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# Fluoxetine, topiramate, and combination of both to stabilize eating behavior before bariatric surgery

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**Introduction.** Pharmacotherapy for the management of obesity is primarily aimed at weight loss, weight loss maintenance and risk reduction (reduction in body fat, risk factors for cardiovascular disease and the incidence of diabetes mellitus). Among drugs that have been evaluated for weight loss include antidepressants (fluoxetine) and antiepileptic (topiramate).

**Material and Methods.** We analyzed eating behavior and weight loss in a sample of morbid obesity patients before bariatric surgery. The patients suffering eating disturbances symptoms were grouped into three groups: one group received 40 mg of fluoxetine/day (Group A); another group received topiramate 200 mg/day (Group B); and the third group of patients were treated with fluoxetine 40 mg and 200 mg of topiramate/day (Group C).

**Results.** Patients treated with fluoxetine plus topiramate lost more weight at 3 and 6 months before surgery.

**Conclusions.** The use of the psychopharmaceutical drug (fluoxetine and topiramate) in morbid obese patients with eating disorders could represent a new approach to the management of eating behavior before bariatric surgery.

**Keywords:** Fluoxetine, Topiramate, Morbid obesity, Bariatric surgery

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## Fluoxetina, topiramato y combinación de ambos en el control de la conducta alimentaria antes de la cirugía bariátrica

**Introducción.** El tratamiento farmacológico de la obesidad está dirigido principalmente a la pérdida de peso, mantenimiento de la pérdida de peso y la reducción del riesgo

(reducción de la grasa corporal, factores de riesgo cardiovascular y la incidencia de diabetes mellitus). Entre los fármacos que han sido evaluados para bajar de peso están los antidepresivos (fluoxetina) y antiepilépticos (topiramato).

**Material y Métodos.** Se analiza la conducta alimentaria y la pérdida de peso en una muestra de pacientes con obesidad mórbida antes de la cirugía bariátrica. Aquellos pacientes que sufrían trastornos alimentarios se agruparon en tres grupos: un grupo recibió 40 mg de fluoxetina/día (Grupo A); topiramato 200 mg/día (Grupo B) y el otro fluoxetina 40 mg y 200 mg de topiramato (Grupo C).

**Resultados.** Los pacientes tratados con fluoxetina más topiramato perdieron más peso a los 3 y 6 meses antes de la cirugía.

**Conclusiones.** El uso de psicofármacos (fluoxetina y topiramato) en pacientes obesos mórbidos con trastornos de la alimentación puede representar una ayuda para el manejo de la conducta alimentaria antes de la cirugía bariátrica.

**Palabras clave:** Fluoxetina, Topiramato, Obesidad mórbida, Cirugía bariátrica

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## INTRODUCTION

Several problems have affected the drug treatment for obesity that are related with the use of unauthorized products for weight loss, combinations of thyroid hormones, diuretics, chorionic gonadotropin and amphetamines. These miracle formulas and illegal sale are creating false expectations in the population with obesity, with rapid weight loss and weight gains after their use. Obesity is a chronic disease in which drugs may cause some weight change during the treatment.

However, a strong tendency exists towards recovering the weight after one stops taking the medication, if there is no significant change in life style.<sup>1</sup> Thus, drug treatment for obesity should be governed by the following criteria:<sup>1,2</sup> a) it

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should not be used as an isolated treatment, but rather complementary to basic therapies of an eating, physical activity and changes in life style plan; b) when weight loss has not been achieved only with changes in life style (for at least 3 month); C) its indication is limited to patients with BMI<30 (or <27 if major comorbidities are associated). Drug treatment should be discontinued if weight loss is less than 5% after the first 12 weeks or if the subject gains weight again during the treatment.

At present, only one drug option has been approved for use in obesity. This is Orlistat, a potent and selective inhibitor of pancreatic lipase that reduces digestion of fats. The drug has a dose-dependent effect on fecal fat loss, increasing this loss by about 30% of the fat intake. Orlistat has little effect in persons on a low fat diet, which is predictable due to its action mechanism.

Included among the unapproved drugs for treatment of obesity are antidepressants (bupropion and fluoxetine) and antiepileptics (topiramate and zonisamide).<sup>2</sup>

Bupropion is a drug approved for the treatment of depression, which causes weight loss and decreases the desire to smoke. It probably acts by modulating the action of norepinephrine (involved in the initiation and maintenance of an addictive behavior and in the symptoms of abstinence of the problem substance) and dopamine (desire to consume). However, it has not been approved for weight loss.<sup>2</sup>

Selective serotonin reuptake inhibitors are serotonergic drugs acting on the specific serotonin receptors, reducing food intake and especially short term fat intake, with minimum long term changes or increases in weight. Clinical trials at 52 weeks made with fluoxetine have not found significant changes in weight loss compared with placebo.<sup>2</sup>

Topiramate and zonisamide are anti-epileptic agents approved for use in mono- or combined therapy.<sup>3</sup> Their action mechanism is based on the inhibition of the carbonic anhydrase enzyme (EC 4.2.1.1), an enzyme involved in cell lipogenesis (on the level of cytoplasm and mitochondria).<sup>4</sup> These drugs (basically topiramate) seem to have a wide action spectrum in the management of binge-eating, purgative behaviors, weight loss, bulimia nervosa, binge eating disorder, nighttime eating disorders and food-related sleep problems.<sup>5-7</sup> Due to the strong inhibitory capacity of carbonic anhydrase, efficacy has been demonstrated in the loss and maintenance of weight in obese patients.<sup>8</sup>

The objective of our study consists in comparing three treatments (fluoxetine, topiramate and the combination of both) in patients with morbid obesity who are candidates for bariatric surgery with eating symptoms and to analyze weight loss between the groups.

## MATERIAL AND METHODS

The present study analyzes the weight loss with psychopharmacological treatment in 75 patients. This group of patients was evaluated prior to undergoing a bariatric surgery operation to lose weight and who were candidates to receive treatment due to having unstructured eating behavior. Women accounted for 80% (n=60) and 20% (n=15) were men with a mean age of 40 years (SD+10) and Body Mass Index of 45.5 Kg/m<sup>2</sup> (SD+9).

The clinical interview and self-applied test was used to measure eating behavior. In the interview, we examined eating behavior disorder symptoms as: eating more than persons in our setting, food snacking and type of preferred food, eating an abundant dinner (in the main dinner or getting up at night to eat), existence of eating binges and number per week (to differentiate binge eating as a symptom or disorder). The questionnaire applied was Eating Disorder Inventory-2 (EDI-2)<sup>9</sup>, as a complement to the clinical history.

We define disruptive behavior as that irregular eating pattern that affects the physical condition of the individual and his/her psychosocial functioning and that is outside of the family food intake pattern and caloric intake. To do so, the existence of at least one of the previous symptoms of eating behavior disorder that causes physical problems and psychosocial functioning was sufficient for us to classify the patients as having eating problems prior to the intervention who could be candidates for pre-surgical treatment.

The 75 patients with disruptive eating behavior were divided into three groups:

- Group A: (n=20). They were prescribed 40 mg of fluoxetine/day.
- Group B: (n=25). They were prescribed 200 mg of topiramate/day.
- Group C: (n=30). They were prescribed 40 mg of fluoxetine plus 200 mg of topiramate per day.

The sampling was systematic randomization, selecting the patients for each group alphabetically and by time of arrival to the clinic. All the patients signed the informed consent when they entered into the care process.

## RESULTS

The most prevalent eating behavior disorder symptoms were: food snacking (81%), abundant intake (52%), binges as symptom (42%) and nighttime eating (13%).

A 24% prevalence was found for binge eating disorder (BED) according to the DSM-5 criteria.<sup>10</sup>

Mean weight loss at 3 months was 5 Kg (range from 0-24) and 7.6 Kg at 6 months (range from 0-19) after initiation of the treatment.

Patients treated with fluoxetine plus topiramate lost more weight at 3 and 6 months before the surgery, this being statistically significant at six months. Topiramate was more effective than fluoxetine in monotherapy for weight loss (Table 1).

*Escalation of the medication was done as follows:*

- FLUOXETINE: 20 mg of fluoxetine at breakfast for one week, then increasing to 40 mg at breakfast afterwards.
- TOPIRAMATE: It was introduced with 50 mg at night in the first week, going to 100 mg in the second week in morning and night dose, 150 mg in the third week (in two doses) and 200 mg after the third week (in two doses).

Fluoxetine and topiramate were always prescribed with the same brand name to avoid biases by the introduction of generics and differences in their bioequivalences.

This type of escalation and dose is performed to avoid side effects due to rapid introduction of these two psychopharmaceuticals and to avoid a greater tendency to drop-out that we have had with higher doses.

### Comparison with Binge Eating Disorder (BED) patients

If we analyze the treatment profile used for Binge Eating Disorder patients (n=15) versus those who only had eating behavior disorder symptoms (n=75) we find that patients with BED have received Fluoxetine and Topiramate in 80% of the cases versus Fluoxetine alone in 20% of the patients.

The mean dose used in BED for the groups was: 60 mg (±10) of Fluoxetine alone and 50 mg (±10) of Fluoxetine plus 300 mg (±250) of Topiramate.

Regarding weight lost in BED patients, we have not found difference in loss at 3 and 6 months.

### DISCUSSION

In our study, we analyzed eating behavior and weight loss in a sample of morbid obesity patients prior to the surgery. We studied if the use of fluoxetine, topiramate or the association of both could help in the treatment of obesity before the surgery. Antiepileptics can be used in the management of eating disorders in patients with morbid obesity.

Table 1	One factor anova			
Weight loss	Range (Kg)	Group A	Group B	Group C
At three months	0-24	1.1 (1.10)	2.5 (2.05)	4.4 (3.15)
At six months*	0-19	3.0 (2.90)	5.4 (4.75)	8.0 (6.08)

In parenthesis % of weight loss versus initial weight.  
 \* One factor anova with Bonferroni correction (F=6.86, GL=2, p<0.002)

Topiramate and zonisamide seem to have beneficial effects on eating disorders and have been shown to help lose more weight than the placebo.<sup>3</sup> The use of antiepileptic drugs in the management of obesity is recommendable for weight loss and its maintenance<sup>5-7</sup> although it has been demonstrated that the use of high doses may cause neurological effects and greater therapeutic non-compliance.<sup>3</sup> In relation to the antidepressant, fluoxetine, 52-week clinical trials conducted have not found significant changes in weight loss compared with placebo.<sup>2</sup>

In our experience, treatment with fluoxetine in monotherapy has not led to substantial changes in weight, which would coincide with other previous results published.<sup>2,11</sup>

Weight loss with topiramate in monotherapy and associated to fluoxetine has been effective in most of the patients, in weight loss at 3 and 6 months, coinciding with other studies.<sup>4,5,8</sup> Furthermore, we have found more statistically significant differences at six months of treatment in which losses of about 6% versus the original weight have been achieved.

However, we believe that the dose should be adapted to each type of patient, finding fewer side effects in the slow escalation of the dose and weight evolution, without it being necessary to use high doses as has been indicated in other studies.<sup>3</sup>

If we analyze the patients with binge eating disorder, the weight losses were the same as in the patients with eating behavior disorder symptoms, even though they had received higher doses of fluoxetine and topiramate. This confirms the need to apply psychotherapeutic interventions in addition to drug treatment in these patients in order to achieve a better result.<sup>6,7</sup>

From the clinical point of view, addition of an antiepileptic agent in monotherapy or in combination with fluoxetine in patients with obesity who have unstructured eating behavior is positive, improving and even stabilizing

said behavior. The sample size and lack of a group with eating dysfunctions in which a placebo is involved limits our results. However, weight loss of 3 and 8 kg (with a range of 0 to 24 kg) could help to improve adherence to presurgical dietary treatment and decrease morbidity-mortality.

We consider the use of monotherapy of topiramate and its association to fluoxetine to lose weight prior to the surgical intervention adequate in patients with morbid obesity who have eating behavior disorders, adapting the treatment to each patient, and slowly introducing the dose until modifying the eating behavior.

If we study the monthly cost per patient and month of the most effective treatment (fluoxetine 40 mg + topiramate 200 mg/day) the cost of 46 Euros/patient/month could help to improve quality of life and decrease morbidity-mortality since it has been evaluated that a 5-10% reduction in body weight decreases cardiovascular risk factors and the possibility of suffering cancer.<sup>1</sup>

Future studies should evaluate if treatment adherence is better with the addition of psychopharmaceuticals and the weight evolution at 12 months concerning the control of the patient while he/she continues to be on the surgical waiting list.

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