Predictors of weight loss and maintenance in patients treated with antiobesity drugs

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Background: The prevalence of obesity and related diseases has increased enormously in the last few decades, becoming a very important medical and social issue. Because of the increasing number of people who need weight loss therapies and the high costs associated with these, the search for reliable predictors of success for weight loss and weight maintenance treatments has become a priority.

Objective: A literature review was undertaken to identify possible predictors of outcome of weight loss and weight maintenance in patients treated with antiobesity drugs.

Results: For the majority of variables, published data are not sufficient to define their role on final outcomes. Among all considered factors, only early response to treatment appeared to be a reliable positive predictor, and diabetes a negative predictor of weight loss and maintenance.

Conclusion: To date, no definitive results have been obtained. Due to the great benefits of reliable predictors of outcome associated to currently available antiobesity drugs and those under development, identifying these predictors has to be supported and encouraged.

Keywords: obesity, weight loss predictors, pharmacological treatment

Introduction

In the last decade, the prevalence of overweight and obesity (defined as BMI > 25 kg/m² and >30 kg/m², respectively) and their complications (especially type 2 diabetes, cardiovascular diseases, obstructive sleep apnea, osteoarthritis, male and female infertility, and certain forms of cancer) has greatly increased among adults and children. It has become an alarming medical and social issue resulting from socioeconomic and behavioral changes in modern society (leading to increased energy consumption and decreased energy expenditure), and biological factors.

Weight loss of 5%-10% of initial body weight reduces cardiovascular and metabolic health risks associated with obesity. International Health Guidelines recommend lifestyle modification as the first strategy in the management of obesity. If lifestyle modification alone is ineffective, pharmacotherapy may be considered for individuals with a BMI ≥ 30 kg/m² or for those with a BMI ≥ 27 kg/m² with comorbidities (e.g., hypertension, diabetes, obstructive sleep apnea, type 2 diabetes) or a family history of overweight. Bariatric surgery should be reserved for individuals with a BMI ≥ 40 kg/m² or ≥35 kg/m² and comorbidities who do not lose weight with lifestyle modification and pharmacotherapy. Very recently, US Food and Drug Administration has approved the use of Allergan’s LAP-Band Adjustable Gastric Banding System for people with a BMI > 35 kg/m² without comorbidities or for >30 kg/m² and at least one comorbidity.
Several studies have shown that the different antiobesity drugs, in conjunction with lifestyle treatments, can induce a weight loss up to 5%–10%, even if there is a great variability in individual response to a specific treatment.\textsuperscript{7–9} Several different treatments, based on lifestyle modifications,\textsuperscript{10–12} drugs,\textsuperscript{13} and surgery\textsuperscript{14,15} have been developed in the past, and some others are currently being studied.\textsuperscript{13}

The investigation for factors responsible for obesity onset and response to antiobesity treatments started in the early 1960s,\textsuperscript{16,17} and the number of studies in this field has multiplied over the years. Most studies showed a wide variability in inter-individual response to all kinds of treatments,\textsuperscript{18} a usually modest result in weight loss and maintenance,\textsuperscript{19} and the involvement of many environmental, genetic, and behavioral factors.\textsuperscript{19–23} However, predictors of outcome continue to be poorly understood. Availability of good predictors would allow physicians to match treatment to patients, and would improve cost-efficacy and patient’s chances of success in losing and maintaining weight.\textsuperscript{22,23}

This article focuses on factors that have been suggested as possible predictors of weight loss and/or weight maintenance in patients treated with orlistat, diethylpropion, mazindol, sibutramine, and topiramate (Table 1).

**Methods and study description**

A literature search was performed using PubMed database entering the drug name “and weight loss” for drugs approved by the FDA specifically for weight loss (orlistat, phentermine, and diethylpropion); drugs previously approved by the FDA that have been recently withdrawn from the market (sibutramine, mazindol, and rimonabant); and drugs approved by the FDA for other indications that exhibit weight loss promoting effects (topiramate, bupropion, and zonisamide). We found articles focusing on predictors in patients treated only with diethylpropion, orlistat, sibutramine, mazindol, and topiramate. Some studies investigated treatment outcomes in patients treated with an association of phentermine and fenfluoramine but, because this compound is no longer available and no comparative data with each single drug exists, these articles have not been included. Additional relevant articles from reference lists were included.

Only articles focusing on adults were included. Absolute or relative weight loss was the only considered variable. Thirty-three studies investigating gender, anthropometric, demographic, psychological, behavioral, and hereditary characteristics, associated medical conditions and habits,

### Table 1 Main characteristics of antiobesity medications included in the study

| Drug                        | Mechanism of action                                                                 | Typical dosing | Adverse effects                                                                 | Effect on weight                                                                 |
|-----------------------------|------------------------------------------------------------------------------------|----------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Orlistat\textsuperscript{a,\textsuperscript{6–9,33}} | Limits fats absorption; pancreatic lipase inhibitor                               | 120 mg tid     | Abdominal pain, bloating, flatulence, oily stools, diarrhea, decreased absorption of fat soluble vitamins | 2.9 kg placebo subtracted weight loss at 1 year                                  |
| Diethylpropion\textsuperscript{a,e,9}       | Appetite suppressant; sympathomimetic amine                                        | Average 75 mg/d | Dizziness, headache, insomnia, restless, increase in blood pressure, palpitations, tachycardia, gastrointestinal symptoms, rash | 3.0 kg placebo-subtracted weight loss in studies ranging 6–52 weeks             |
| Sibutramine\textsuperscript{b,9,33}        | Appetite suppressant; serotonin and norepinephrine reuptake inhibitor              | 10–15 mg/d     | Hypertension, tachycardia                                                        | 4.2 kg placebo-subtracted weight loss at 1 year                                  |
| Mazindol\textsuperscript{b,13}             | Appetite suppressant; norepinephrine inhibitor. Inhibitor of gastric acids and insulin secretion | 1–4 mg/d       | Restlessness, hypertension, nervousness                                          | Average 3 kg placebo subtracted weight loss in 12 week studies                  |
| Topiramate\textsuperscript{c,33}           | Weight loss mechanism unknown. Supposed monoamine-mediated appetite suppression; increase in fat metabolism and reduction in lipogenesis | 90–200 mg/d    | Cognitive impairment, peripheral neuropathy                                      | 6.5% pooled random-effects of topiramate on weight loss compared with placebo   |

**Notes:** \textsuperscript{a}Drugs approved by FDA specifically for weight loss; \textsuperscript{b}Drugs previously approved by FDA specifically for weight loss and recently withdrawn from the market; \textsuperscript{c}Drugs approved by the FDA for the other indications that exhibit weight loss promoting effects; \textsuperscript{d}Drug approved by FDA for long-term treatment; \textsuperscript{e}Drug approved by FDA for short-term treatment (12 weeks).
dietetic advices, and environmental factors were identified and included in this review.

All studies included subjects with a $\geq 25$ kg/m$^2$ of both genders, except for two$^{24,25}$ including females only. Age ranged from 16 to 70 years. The number of patients included in the different studies ranged from 36 to 3277. The duration of the study varied from 8 to 208 weeks. Some included a run-in phase.$^{26-31}$ The main characteristics of the patient sample and program of the considered studies are displayed in Table 2.

**Predictors associated with orlistat treatments**

Orlistat is a semisynthetic derivative of lipstatin which irreversibly and selectively binds to pancreatic lipases, reducing fat absorption by approximately 30% (Table 3).$^{32}$ The prescribed dose is 120 mg, three times/day with meals. A meta-analysis$^{33}$ including approximately 10,000 participants treated for at least 1 year, reported a mean placebo-subtracted weight loss of 2.9 kg. Abdominal pain, bloating, flatulence, oily stools, and diarrhea represent common adverse effects; severe liver injury is rare.$^{34}$

**Demographic variables**

Only one study$^{35}$ investigated the impact of gender on weight loss, and found no significant difference in the percentage of initial body weight lost by males and females.

**Psychological factors and eating behaviors**

Orlistat weight loss was positively related to the traits ‘order’ ($P < 0.05$), ‘deliberation’ ($P < 0.01$), and ‘self-discipline’, included in the main personality factor conscientiousness$^{35}$ (which reflect the ability to have and to persist with a goal-directed and motivated behavior, hence to consider matters before acting, to be methodical, well organized, and self-disciplined). This suggests that people with a stronger personality and great conscientiousness can achieve higher levels of long-term compliance towards a high demanding treatment like orlistat, a characterized thrice-daily regimen, and dietary fat restriction. The importance of determination on treatment’s results is evident in European prescribing information$^{36}$ that, based on several observations,$^{26}$ orlistat is only recommended to those patients who have previously lost at least 2.5 kg by diet alone in a 4-week period, as an indication of their capacity to comply with prescribed dietary changes. Conversely, levels of restrained eating, anxiety, and depression showed no impact on the final outcome.$^{35}$

**Diabetes**

Two studies$^{30,37}$ pointed out the difficulty in losing weight experienced by diabetic patients treated with orlistat.

**Initial weight loss**

A study conducted on 229 patients who completed a 2-year treatment$^{26}$ showed that people who lost $\geq 5\%$ of their initial weight in the first 12 weeks achieved better final results than people who did not ($-11.9 \pm 0.8%$ vs $-4.7 \pm 0.5%$; $P = 0.0001$). This finding was confirmed by another study$^{38}$ in which $>80\%$ of patients who achieved $\geq 5\%$ reduction in their body weight after 3 and 6 months maintained $>5\%$ weight loss and $>50\%$ achieved $\geq 10\%$ weight loss after 12 months ($P < 0.01$). Accordingly, European$^{36}$ and National Institute for Clinical Excellence$^{39}$ prescribing guidelines, which recommend that only people who lose $\geq 5\%$ of initial body weight after 12 weeks and $\geq 10\%$ after 6 months should continue taking orlistat.

**Associated dietetic and environmental factors**

Pharmacist’s support was shown to improve patient’s persistence with orlistat therapy but it did not improve the total amount of weight loss.$^{40}$ The total daily calories assumed with diet (500 vs 1000 kcal/day)$^{38}$ did not have a marked impact on the overall clinical outcome of weight reduction (average weight loss 11.8 and 11.4 kg respectively), while a low fat, but also carbohydrate, consumption was essential to lose weight.$^{31}$

**Predictors associated with diethylpropion treatments**

Diethylpropion is an amphetamine like analog currently approved by FDA for short-term weight loss.$^{9}$ A meta-analysis conducted on several studies in which patients were treated with diethylpropion 75 mg/day in combination with lifestyle treatment showed an average 3.0 kg of additional weight loss, compared with placebo.$^{5}$ Common side effects include central nervous system stimulation, dizziness, headache, insomnia, restlessness, mild increases in blood pressure, palpitations, mild tachycardia, mild gastrointestinal symptoms, and rash.$^{9}$

To our knowledge, only one study$^{41}$ focused on predictors of weight loss in patients treated with diethylpropion, showing no statistically significant effect of patients’ personality on weight loss, but just a positive correlation between social conformity and treatment completion ($P < 0.004$).
| Author, year | Sample | Type of study | Program |
|--------------|--------|---------------|---------|
| Alberici et al77 | BL: 51 p. ET: 49 p. BLCPCS: mA 44.1 ± 11.5. F 36. mBMI 24.0 ± 3.4. | Prospective study | Treatment: Topiramate was administered following slow up titration; full dosage of 100 mg/day, bid regimen, reached within 4 weeks. 4 months treatment |
| Ben-Menachem et al75 | BL: 49 p. F 28. mA 36.2 ± 11.7. mBW 77.8 ± 16.8. mBMI 26.9 ± 5.9. ET: 38 p. F 22. mA 35.9 ± 11.5. mBW 75.8 ± 14.8. mBMI 26.3 ± 9.3. | Prospective study | Treatment: 1 year. Topiramate added to pre-existing anticonvulsant therapy. Starting dose 25 mg/day, increased biweekly in 25 or 50 mg increments to the best-tolerated dosage providing maximum seizure control mean dosage after 3 months 81 mg/day (21–154 mg/day) |
| Elfag et al27 | BL: 36 p. ET: 30 p. BLCPCS: F 22. mA 43 ± 12 (20–64). mBMI 40 ± 4 (33–45). | Prospective study | Run in phase: 6 weeks. Clinical trial evaluating the effect of sibutramine on food consumption in laboratory test meals. 2 weeks each of: sibutramine, placebo, and a wash out period (crossover design) Treatment: 26 weeks. Sibutramine (15 mg/day) + monthly dietary advice |
| Elfag and Rossner19 | BL: 36 p. F 27. mA 43 ± 12 years (20–64). mBMI 39 ± 4 (30–45). ET: 31 p. | Prospective study | Run in phase: 6 weeks. Sibutramine/placebo and wash out period Treatment: 26 weeks. 15 mg/day sibutramine and dietary advice in monthly group sessions with a dietician |
| Elfag et al35 | BLCPCS: 478 p. F 301. mA 42.4 ± 12.2 (16–70). mBMI 42.4 ± 12.2 (26–68). | Retrospective analysis of patients who completed the study | 1. Weight Watcher treatment (control) or 2. Sibutramine or 3. Orlistat |
| Fabricatore et al45 | BL: 224 P. F 180. mA 43.8 ± 10.2. C 146. OE 76. Sibutramine: 55 p. Lifestyle modification: 55 p. Combined therapy: 60 p. Sibutramine + brief behavioral therapy: 54 p. ET: 185 p. | Prospective study | 52 weeks treatment: 1200–1500 kcal/day diet (15% proteins, 30% fats, 55% carbohydrates) + walking + random assignment to: a. Sibutramine: 8 visits of 10–15 minutes with a primary care provider + pamphlet providing tips for healthy lifestyle + sibutramine 15 mg/day b. Lifestyle modifications: 30 group behavior modification sessions c. Combined therapy (a + b) d. Sibutramine + brief therapy: sibutramine 15 mg/day + 8 sessions of 10–15 minutes behavior therapy sessions |
| Finer et al29 | BL: 928 p. Nondiabetic: 771 p. F 611. C 763. mA 42.4 ± 10.7. mBW 97.5 ± 15.2. mBMI 35.0 ± 4.1. Diabetic: 157 p. mA 51.4 ± 9.6. F 84. C 153. mBW 101.3 ± 17.7. mBMI 35.7 ± 5.4. | Retrospective analysis of patients included in 7 different studies | Run in phase: placebo run-in phase (3 studies); open-label sibutramine run-in phase (2 studies); very low calorie diet (1 study) Treatment: 52 weeks; random assignment to sibutramine (10 mg/day) or placebo (6 studies with fixed dose; 1 study with dose titrated depending on patient’s weight maintenance) |
| Frey et al10 | BLCPCS: 110 p. C. F 74. A 42–48. BMI 35.3–35.4. Sibutramine group: 54 p. F 38. mA 46.8 ± 10.5. mBW 99.2 ± 14.1. mBMI 35.1 ± 4.2. Placebo group: 56 p. F 36. mA 49.3 ± 11.0. mBW 104.5 ± 15.2. mBMI 35.5 ± 3.3. | Retrospective study on a part of patients who had completed the program | 54 weeks treatment: random assignment to 15 mg/day of sibutramine or placebo + behavior program (16 group sessions) + physical activity + diet (daily energy requirement minus 500 to 1000 kcal/day) |

(Continued)
### Table 2 (Continued)

| Author, year | Sample | Type of study                                                                 | Program |
|--------------|--------|--------------------------------------------------------------------------------|---------|
| Greenway78 | SiBUTRAMiNe: 83 obese patients with diabetes; 2004 obese patients without diabetes. ORLISiSTAT: 321 obese patients with diabetes; 2404 obese patients without diabetes. MAZiNDOL: 40 obese patients with diabetes; 998 obese patients without diabetes. | Retrospective comparative analysis between a study focusing on diabetic patients and an average of studies in nondiabetic patients for each type of drug | 12 weeks sibutramine treatment or 52 weeks orlistat treatment or 12 weeks mazindol treatment |
| Grudell et a47 | BL: 181 p. Placebo: 62 p. F 54. mA 41.3 ± 1.4. mBW 95.9 ± 2.1. mBMI 34.5 ± 0.6. Sibutramine 10 mg: 58 p. F 53. mA 42.2 ± 1.4. mBMI 34.8 ± 0.7. Sibutramine 15 mg: 61 p. F 54. mA 44.8 ± 1.3. mBMI 33.9 ± 0.6. | Prospective study | 12 weeks treatment: behavioral therapy (LEARN manual + 1 group session of 15 minutes each week led by a psychologist) + placebo or sibutramine 10 mg/day or 15 mg/day |
| Hainer et al24 | BL: 80 p. F. mA 43.9 ± 10.6 (18–65). mBMI 36.7 ± 4.8 (30–45). 1st phase: sibutramine 38 p. Placebo 42 p. 2nd phase: 80 p. ET: 67 p. | Prospective study | 1st phase: 4 months; random assignment to sibutramine 10 mg/day or placebo 2nd phase: 8 months; sibutramine + 5–6 MJ/day diet (50%–60% carbohydrates; 15%–20% proteins; 25%–30% fat) + physical activity + food diary records |
| Hansen et al46 | BL: 605 p. BMI 30–45; 18–65 yr Completers of the 1st phase: 505 p. mA 40.4 ± 10.4. mBW 102.5 ± 15.3. mBMI 36.7 ± 4.1. Enrolled in the 2nd phase: 467 p. 352 sibutramine. 115 placebo. ET: 263 p. | Prospective study | 1st phase: 6 months; sibutramine (10 mg/day) and LCD (patient’s estimated daily energy expenditure minus 600 kcal/day; 45%–50% carbohydrates; 30% fats; 15%–20% proteins) 2nd phase: 18 months; random assignment for patients who achieved ≥5% of weight loss to sibutramine 10 mg/day (352 p) or placebo (115 p) |
| Hauner et al53 | BL: 348 p. BMI 30–40; 18–65 yr Sibutramine: 174 p. F 136. mA 44.5 ± 1.2. mBW 100.2 ± 1.9. mBMI 35.6 ± 0.6. Placebo: 174 p. F 123. mA 47.3 ± 1.3. mBW 105.4 ± 2.0. mBMI 35.7 ± 0.5. | Retrospective analysis of patients included in the study | 54 weeks treatment: 20 group sessions and prescription of a diet (500/1000 kcal minus of the daily required energy expenditure) + physical activity + sibutramine or placebo (random assignment) 2 years follow up |
| Hsiao et al54 | BL: 131 p. Sibutramine: 87 p. Placebo 44 p. ET: 118 p. BLCPCS: Sibutramine 82 p. F 41. mA 31.7 ± 4.9. mBW Placebo 37 p. F 17. mA 31.1 ± 5.8. mBW 83.8 ± 15.0. mBMI 29.8 ± 3.4. | Prospective study | 12 weeks treatment: sibutramine 10 mg/day or placebo |
Table 2 (Continued)

| Author, year | Sample | Type of study | Program |
|--------------|--------|---------------|---------|
| Hsiao et al57 | BL: 131 p. Sibutramine: 87 p. Placebo: 44 p. ET: 118 p. BLCPCS: Sibutramine 82 p. F 41. mA 31.7 ± 4.9. mBw Placebo 37 p. F 17. mA 31.1 ± 5.8. mBw 83.8 ± 15.0. mBMI 29.8 ± 3.4. | Prospective study | 12 weeks treatment: sibutramine 10 mg/day or placebo |
| Klein et al76 | BL: 26 p. ET: 22 p. F 13. BLCPCS: mA 41.5. mBMi 28.0 ± 6.6. mBw 80.3 ± 19.3. | Prospective study | 6 months treatment: topiramate |
| Lloret-Linares et al37 | BL: Sibutramine (3 studies): 115–467 p. F 76%–84%. mA 40.4–43.3. mBMI 32.4–37.9. Orlistat (12 studies): 422–3277 p. F 55%–87%. mA 40–53. mBMI 34.7–37.4. | Retrospective comparative analysis between studies considering nondiabetic and diabetic subjects for each type of drug | Sibutramine: 10 or 20 mg once a day for 52 or 104 weeks or Orlistat: 120 mg three times a day for 52/76/104/208 weeks or Rimonabant: 20 mg daily for 52 or 104 weeks. All trials combined pharmacological therapy with a reduced-calorie diet |
| Malone and Alger-Maye40 | BL: 30 p. F 26. mA 43.8 ± 9.7. mBw 127 ± 34. mBMI 45.5 ± 11.8. Intervention group: 15 p. F 14. mA 44.9 ± 10.5. BW 130 ± 39. BMI 48.3 ± 14.6. Control group: F 12. mA 42.8 ± 9. BW 124 ± 30. BMI 42.8 ± 8.1. ET: 9 p. Intervention group: 7 p. Control: 2 p. | Prospective study | Patients randomly assigned to the group followed by a community pharmacist (trained and educated for 1 day to support clients during weight loss treatment with orlistat) or to the group not followed by a pharmacist and followed for 26 weeks |
| Norris et al30 | BL: 31 studies. mA 48–66. F 50%. Fluoxetine (6 studies): 296 p (total number). Orlistat (8 studies): 2036 p (total number). Sibutramine (8 studies): 1047 p (total number). Cimetidine 1 study. Dietethylpropion (3 studies): 40–58 p (single study). Mazindol (3 studies): 10–64 p (single study). Phentermine (2 studies). | Meta-analysis of studies considering nondiabetic and diabetic subjects for each type of drug | Run-in period: 1–5 weeks in most studies; placebo + dietary counseling Treatment: Fluoxetine: 8 to 52 weeks or Orlistat: 12 to 57 weeks or Sibutramine: 12 to 52 weeks or Cimetidine: 12 weeks Dietethylpropion: 8 to 40 weeks or Mazindol: 6 to 12 weeks or Phentermine: 16 to 26 weeks |
| Peters et al25 | BL: 149 p. F 54 ± 5.78 (45–65). BW 103.41 ± 20.65 (68.03–175.54). mBMI 40.10 ± 8.01 (30–76). FLU: 74 p. | Prospective study | 6 months treatment: sibutramine 15 mg/day + 1 hour/month behavior modification seminar + daily exercise |
| Rissanen et al26 | BLCPCS: 220 p. F 178. A 42–49. BW 90.3±101.9. BMI 32.7–36.1. | Retrospective analysis of patients who completed the treatment in two different studies | Run in phase: 4 weeks; hypocaloric diet (30% fat; 500 kcal/day energy deficit) + placebo Treatment: 2 years; random assignment to: 120 mg/day orlistat or placebo + diet |
## Table 2 (Continued)

| Author, year | Sample | Type of study | Program |
|--------------|--------|---------------|---------|
| Risser et al\(^6^3\) | BL: PAR1: 22 p. F 90.9%. mA 4 9.9 ± 12. mBMI 39.3 ± 7. Non-PAR: 47 p. F 78.7%. mA 47.1 ± 10. mBMI 37.1 ± 6.12. | Retrospective analysis | 1st phase: 8 weeks; 800–1220 kcal/day diet + 24-hour food diary + visits (first 10 weeks: 2–5 days/week) + sibutramine 15 g/daily (flexible doses adjusted depending on patient) 2nd phase: 40 weeks; weight maintenance through well-balanced meals and regular exercise + sibutramine 15 mg/day (flexible doses adjusted depending on patient) |
| Rodin et al\(^4^1\) | BL: 204 p. Clinic 1: 144 p. F 129. A 18–59. BW 28%–199% overweight. Clinic 2: 60 p. F 60. A 18–54. BW 17%–183% overweight. eT: clinic 1: 33 p. Clinic 2: 56 p. | Prospective study | Clinic 1: 14 weeks (8 weeks treatment): random assignment to 4 groups: behavior modification treatment, diethylpropion 65 mg/day, mazindol 2 mg/day, placebo Clinic 2: 10 weeks; (9 weeks treatment): behavior therapy for all patients + random assignment to two different formulations of mazindol or placebo |
| Shimizu and Mori\(^6^6\) | BL: 24 p. Trp64Trp: 16 p. Trp64Arg: 8 p. BMi 35 kg/m². | Prospective study | 12 weeks treatment: mazindol (starting dose 0.5 mg/day. Increments of 0.5 mg/day every 2 weeks up to 1.5 mg/day at week 6 and then continued until week 12) |
| Shimizu et al\(^6^7\) | BL: 24 p. Trp64Trp: 16 p. Trp64Arg: 8 p. BMI > 35 kg/m². | Prospective study | 3 months treatment: hypocaloric diet (600 kcal/day deficit on the estimated total daily energy expenditure. <30% fat, 15% protein, 55%–60% carbohydrates) +30 minutes walking/day + random assignment to sibutramine once daily or placebo. First month dosage of sibutramine was 10 mg/day replaced by 15 mg/day in case of no change in body weight |
| Toplak et al\(^3^8\) | BL: 430 p. BMI 30–43; 18–70 yr; BW ≥90, waist circumference ≥88 cm (F) or ≥102 cm (M). Orlistat + 500 kcal/day diet: 215 p. F 168. mA 41.3 ± 11.0. mBW 103.4 ± 11.2. mBMI 37.3 ± 3.4. Orlistat + 1000 kcal/day diet: 215 p. F 166. mA 41.1 ± 12.1. mBW 104.7 ± 12.8. mBMI 37.4 ± 3.6. ET: 264 p. | Prospective study | 1 year treatment: orlistat 120 mg 3 times/day + dietary counseling + daily food diary + random assignment to a diet (50% carbohydrates, 30% fat, 20% protein) of 500 or 1000 kcal/day deficit Patients who achieved a 5% weight loss at both months 3 and 6 (295 p) were allowed to continue the study until month 12 |
| Theisen et al\(^7^4\) | BL: 26 p. F 10. mA 37.4 ± 10.3 (20.7–65.3). M mBMI 28.1 ± 6.4. F mBMI 22.5 ± 3.5. ET: 18 p. | Prospective study | 25 weeks treatment with topiramate added to existing anticonvulsant therapy (carbamazepine 12 p; carbamazepine + valproate 3 p; carbamazepine + lamotrigine 3 p; carbamazepine + valproate + lamotrigine 3 p; carbamazepine + valproate + phenobarbital 1 p; carbamazepine + phenobarbital 1 p; carbamazepine + phenytoin 1 p; phenytoin + phenobarbital 1 p; phenytoin + lamotrigine + phenobarbital 1 p) |
Table 2 (Continued)

| Author, year | Sample | Type of study | Program |
|--------------|--------|---------------|---------|
| Ullrich et al31 | BL: 261 p. F 214. mA 41.4 ± 9.8. mBMI 36.8 ± 4.2. Sibutramine group: 204 p. F 168. mA 41.4 ± 9.7. mBMI 36.6 ± 4.2. Placebo group: 57 p. F 46. mA 41.3 ± 10.0. mBMI 37.1 ± 3.8. | Retrospective analysis of people who completed the study | Run in phase: 4 weeks; hypocaloric diet (600 kcal/day deficit on patient’s estimated basal metabolic rate, ≥30% fat; protein and carbohydrate ad libitum) + placebo (3 times/day with meals) Treatment: 72 weeks; orlistat (120 mg × 3/day). 4-day food diary at weeks –4, –2, 0, 12, 24, 36, 48, 64. Group weight management program sessions (one each 4 weeks) |
| Van Baak et al48 | BL: 605 p. BMI 30–45; 17–65 yr. After 6 mo run in phase: 467 p. ET: 261 p. F 214. mA 41.4 ± 9.8. BMI 36.8 ± 4.2. | Prospective study | 1st phase: 6 months; sibutramine (10 mg/day) and LCD (patient’s estimated daily energy expenditure minus 600 kcal/day. 45%–50% carbohydrates; 30% fats; 15%–20% proteins) 2nd phase: 18 months; random assignment for patients who achieved ≥5% of weight loss to sibutramine 10 mg/day (352 p) or placebo (115 p). Dietary advice and one meeting with a dietician a month |
| Vazquez Roque et al44 | BL: 48 p. Sibutramine 25 p. Placebo 23 p. Overweight: 24 p. mA 36.7 ± 1.7. F 17. C 87.5%. mBW 79.6 ± 1.6. mBMI 27.9 ± 0.3. Obese: 24 p. mA 44.2 ± 2.6. F 13. C 95.8%. mBW 98.2 ± 2.7. mBMI 34.8 ± 0.7. ET: 43 p. Sibutramine 22 p. Placebo 21 p. | Prospective study | 12 weeks treatment: LEARN manual (self-help behavioral manual for weight loss) + 10–15 minutes behavior therapy sessions (one every 4 weeks) + random assignment to sibutramine 15 mg/day or placebo |
| Womble et al65 | BL: Group 1: 59 p. F 31. M: mA 50.2 ± 7.39; mBMI 39.94 ± 5.99. F: mA 45.72 ± 9.2. mBMI 40.34 ± 8.20. Group 2: 32 p taken from group 1. F 15. ET group 1: 59 p. Group 2: 32 p. | Prospective study | 6 months treatment for group 1: 12 months treatment for group 2 For both groups, random assignment to: a. Fenfluramine + mazindol (6 months; 29 p. 12 months; 18 p) or b. Fenfluramine + phentermine (6 months; 25 p. 12 months; 11 p) or c. Caffeine + ephedrine (6 months; 2 p. 12 months, 1 p) or d. Mazindol (6 months, 3 p. 12 months, 2 p) |

Notes: 1Cases: patients who had received a prescription for sibutramine in response to priori authorization through their health care insurer (PAR). Controls: subjects who did not receive reimbursement, although they were prescribed, sibutramine (non-PAR).

Abbreviations: BL, sample characteristics at base line; BMI, body mass index (kg/m²); BLCPCS, baseline characteristics of people who completed the study; Bw, body weight; C, Caucasians; F, number of female patients; ET, sample characteristics at the end of the program; mA, mean age; mBMI, mean body mass index (kg/m²); mBW, mean body weight; OE, other ethnicity; p, number of patients; yr, years old; LCD, low-calorie diet.

Predictors associated with sibutramine treatments

Sibutramine is a centrally-acting drug that reduces energy intake and increases satiety mainly through the inhibition of serotonine and norepinephrine reuptake (Table 4).8 Weight loss is enhanced by the stimulation of thermogenesis42,43 and the delay in gastric emptying.44 The prescribing dose was 10–15 mg once daily. A recent meta-analysis13 that included 2,838 participants treated with sibutramine for at least 1 year, showed a mean placebo-subtracted weight loss of 4.2 kg. The drug was withdrawn from the market in October 2010 because of cardiovascular side effects.13

Psychological factors and eating behaviors

A study in 200327 demonstrated that patients with more deviating levels (elevated or lowered from the mean) of physical demand states (inborn and natural primary drives, including hunger) and dependency orientation (which implies preoccupation with oral activity such as eating and dependency on food, and which is typical of
people vulnerable to social isolation) lost more weight when treated with sibutramine ($r = 0.533$, $P = 0.002$ and $r = 0.478$, $P = 0.008$, respectively). Initial signs of difficulties concerning physical demand states were strong positive predictors of weight loss ($r = 0.533$, $P = 0.002$), explaining 27% alone. These findings suggest that the drug could improve conscious control over instinctual drives; alternatively, it could increase the sensitivity to alterations in hunger and satiety, helping people with initial high levels of hunger urges to improve control on food intake. The enhanced satiety effect of sibutramine could also have helped patients with high oral dependency to give less importance to food and the support provided by being enrolled in a treatment program could have helped them to abstain from food.

In the same study, self-inspect ability (which means an ability to monitor and reflect on one’s behavior and thinking) was related to weight loss but was not a predictor.

Several studies have found that patients with more unrestrained eating (less cognitive control and conscious determination to resist eating, less strategic dieting) achieved greater weight loss, suggesting a negative influence of a pre-trial weight suppression on the subsequent treatment with sibutramine. At the same time, the increase in dietary restraint and the decrease in disinhibition score during weight reduction phase guaranteed the success of weight loss maintenance.

Discordant results were obtained about the role of depression on weight loss. Two studies pointed out no correlations between depression and weight loss; two found a negative association between depression and weight loss; one showed depression as a positive predictor ($r = 0.40$, $P < 0.05$).

### Demographic and anthropometric factors

Except for one study that pointed out a positive association between younger age and weight loss, age and gender appeared to be unrelated to the ability to lose weight. According to the only study that considered the influence of race on weight loss, Caucasian ethnicity appeared a positive predictor (odds ratio [OR]: 0.42, $P = 0.003$). Two authors speculated that patients with higher pre-treatment body weight could achieve greater weight loss ($r = 0.27$, $P < 0.001$) because of their higher energy expenditure (resting metabolic rate) ($r = 0.13$, $P = 0.003$). Conversely, another study found no association between initial weight and weight loss at 6 months ($r = -0.220$, $P = 0.242$).

### Familial obesity and personal weight history

One study pointed out the positive effect that the absence of familial obesity and having been normal weight at some points as an adult had on weight loss, even if these factors were not statistically selected as predictors (Student’s $t$-value = 3.239, $P = 0.003$; Student’s $t$-value = 2.194, $P = 0.037$ respectively). Conversely, Fabricatore et al obtained better results treating patients with a longer history of overweight. Hansen et al showed the number of previous slimming attempts and the age of onset of obesity had no influence on final weight loss.

### Initial weight loss under treatment

Several studies showed that early adherence to the program, early weight loss in the lead-in period and in the first 4 weeks of treatment were the strongest positive predictors of weight loss and maintenance, both in diabetic and nondiabetic patients. Accordingly, sibutramine prescribing guidelines.

## Table 3 Predictors of weight loss and maintenance in patients treated with orlistat

| Author, year | Predictors |
|--------------|------------|
| Demographic and anthropometric factors | Elfhag et al |
| Psychological factors and eating behaviors | Elfhag et al |
| Initial weight loss in the lead-in period and under treatment | Rissanen et al |
| Associated medical, dietetic, and environmental factors | Malone and Alger-Mayer |
| Malone and Alger-Mayer | ppwL: male gender |
| Malone and Alger-Mayer | ppwL: high levels of order and deliberation (consciousness) |
| Malone and Alger-Mayer | ppwL: high levels of eating restraint, neuroticism, anxiety, and depression |
| Malone and Alger-Mayer | ppwL: Weight loss ≥2.5 kg during 4 weeks lead-in period; weight loss ≥5% body weight after 12 weeks treatment; ≥10% body weight after 6 months |
| Malone and Alger-Mayer | ppwL: ≥5% weight loss at 3 and 6 months |
| Malone and Alger-Mayer | ppwL: pharmacist’s support |
| Malone and Alger-Mayer | ppwL: low fat and carbohydrate intake |
| Malone and Alger-Mayer | ntPwL: positive predictor of weight loss; PPW, positive predictor of weight maintenance. |

**Abbreviations:** NPWL, negative predictor of weight loss; NPWLM, negative predictor of weight maintenance; nPWL, not predictor of weight loss; nPwM, not predictor of weight maintenance; PPWL, positive predictor of weight loss; PPWM, positive predictor of weight maintenance.
Table 4 Predictors of weight loss and maintenance in patients treated with sibutramine

| Author, year | Predictors |
|--------------|------------|
| **Psychosocial factors and eating behaviors** | | |
| Elfhag et al¹⁷ | PPWL: high deviating levels of demand states (hunger); high levels of dependency orientation and oral traits. Self-inspective ability ntPWL: levels of anxiety, depression, bodily concern; eating disorders; affective response to external stimuli |
| Elfhag and Rossnerl⁹ | PPWL: unrestrained eating (less cognitive control and conscious determination to resist from eating, less strategic dieting) ntPWL: unrestrained eating (emotional and external eating); high levels of neuroticism, anxiety and depression. High levels of self-consciousness and hostility² |
| Elfhag et al³⁵ | PPWL: unrestrained eating (emotional and external eating); high levels of neuroticism, anxiety and depression. High levels of self-consciousness and hostility² |
| Fabricatore et al⁴⁵ | NPWL: depressive symptoms |
| Hainer et al⁴⁴ | NPWL: high dietary restraint at baseline; high initial depression score PPWM: increase in dietary restraint during first months of treatment PPWM: decrease in disinhibition scores |
| **Demographic and anthropometric factors** | | |
| Elfhag et al²⁷ | NPWL: age; gender; pretreatment body weight |
| Elfhag et al³⁵ | PPWL: young age |
| Fabricatore et al⁴⁵ | PPWL: Caucasian ethnicity ntPWL: age |
| Hansen et al³⁶ | PPWL: high baseline body weight (high resting metabolic rate) ntPWL: age; gender |
| **Familial obesity and personal weight history** | | |
| Elfhag et al³⁷ | NP: familial history of obesity; being obese during all adulthood |
| Fabricatore et al³⁵ | PPWL: having been overweight for a long time |
| Hansen et al³⁶ | ntPWL: age of obesity onset; number of previous slimming attempts |
| Elfhag et al³⁷ | PPWL: great initial weight loss |
| Fabricatore et al³⁵ | PPWL: early adherence and weight loss |
| Finer et al²⁹ | PPWL: high early weight loss (≥ 4 kg at 3 months) |
| Hainer et al⁴⁴ | PPWL: high initial weight loss |
| Hansen et al³⁶ | PPWL: high initial weight loss in the run-in period; high initial weight loss under treatment |
| | ntPWL: number of previous slimming attempts; age of onset of obesity |
| van Baak et al⁴⁸ | PPWM: high initial weight loss |
| Grudell et al¹⁷ | PPWL: high initial (4 weeks) weight loss |
| Frey et al³⁰ | PPWL: A allele carriers position −1211 of GNAS gene promoter |
| Grudell et al³⁷ | PPWL: gene pairs 5HTTLPR LS/SS and GNβ3 GNβ3 rs5443 TC/TT; α2A CC and GNβ3 rs5443 TC/TT |
| Hauner et al³³ | PPWL and PPWM: CC genotype of GNβ3 rs5443 |
| Hsiao et al³⁴ | PPWL: T allele carriers (TT or TC genotype) of GNβ3 rs5443 |
| Hsiao et al³⁷ | PPWL: ~866 A polymorphism of UCP2: association between ~866A polymorphism of UCP2 and rs5443 T polymorphism of GNβ3 |
| Peters et al³¹ | PPWL: homozygous A148A or G148G polymorphism of PNMT |
| Vazquez | PPWL: LS/SS genotype of SLC6A4 ntPWL: α2A-1291 C/G; |
| Roque et al⁴⁶ | PNMT G148A polymorphism; GNβ3 genotypes |
| Fabricatore et al⁴⁵ | PPWL: combined therapy (sibutramine + behavioral therapy) ntPWL: distance from clinic |
| Finer et al²⁹ | NPWL: diabetes |
| Greenway⁷⁸ | NPWL: diabetes |
| Hainer et al⁴⁴ | PPWM: increase in protein intake; decrease in fat intake ntPWL: 8 or 12 months of treatment |
| Hansen et al³⁶ | ntPWL: smoking history |
| Lloret-Linares et al³⁷ | NPWL: diabetes |
| Norris et al³⁰ | NPWL: postmenopausal state, hysterectomy, hormone replacement. |
| Peters et al³¹ | ntPWL: postmenopausal state, hysterectomy, hormone replacement. Fiber intake, total caloric intake, total fat intake |
| Risser et al³¹ | PPWL: priori authorization to have sibutramine as a prescription partially reimbursed (PAR) |
| Tankova et al³⁹ | NPWL: diabetes |
| van Baak et al⁴⁸ | PPWM: high levels of leisure-time physical activity ntPWL: macronutrient composition of the diet during weight maintenance period |

**Abbreviations:** NPWL, negative predictor of weight loss; NPWM, negative predictor of weight maintenance; ntPWL, not predictor of weight loss; ntPWL, not predictor of weight maintenance; PPWL, positive predictor of weight loss; PPWM, positive predictor of weight maintenance.
recommend physicians to increase the dose to 15 mg/day or discontinue treatment in patients who have not lost 2 kg in the first 4 weeks of treatment with the dose of 10 mg, and to avoid treatment beyond 12 weeks in people who fail to lose 5% of their initial body weight.

Genetic factors

Some authors focused on the effect that several genetic polymorphisms could have on weight loss and maintenance. Frey et al\textsuperscript{50} investigated the role of the G \textgreater A transition at position \textasciitilde1211 of the human G protein \(\alpha\)-subunit gene (GNAS) promoter, showing that sibutramine was effective only in A carriers (\(P = 0.002\)) (GG genotypes showed no additional weight loss under sibutramine compared to placebo). G protein \(\alpha\)-subunit is responsible for hormones coupling to the enzyme adenylcyclase and is required in adipocytes for the lipolytic response to \(\beta\) adrenergic agonists.\textsuperscript{50}

Four studies investigated \(\text{GNB3}\), which encodes for the \(\text{G}\)-protein \(\beta\)-subunit of heteromeric \(G\) proteins (coupled to specific receptors, including serotonin and norepinephrine), key components of intracellular signal transduction, with a prominent role in body weight regulation. C825T (rs5443) polymorphism on exon 10 reduces lipolytic response to catecholamines in fat cells\textsuperscript{51,52} and is associated with obesity, hypertension, and diabetes. Hauner et al\textsuperscript{53} showed that sibutramine treatment was more effective in individuals with the CC genotype than in subjects with the TT/TC genotypes (weight loss: 7.2 \pm 2.2 vs 4.1 \pm 2.1 kg, \(P = 0.0013\)). In the CC group, the OR for a weight loss >5% (sibutramine vs placebo) was 6.6 (\(P = 0.004\)) and for a weight loss >10% was 9.6 (\(P = 0.010\)). This was in contrast with two studies\textsuperscript{47,54} showing that patients with TT/TC genotypes achieved better results than CC genotype (\(P = 0.018\) and \(P < 0.001\) respectively), and another study\textsuperscript{44} pointing out no association between \(\text{GNB3}\) polymorphisms and weight loss.

One study\textsuperscript{25} focused on the positive association (\(P = 0.003\)) between weight loss and the homozygous variant (either G/G or A/A) G148A of \(\text{PNMT}\) (phenylethanolamine N-methyltransferase) encoding for a adrenal enzyme catalyzing the conversion of norepinephrine to epinephrine\textsuperscript{55} but, in a second study, this result was not confirmed.\textsuperscript{44}

Vazquez-Roque et al\textsuperscript{44} investigated also the role of “short” (S) and “long” (L) repeats in the 5-HTT-linked region of the promoter of gene SLC6A4 (solute carrier family 6, member 4; chromosome 17q11.1–q12) encoding for the soluble serotonin transporter\textsuperscript{56} and pointed out the positive effect of SLC6A4 LS/SS genotype on weight loss (subjects with SLC6A4 LS/SS genotype had an average weight loss of 6.1 \pm 1.0 kg, compared with a 0.1 \pm 0.9 kg average weight increase with placebo; subject with SLC6A4 LL genotype showed an average weight loss of 3.3 \pm 1.8 kg on placebo, compared with 3.9 \pm 1.6 kg weight loss in sibutramine group).

Grudell et al\textsuperscript{47} found the positive effect of the association of TC/TT genotype of C825T polymorphism of \(\text{GNB3}\) gene and the CC genotype of \(\alpha2\)A adrenoreceptor C1291G polymorphism or the 5HTTLPR LS/SS genotype.

Very recently, Hsiao et al\textsuperscript{57} used the same patients in which they had investigated the role of \(\text{GNB3}\) polymorphism\textsuperscript{44} to study the role of \(\sim866\)G/A polymorphism on weight loss in patients treated with sibutramine. The uncoupling protein 2 (UCP2) gene encodes a mitochondrial transporter protein, which is highly expressed in adipose tissue, skeletal muscle, and pancreatic islets.\textsuperscript{58} A strong effect of sibutramine on weight loss was observed in individuals with the AA, GA, and AA + GA genotypes (\(P = 0.019\), \(P < 0.001\), and \(P < 0.001\), respectively) whereas the drug caused no significant effect in individuals with the GG genotype (\(P = 0.063\)). For the combination of UCP2 AA + GA with \(\text{GNB3}\) TT + TC (carriers of at least one variant allele for each polymorphism), the \(P\)-value for treatment effects on weight loss was <0.001. In contrast, no effects were observed in patients with the wild type genotype combination of UCP2 GG and \(\text{GNB3}\). A significant (\(P < 0.001\)) gene interaction between UCP2 and \(\text{GNB3}\) was identified by a 2-locus model.

Associated pathologies, habits, nutritional, and environmental factors

Diabetes represents the chronic disease that most often is associated with obesity. Weight loss improves glycemic control and can be achieved using pharmacological therapy.\textsuperscript{30,37,59} However in diabetic patients weight management is more challenging, in part because of the weight-promoting effects of the majority of anti-diabetic drugs\textsuperscript{37} and, on average, is achieved slower and less (up to 69%) than in nondiabetic patients.\textsuperscript{29,30,37,59} This final aspect is recognized by the Australian regulatory authorities who suggest to withdraw sibutramine after 3 months in nondiabetic patients who have failed to lose 5% of their initial body weight but after 6 months in diabetic patients.\textsuperscript{60}

On the other side, estrogen levels (ie, menopause, hormone replacement), hysterectomy,\textsuperscript{25} and smoking habit\textsuperscript{46} were demonstrated to not have a significant effect on weight loss in response to sibutramine.

The addition of behavioral therapy\textsuperscript{45} or high leisure-time physical activity\textsuperscript{48} to sibutramine showed a strong
favorable effect on weight loss and maintenance, while
dietetic modifications in fat, protein, and fiber intake during the treatment, and the choice of 8 vs 12 months period of treatment did not have a great impact on outcomes. This is in accordance with most of studies on obesity drugs that demonstrate that the maximum weight loss is achieved after 6–8 months, whereas after 12–16 months of treatment, minor weight regain usually occurs.

A priori authorization to have sibutramine partially reimbursed improved patients’ compliance and weight loss. Distance to the clinic was marginally related to treatment success.

Predictors associated with mazindol treatments
Mazindol is a centrally acting drug that blocks the reuptake of norepinephrine by presynaptic neurons, increasing norepinephrine levels within the synaptic cleft (Table 5). The result is the stimulation of the β2 adrenergic receptors in the lateral hypothalamus and the inhibition of feeding. It also inhibits gastric acid and insulin secretion, and increases locomotor activity.

Psychosocial factors and eating behavior
A study in 1977 found that high social conformity and emotional stability, extraversion, and need for social acceptance improved patients’ adhesion to the program, whereas no personality characteristic predicted weight loss.

According to a more recent study, high levels of hunger, anxiety, and dietary restraint, and small perceived body size had a negative influence on weight loss in patients treated with mazindol. Suggested explanations for these findings were the drug incapability of controlling extreme levels of hunger, the limited slimming possibility in patients dieting before entering the treatment, and the individual lacking perception of the need for weight loss.

Table 5 Predictors of weight loss and maintenance in patients treated with mazindol

| Author, year | Predictors |
|--------------|------------|
| Psychosocial factors and eating behaviors | Rodin et al 141  PPWL: high levels of social conformity; belief that poor eating habits are crucial in producing obesity NPWL: high levels of responsiveness to external, non-food relevant stimuli; belief that hereditary or physical factors are causes of primary importance in producing overweight ntPWL: self-esteem and self-concept; emotional stability; extraversion; internal locus of control. |
| Genetic predictors | Womble et al 65  NPWL: high levels of dietary restraint, perceived hunger and trait anxiety; small perceived body size | Shimizu and Mori 67  NPWL: Trp64Arg mutation of GNβ3 gene (vs Trp64Trp) |

Abbreviations: NPWL, negative predictor of weight loss; NPWM, negative predictor of weight maintenance; ntPWL, not predictor of weight loss; ntPWL, not predictor of weight maintenance; PPWL, positive predictor of weight loss; PPWM, positive predictor of weight maintenance.

Genetic factors
Two studies pointed out a significantly greater body weight reduction in subjects with the Trp64 Trp allele than in those with Trp64Arg allele of ADRβ3 gene (encoding for a protein which regulates catecholamine-induced lipolysis mainly expressed in white adipose tissue) (6.9 ± 1.0 kg vs 3.6 ± 0.7 kg in the first study and 8.4 ± 1.7 kg vs 3.7 ± 0.8 kg in the second study; P < 0.05).

Predictors associated with topiramate treatment
Topiramate is an anticonvulsant drug acting on sodium and calcium T-type channels (Table 6). The way in which it could promote weight loss is still unknown. Some authors have shown an increase in extraneuronal levels of dopamine, norepinephrine, and serotonin in the hippocampus and have speculated that a similar effect in the hypothalamus could explain topiramate action as an appetite suppressor. Other studies have demonstrated an increase in fat metabolism (through the increased activity of lipoprotein lipase in adipose tissue and promotion of hepatic fat metabolism and decreased fatty acid synthesis) and the inhibition of lipogenesis through the inhibition of carbonic anhydrase II and V.

A recent meta-analysis based on studies conducted on epileptic patients reported an average placebo-subtracted weight loss of 6.5% in topiramate-treated patients (P < 0.001). Adverse effects are paresthesia, changes in taste, dizziness, memory impairment, insomnia, and somnolence.

Demographic and anthropometric factors
Three studies pointed out a correlation between higher initial BMI and a greater weight loss (P < 0.001) in epileptic patients treated with topiramate for a period of 10 weeks to 6 months. Only one study conducted on migraine patients treated for 4 months found no correlation between initial BMI, gender, and total weight loss (P = 0.44).
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Predictors of outcome in pharmacological antiobesity treatments

Table 6 Predictors of weight loss and maintenance in patients treated with topiramate

| Author, year       | Predictors                                                                 |
|--------------------|-----------------------------------------------------------------------------|
| Demographic and anthropometric factors | Alberici et al.17 ntPwL: gender; initial BMI                                   |
|                    | Theisen et al.18 PPWL: high initial BMI                                      |
|                    | Ben-Menachem et al.19 PPWL: high initial BMI                                 |
|                    | Klein et al.20 PPWL: high initial BMI and body fat                           |
| Eating behavior    | Klein et al.21 PPWL: reduction in hunger at 3 months                        |

Abbreviations: ntPwL, not predictor of weight loss; PPWL, positive predictor of weight loss.

Eating behavior

One study76 reported a positive ($P = 0.002$) association between a reduction in hunger after 3 months of treatment and total weight loss at month 6.

Results

Our analysis pointed out the overall paucity of reliable predictors of weight loss and maintenance associated with pharmacological antiobesity treatments, a characteristic previously described by studies focusing on lifestyle modification treatments.18,19

Indeed, among all considered factors, the early response to treatment was demonstrated to be a sure positive predictor of weight loss and maintenance. Conversely, diabetes appeared to have a strong negative impact on patients’ ability to lose weight when treated with the different drugs.

A more unrestrained eating at baseline and high levels of determination and self-discipline appeared to be positive predictors of outcome in patients treated with sibutramine and orlistat, respectively, even if the statistical association was less strong.

For all other considered variables, published data are not sufficient to define their role on final outcomes.

Conclusion

Limitations related both to the disease and to the intervention program could explain these inconclusive and often conflicting results. Indeed, the multitude of factors involved in obesity’s development and weight loss, and their complex interactions make each patient different from the other and the investigation of reliable predictors particularly challenging. Furthermore psycho-behavioral difficulties experienced by patients when starting a new treatment, and the lack of significant results often associated with the different therapies, are responsible for the high levels of attrition of patients from the weight-loss programs.

At the same time, our analysis pointed out important limitations related to currently available literature investigating outcomes associated to antiobesity pharmacological treatments. First of all, few studies have been conducted with the primary aim to point out the role of specific factors on weight loss and maintenance. Second, a minor part of these studies have included a large cohort of patients. Third, studies are very heterogeneous from the point of view of the number and characteristics of patients included, the duration and type of program, and the tests and parameters used for patients’ evaluation. Finally, very often, the analysis and interpretation of the achieved results are very difficult and the power of the associations is reduced because of the limited number of subjects included.

Probably, the enrollment of a greater number of patients in future trials, the use of common protocols of treatment and parameters (for each category of predictors) to assess final outcomes could improve statistical significance of results and the ability to compare data. Moreover, because both obesity onset and weight loss are dependent on the interaction of a great number of different factors, it could be important to test different categories of predictors on the same group of patients.

Despite the above mentioned difficulties and the discouraging results obtained until recently, we believe that, because of obesity’s social and medical impact and the availability of new promising antiobesity drugs (whose mechanisms of action are very often similar to those of old drugs; the most promising one is the association of bupropion and naltrexone),79 the search for reliable predictors of outcome associated to antiobesity treatments has to be supported and encouraged.

Being able to find reliable predictors of successful outcome for pharmacological treatments would mean to give prescribing physicians, patients, and the authorities a tool for antiobesity drug management.

Disclosure

No conflicts of interest were declared in relation to this paper.

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