and Topiramate in the treatment of overweight and obesity, especially in the last decade.

According to the research articles included, there was moderate evidence that the phentermine/topiramate combination is effective and safe in treating overweight and obesity. The doses of these drugs for chronic weight control in adults are 3,75 mg, 7,5 mg, and 15 mg for Phentermine, and 23 mg, 46 mg, and 92 mg for topiramate, with the maximum recommended dose being 15 mg/92 mg. If a 5 % weight loss is not achieved after 12 weeks with this dose, its use should be reconsidered.

The result obtained was the change in weight from the start of treatment until at least 20 weeks after initiation. Secondary outcomes were percentage changes in weight, as well as changes in blood pressure, triglyceride level, high-density lipoprotein (HDL) cholesterol level, level of low-density lipoprotein (LDL) cholesterol, and glycosylated hemoglobin (A1C) from the start date.

The relationship between treatment duration and efficacy was also examined, and it was found that the average estimated extra weight loss in patients who used phentermine/topiramate for more than 20 weeks was over 8,07 kg. Research has confirmed the efficacy and safety of the association of Phentermine and topiramate in treating overweight and obesity. Therefore, the American Gastroenterological Association (AGA) is prioritizing the development of clinical guidelines that inform the use of pharmacological therapies for treating overweight and obesity in adolescents and adults.

DISCUSSION

This systematic review aimed to evaluate the efficacy and safety of the association of Phentermine and Topiramate in treating overweight and obesity in adolescents and adults. The systematic review of randomized clinical trials on the use of phentermine and topiramate demonstrated a remarkable statistically significant effectiveness in weight loss from the first weeks of treatment, in addition to establishing a close relationship between the dose of the drugs and the degree of weight loss within a specific range.

Although the effectiveness of phentermine/topiramate for weight loss decreased after 108 weeks of treatment, most patients were able to maintain the weight loss at 56 weeks, so treatment with phentermine/topiramate resulted in an average weight loss of between 7,73 kg and 8,10 kg and also improved cardiovascular indicators such as waist circumference, blood pressure, blood glucose levels, and blood lipids.

It is important to emphasize that in addition to the effectiveness of phentermine/topiramate combination therapy in treating overweight and obesity, several articles also mention the adverse effects associated with this treatment, especially those that have a direct impact on the nervous system, such as paresthesias, dry mouth, constipation, dysgeusia, and dizziness. Although not enough

studies highlight these effects, they must be considered when deciding to use this pharmacological treatment for obesity.

Finally, it is interesting to mention that mechanisms of action have been proposed for phentermine/topiramate, including the release of neurotransmitters such as dopamine and norepinephrine and the inhibition of catecholamine reuptake, which reduces appetite. Topiramate acts on ion receptors and calcium channels, regulating neuronal activity. In addition, it is suggested that phentermine/topiramate increases heat production, glucose absorption, and tissue energy use. Due to its effects on lipids and glucose, phentermine/topiramate could reduce the need for antihypertensive and lipid-lowering drugs.

Given obesity's relevance to health,[12,13] new research is necessary to treat it using different approaches, including pharmacological ones.

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CONFLICT OF INTEREST

No conflict of interest is reported by the researchers**.**

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AUTHORSHIP CONTRIBUTION

Conceptualization: Juan José Izquierdo Miranda, Marcelo Adrián Estrín.
Research: Juan José Izquierdo Miranda, Marcelo Adrián Estrín.
Methodology: Juan José Izquierdo Miranda, Marcelo Adrián Estrín.
Visualization: Juan José Izquierdo Miranda, Marcelo Adrián Estrín.
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