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SYSTEMATIC 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 characterized by excessive calorie consumption, leading to fat storage, and can manifest at any stage of life, with prevalence increasing progressively over the years, contributing to other health problems such as diabetes, cardiovascular diseases, and even certain types of cancer. The imminent global prevalence of obesity has emphasized the need for weight loss methods, including dietary adjustments, physical activity, and pharmacological therapy, which has significantly improved weight loss in individuals with obesity and overweight. Fentermina is a medication used to aid adolescents and adults with obesity who have not achieved sufficient weight loss through conventional methods such as diet and exercise. It acts as an appetite inhibitor by releasing dopamine and noradrenaline. Topiramate, a D-fructose derivative anticonvulsant, has a mechanism of action that is not yet fully understood, but it is known for its anticonvulsant action and participation in treating compulsive eating disorders, overweight, and obesity.
Method: a systematic review of the literature was conducted based on clinical trials and randomized controlled trials to collect publicly available information. The search was carried out thoroughly in four different search engines/databases: PubMed, Cochrane Library, Scopus, Google Scholar, and Web of Science. All identified publications were carefully examined and analyzed to ensure the quality and relevance of the collected information.
Results: the literature review yielded a total of 21 references, of which 11 met the inclusion criteria. The research articles provided moderate evidence that the combination of Fentermina and Topiramato is effective and safe for obesity treatment. A gradual decrease in body weight was observed in patients from the beginning of treatment up to 20 weeks post-treatment. Additionally, notable secondary results were found, such as changes in blood pressure, triglyceride levels, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and hemoglobin A1C levels from the beginning of treatment.
Conclusions: the recommended doses for long-term weight control in adults are 3,75 mg, 7,5 mg, and 15 mg for Fentermina and 23 mg, 46 mg, and 92 mg for Topiramato. If a 5 % weight loss is not achieved after 12 weeks with this dose, its use should be reconsidered.

Keywords: Obesity; Phentermine-Administration and Dosage; Topiramate/Administration and Dosage.

RESUMEN

Introducción: la obesidad es una enfermedad crónica caracterizada por el consumo excesivo de calorías que el cuerpo almacena como grasa, puede manifestarse en cualquier etapa de la vida y su prevalencia aumenta progresivamente con el pasar de los años contribuyendo con otros problemas de salud, tales como diabetes, enfermedades cardíacas e incluso algunos tipos de cáncer. La inminente prevalencia de la obesidad a nivel

Método: se llevó a cabo una revisión sistemática de la literatura basada en ensayos clínicos y ensayos controlados randomizados, con el objetivo de recopilar toda la información pública disponible. La búsqueda se realizó de manera exhaustiva en cuatro buscadores/bases diferentes: PubMed, Cachrane Library, Scopus, Google Académico y Web of Science. Todas las publicaciones identificadas fueron cuidadosamente examinadas y analizadas para garantizar la calidad y relevancia de la información recopilada.
Resultados: la revisión de la literatura arrojó un total de 21 referencias, 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.
Conclusiones: 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; Administración y Dosis de Fentermina; Topiramato/Administración y Dosis.

INTRODUCTION

Obesity is a chronic disease characterized by excessive consumption of calories that the body stores as fat. It can manifest at any stage of life, and its prevalence increases progressively with age, contributing to other health problems such as diabetes, heart disease, peripheral vascular disease, stroke, 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 easy and inexpensive way to measure a person's weight and height to categorize their weight as underweight, healthy, overweight, or obese.[1,3,4,5,6,7] For this assessment, 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 25 kg/m2 or higher as overweight and a BMI of 30 kg/m2 or higher as obese.[2,8]

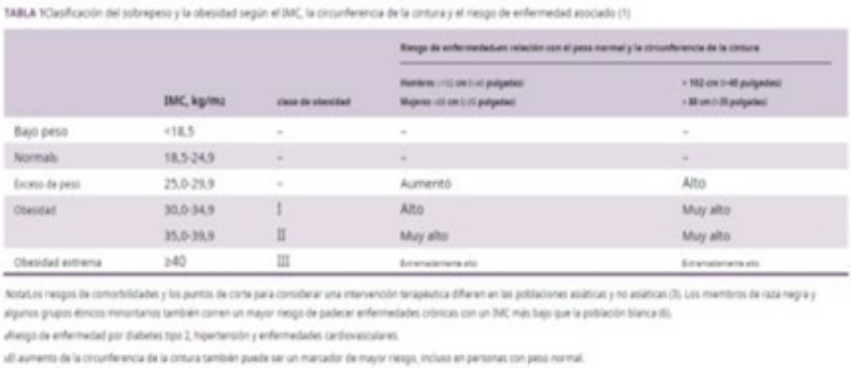

Figure 1. Classification of overweight and obesity by BMI, waist circumference and associated disease risk

The imminent prevalence of overweight and obesity worldwide has highlighted the importance of methods for losing weight through dietary adjustments and physical activity. However, the results are mostly short-term.[2] Drug 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 drugs to complement and synergize the effectiveness of conventional weight loss methods. One such drug is the combination of phentermine and topiramate, which has not only been shown to be effective in treating overweight and obesity but also improved specific comorbidities such as blood pressure, cholesterol and triglyceride levels, and blood glucose.[5]

Phentermine is a drug used to help adolescents and adults with obesity who have not been able to lose enough weight with conventional methods such as diet and exercise, and even as a complementary treatment in less traditional methods such as bariatric surgery. This drug works by suppressing appetite through interaction with biogenic amines, improving the release of dopamine and norepinephrine.[2,5]

Topiramate is an anticonvulsant derived from D-fructose. Its mechanism of action has not been discovered with certainty; however, it is classified as a glutamate antagonist and a carbonic anhydrase inhibitor. It also blocks sodium channels and increases GABA-mediated chloride 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, compulsive eating disorders, and migraine prophylaxis.[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 a maximum recommended dose of 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 to at least 20 weeks after initiation. Secondary results were percentage changes in weight, as well as changes in blood pressure, triglyceride levels, high-density lipoprotein (HDL) cholesterol level, low-density lipoprotein (LDL) cholesterol level, and glycated hemoglobin (A1C) from the start date.[10]

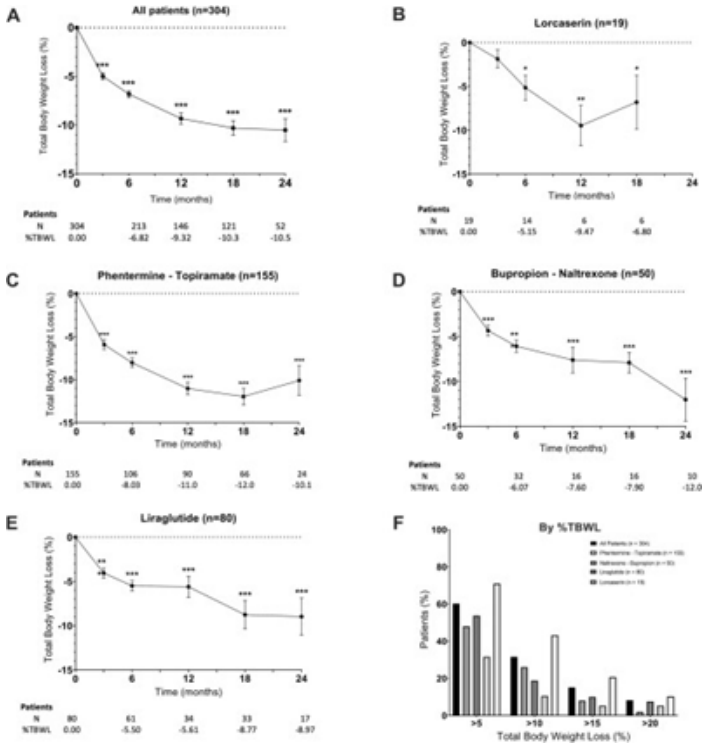

Figure 2. Change in weight from start of treatment to at least 20 weeks

Weight loss results after starting obesity medication. Body weight changes from baseline (% TBWL) at each visit over 24 months. A) All, b) Lorcaserin, c) phentermine/topiramate-ER, d) Bupropion/naltrexone-SR, e) Liraglutide, and f) Percentage of participants who, at their last clinic visit, had lost at least 5 %, 10 %, 15 %, and 20 % of their total body weight in there are several articles published to date that mention the adverse effects produced by pharmacological treatment with the combination of phentermine and topiramate, such as paresthesias, constipation, diarrhea, nausea, dry mouth, depressed mood, agitation, suicidal ideation, or self-harming behavior. However, greater adverse effects have been reported due to digestive intolerance to the medication than to neurological complications.

Multiple studies have shown a prevalence of cases where treatment has obtained safe and favorable results over those that have presented some complication or adverse effect to treatment.[8,11]

METHOD

Study design

This study is a systematic review that allows us to synthesize and critically and comprehensively analyze the available scientific evidence on the efficacy and safety of the combination 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 a significant public health challenge.

Study population

Articles such as clinical trials and randomized controlled trials on the combination of phentermine and topiramate in treating obesity and overweight in adolescents and adults were used, with no restrictions on time or sex.

Inclusion criteria

- Scientific studies and publications that evaluate the effectiveness and safety of the combination of phentermine and topiramate in the treatment of 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 25kg/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 treatment evaluation.
- Addicts to narcotic drugs.

Scope of the study

The scope of the study is university-based, and it was conducted for the Inter-American Open University as a final thesis project.

Table 1. Operational description of variables

Variable	Definition	Type	Scale
Phentermine	Drug that acts as an appetite inhibitor by releasing noradrenaline and dopamine, being chemically similar to amphetamine.	Qualitative	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 chloride 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 its use has also been implemented to treat alcohol dependence and for the treatment of compulsive eating disorder and essential tremor.	Qualitative	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.	Qualitative	Ordinal

RESULTS

Our literature and electronic search yielded 21 citations, from which the complete texts were obtained and investigated further. Upon 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 results 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 subject of study and debate in medicine for many years due to the initial choice of usual methods such as exercise and healthy eating. However, multiple studies have demonstrated 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 combining phentermine and topiramate in treating overweight and obesity is effective and safe. 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 a maximum recommended dose of 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 a change in weight from the start of treatment to at least 20 weeks after initiation. Secondary results were percentage changes in weight, as well as changes in blood pressure, triglyceride levels, high-density lipoprotein (HDL) cholesterol level, low-density lipoprotein (LDL) cholesterol level, 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 greater than 8,07 kg. It is important to note that research has confirmed the efficacy and safety of the combination of phentermine and topiramate in the treatment of overweight and obesity. Therefore, the American Gastroenterological Association (AGA) is prioritizing the development of clinical guidelines to inform the use of drug therapies for treating overweight and obesity in adolescents and adults.

DISCUSSION

This systematic review aimed to evaluate the efficacy and safety of the combination 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 remarkable efficacy in statistically significant weight loss from the first weeks of treatment and established a close relationship between the dose of the drugs and the degree of weight loss within a specific range.

Although the efficacy of phentermine/topiramate for weight loss decreased after 108 weeks of treatment, most patients were able to maintain their 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 efficacy of phentermine/topiramate combination therapy in the treatment of 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 confirm these effects, they should be considered when deciding to use this pharmacological treatment for obesity.

Finally, it is interesting to note 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 channels and calcium channels, regulating neuronal activity. In addition, it is suggested that phentermine/topiramate increases heat production, glucose absorption, and energy use by tissues. Due to its effects on lipids and glucose, phentermine/topiramate could reduce the need for antihypertensive and lipid-lowering medications.

CONCLUSIONS

The evidence gathered in this systematic review supports the pharmacological combination of phentermine and topiramate as an effective and safe therapeutic option for the treatment of overweight and obesity in adolescents and adults. A significant reduction in body weight has been demonstrated from the first weeks of treatment, accompanied by improvements in various metabolic and cardiovascular parameters. However, it is essential to consider the potential adverse effects, especially those related to the nervous system, which could limit its use in certain patients. The dosage should be carefully individualized, and its efficacy should be evaluated at 12 weeks, with the continuation of the study reconsidered if a 5 % reduction in body weight is not achieved. In short, this drug combo can be a valuable tool in a comprehensive approach to managing obesity, always under proper medical supervision.

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FINANCING

None.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

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Data curation: Juan José Izquierdo Miranda.
Formal analysis: Juan José Izquierdo Miranda.
Drafting - original draft: Juan José Izquierdo Miranda.
Writing - proofreading and editing: Juan José Izquierdo Miranda.