Use of Fluoxetine to Reduce Weight in Adults with Overweight or Obesity: Abridged Republication of the Cochrane Systematic Review

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\textbf{Keywords}
Fluoxetine · Weight loss · Adverse events · Obesity

\textbf{Abstract}

\textbf{Introduction}: Using fluoxetine is one of many weight loss strategies. A serotonin reuptake inhibitor indicated for depression believed to impact weight control by changing an individual’s appetite; however, its benefit-risk ratio is unclear. The aim of this review was to assess the efficacy and safety of fluoxetine in reducing weight in adults with overweight or obesity.

\textbf{Methods}: We searched Cochrane Library, MEDLINE, Embase, and other databases without language restrictions. Cochrane Collaboration tool and GRADE instrument assessed the risk of bias of randomized controlled trials and certainty of their evidence. We conducted random-effects meta-analyses and calculated the risk ratio/mean difference with 95\% confidence intervals for the outcomes.

\textbf{Results}: We included 19 trials (2,216 adults) and found that fluoxetine may reduce weight by \(-2.7\) kg (95\% CI \(-4\) to \(-1.4\); \textit{p} < 0.001) and body mass index by \(-1.1\) kg/m\(^2\) (95\% CI \(-3.7\) to 1.4), compared with placebo; however, it would cause approximately twice as many adverse events, such as dizziness, drowsiness, fatigue, insomnia, or nausea.

\textbf{Conclusions}: Although low-certainty evidence suggests that off-label fluoxetine may reduce weight, high-certainty research is needed to be conducted in the future to determine its effects exclusively as well as whether it is useful when combined with other agents. This article is based on a Cochrane Review published in the Cochrane Database of Systematic Reviews 2019, Issue 10, DOI: 10.1002/14651858.CD011688.pub2. Cochrane Reviews are regularly updated as new evidence emerges, and in response to feedback, it should be consulted for the most recent version of the review.

\textbf{Introduction}

Excess body weight is the sixth most important risk factor that contributes to the overall burden of non-communicable diseases worldwide [1]. Over the past 30 years, the prevalence of weight gain has increased considerably to become an important public health issue as it has multiple consequences such as the risk of developing cardiovascular diseases (hazard ratio [HR] 1.27; 95\% confidence interval [CI] 1.23–1.31), cerebrovascular accidents, hypertension, respiratory disorders (odds ratio [OR] 1.58; 95\% CI 1.22–2.03; \textit{p} < 0.001), osteoarthritis, metabolic syndrome, type 2 diabetes mellitus (HR 1.86; 95\% CI

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Although we identified 1,036 potential studies for inclusion, 32 trials were excluded due to different reasons [41–72] (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000524995), and 19 trials were included with 2,216 participants with a mean age of 30–51 years, a wide variety of comparisons according to fluoxetine doses (10, 20, 40, and 60 mg once a day), and time of administration (from 3 days to 12 months) (Fig. 1; Table 1) [19–37].

In most trials, the risk of selection bias was unclear because their reports provided no details of the methods of random sequence generation and blinding of outcome assessment. Approximately one-third of the trials had a high risk of bias due to an attrition rate of 20% (Fig. 2).

Fluoxetine versus Placebo
Weight Loss in Kilograms
Ten trials compared fluoxetine with placebo. Seven trials used a dose of 60 mg/day [21, 25, 26, 30, 31, 33, 36]; two trials used a dose of 40 mg/day [29, 30]; and three trials used a dose of 20 mg/day [31, 35, 37].

We identified a weight loss of −2.5 kg (95% CI −3.8 to −1.2; p = 0.0001; 7 trials) in 819 participants who received fluoxetine 60 mg/day, while for the adults who received fluoxetine 40 mg/day, the weight loss was −3.97 kg (95% CI −5.42 to −2.52; p < 0.001; 10 trials).

We calculated the mean difference (MD) with 95% CI. Heterogeneity was identified by visual inspection of forest plots and using a random-effects model, with the inverse variance method. For dichotomous data, we obtained RRs; for continuous outcomes, we used a random-effects model with the inverse variance method. Heterogeneity was identified by visual inspection of forest plots and using a random-effects model, with the inverse variance method.

### Methods

#### Search Strategy

Two reviewers conducted a search without language restriction up to January 2021 on the following databases: MEDLINE, Embase, LILACS, Cochrane CENTRAL, the ICTRP Search Portal, and ClinicalTrials.gov. The following MeSH terms were searched: (Obesity, Morbid OR Adiposity/OR Body Weight/Weight Loss/OR Overweight/OR fat) AND (Fluoxetine/AND (randomized controlled trial OR controlled clinical trial) AND (exp animal/ not humans)).

#### Study and Participant Selection Criteria

We included randomized controlled trials that examined the administration of fluoxetine for adults (>18 years) with overweight (body mass index [BMI] 25–29.9 kg/m²) or obesity (BMI ≥30 kg/m²) according to the WHO’s criteria compared with placebo, other anti-obesity agents, non-pharmacological therapy, and no treatment [1]. Trials in which participants presented with diabetes mellitus, polycystic ovary syndrome, eating disorders, schizophrenia, HIV infection, cancer, and pregnancy were excluded. Fluoxetine regimens were dose-adjusted to assess the following outcomes: (A) weight loss; (B) BMI reduction; (C) adverse events; (D) mortality; and (E) socioeconomic effects, with 12-month follow-up.

#### Assessment of Risk of Bias

Two independent reviewers used the Cochrane tool [16] and GRADE instrument [17] to assess the risk of bias of the randomized controlled trials and the certainty of their evidence. Disagreements were resolved by discussion and consultation with a third reviewer. For cases with unclear information, the authors were contacted through email.

#### Statistical Analysis

For dichotomous data, we obtained RRs; for continuous outcomes, we calculated the mean difference (MD) with 95% CI. Meta-analyses were performed using a random-effects model, with the inverse variance method. Heterogeneity was identified by visual inspection of forest plots and using a standard χ² test with a significance level of 0.1 and I² statistic using the Review Manager V5.4 software. For more details, see the Cochrane systematic review [18].

#### Results

Although we identified 1,036 potential studies for inclusion, 32 trials were excluded due to different reasons [41–72] (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000524995), and 19 trials were included with 2,216 participants with a mean age of 30–51 years, a wide variety of comparisons according to fluoxetine doses (10, 20, 40, and 60 mg once a day), and time of administration (from 3 days to 12 months) (Fig. 1; Table 1) [19–37].

In most trials, the risk of selection bias was unclear because their reports provided no details of the methods of random sequence generation and blinding of outcome assessment. Approximately one-third of the trials had a high risk of bias due to an attrition rate of 20% (Fig. 2).

Fluoxetine versus Placebo
Weight Loss in Kilograms
Ten trials compared fluoxetine with placebo. Seven trials used a dose of 60 mg/day [21, 25, 26, 30, 31, 33, 36]; two trials used a dose of 40 mg/day [29, 30]; and three trials used a dose of 20 mg/day [31, 35, 37].

We identified a weight loss of −2.5 kg (95% CI −3.8 to −1.2; p = 0.0001; 7 trials) in 819 participants who received fluoxetine 60 mg/day, while for the adults who received fluoxetine 40 mg/day, the weight loss was −3.97 kg (95% CI −5.42 to −2.52; p < 0.001; 10 trials).
CI −8.8 to 0.8; \( p = 0.10; 2 \) trials, 182 participants), and for individuals who received fluoxetine 20 mg/day, the weight loss was −1.5 kg (95% CI −3.5 to 0.5; \( p = 0.15; 3 \) trials, 279 participants). However, the test for subgroup differences did not indicate a statistically significant difference (\( p = 0.62 \)). Overall, across all fluoxetine dosages and durations of treatment, the weight loss was −2.7 kg (95% CI −4 to −1.4; \( p = 0.0001; 10 \) trials, 956 participants; low-certainty evidence in favour of fluoxetine) [21, 25, 26, 30–33, 35–37]. The 95% prediction interval ranged between −7.1 kg and 1.7 kg (Fig. 3).

**BMI Reduction**

Three trials compared fluoxetine with placebo. We identified that 19 participants who received fluoxetine 60 mg/day showed a BMI reduction of −3.3 kg/m² (95% CI...
| Author/year | Sex (female), % | Age (range), years | BMI (mean or range), kg/m² | Intervention | Comparator | Outcomes                                                                 | Cointerventions |
|-------------|----------------|--------------------|---------------------------|--------------|------------|--------------------------------------------------------------------------|-----------------|
| Al-Helli 2015 [13] Iraq (parallel RCT) | – | 18–40 | ≥30 | N = 12 Fluoxetine 20 mg orally, once a day for 2 months | N = 12 Placebo orally once daily for 2 months | BMI, serum lipids: total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting blood glucose, malondialdehyde, leptin | – |
| Suplicy 2014 [29] Brazil (parallel RCT) | 100 | 33.1–39 | 33.6–35.6 | N = 30 Diethylpropion 75 mg orally, once per day for 52 weeks | N = 29 Placebo orally once daily for 52 weeks | Differences in weight loss, waist circumference, BMI, adverse events, blood pressure, heart rate, serum lipids, fasting glucose, fasting insulin, glycated haemoglobin, quality of life | Hypocaloric diet and encouraged to maintain at least 150 min per week of moderate physical activity |
| Guimaraes 2006 [20] Brazil (parallel RCT) | 88.5 | 30.2–38.9 | 32–37.2 | N = 8 Sibutramine 15 mg orally, once per day for 90 days | N = 10 Placebo orally, once daily for 90 days | Cognitive and critical, behavioural, and cognitive aspects of the patient’s dietary habits | Dietary reeducation containing on average 1,500 kcal/day |
| Bondi 2000 [15] Italy (parallel RCT) | 100 | 47.8–51.4 | 38.8–42.8 | N = 8 Fluoxetine 40 mg orally, once per day for 12 weeks | N = 12 Placebo orally, once daily for 12 weeks | Resting respiratory quotient, resting energy expenditure, fasting blood glucose, plasma insulin | Diet (55% carbohydrates, 20% protein, 25% fat), a caloric deficit of 500 kcal/day of 70% energy expenditure by indirect calorimetry |
| Huang 1998 [21] China (parallel RCT) | 54 | 41.2–44.5 | 32.6–33.5 | N = 30 Fluoxetine 60 mg orally, once per day for 12 weeks | N = 30 No treatment | Body weight, BMI, fasting blood sugar, triglycerides, cholesterol, uric acid, adverse events | Weight-reducing low-calorie diet (25–35 kcal/day adjusted to workload × ideal body weight – 500 kcal) |
Table 1 (continued)

| Author/year | Sex (female), % | Age (range), years | BMI (mean or range), kg/m² | Intervention N/dose | Comparator N/dose | Outcomes | Cointerventions |
|-------------|----------------|-------------------|-----------------------------|---------------------|------------------|----------|-----------------|
| Bross 1995 [16] Canada (parallel RCT) | 100 | 32–33 | 34–34.1 | N = 10 Fluoxetine 60 mg orally, once per day for 3 weeks | N = 10 Placebo orally, once daily for 3 weeks | Body weight, resting energy expenditure, thermic effect, serum triiodothyronine and thyroxine, adverse events | Formula diet (420 kcal including 70 g protein/day and 100% RDA vitamins and minerals) |
| Fernández-Soto 1995 [17] Spain (crossover RCT) | 100 | 39 | 35.1–36.8 | N = 23 Fluoxetine 60 mg orally, once per day for 3 months | N = 19 Placebo orally, once daily for 3 months | Weight, pulse, adverse events, glucose, urea, uric acid, creatinine, cholesterol, triglycerides | Diet 1,200 kcal maintained throughout the trial; no caloric liquids; psychotherapy |
| Lawton 1995 [23] United Kingdom (crossover RCT) | 100 | 32.8 | 39.9 | N = 13 Fluoxetine 60 mg orally, once per day for 2 weeks | N = 13 Placebo orally, once daily for 2 weeks | Satiety, weight loss, adverse events, appetite, energy intake, motivational ratings (hunger), post-lunch meal palatability rating | Diet: each treatment phase incorporated 2 separate test days on which the participants response to either a high-carbohydrate or a high-fat meal was assessed |
| Goldstein 1994 [19] USA (parallel RCT) | 81 | 43 | 35.8–36.2 | N = 230 Fluoxetine 60 mg orally, once per day for 52 weeks | N = 228 Placebo orally, once daily for 52 weeks | Weight loss, adverse events, heart rate, blood chemistry, haematology, and urinalysis | Diet with caloric intake designed to produce a weight loss of 0.45 kg per week |
| Goldstein 1993 [18] USA (parallel RCT) | 87 | 42.6–44.9 | 31.6–31.9 | N = 106 Fluoxetine 60 mg orally, once per day for 40 weeks | N = 104 Placebo orally, once daily for 40 weeks | Pulse rate, carbohydrate craving scores, adverse events, urinalysis and blood chemistry, haematology | Advised to reduce overall caloric consumption and offered a diet to lose 0.45 kg per week |
| Pedrinola 1993 [26] Brazil (parallel RCT) | – | 20–50 | 33.6–35.1 | N = 10 Fluoxetine 40 mg orally, once per day for 12 weeks | N = 10 Placebo orally, twice daily for 12 weeks | Weight loss, BMI, adverse events, cholesterol, triglycerides | Standard 1,000-kcal diet |
| Visser 1993 [30] The Netherlands (parallel RCT) | 0 | 38.8–42.6 | 27.9 | N = 20 Fluoxetine 60 mg orally, once per day for 12 weeks | N = 20 Placebo orally, once daily for 12 weeks | Body weight, waist-hip ratio, abdominal fat areas, adverse events | Received dietary advice on healthy nutrition and means to lose weight |
| Wurtman 1993 [31] USA (parallel RCT) | 100 | 39.5–41.2 | 32–33.1 | N = 30 Fluoxetine 20 mg orally, once per day for 12 weeks | N = 28 Desfenfluramine mg orally, once per day for 12 weeks | Weight, adverse events, glucose, triglycerides, urinalysis, thyroid profile, depression | – |
| Kopelman 1992 [22] United Kingdom (crossover RCT) | 9 | 25–53 | 44 | N = 11 Fluoxetine 60 mg orally, once per day for 3 days | N = 11 Placebo orally, once daily for 3 days | Sleep-breathing patterns, weight loss, adverse events, hematology, oxygen saturation, apnea/hypopnea index, total sleep time, qualitative assessment of sleep | – |
| Author/year | Sex (female), % | Age (range), years | BMI (mean or range), kg/m² | Intervention N/dose | Comparator N/dose | Outcomes | Cointerventions |
|-------------|----------------|--------------------|-----------------------------|---------------------|-------------------|----------|----------------|
| Stinson 1992 [28] Ireland (crossover RCT) | 61.7 <65 36.7 | N = 13 Fluoxetine 60 mg orally, once per day for 2 weeks | N = 17 Placebo orally, once daily for 2 weeks | Resting metabolic rate, diet-induced thermogenesis, weight reduction, serum urea and creatinine levels, hematocrit | – |
| Bagiella 1,991 [14] Italy (parallel RCT) | – 18–57 30–40 | N = – Fenfluramine 20 mg orally, once per day for 12 weeks N = – 5-hydroxy-tryptophan 300 mg orally, once per day for 12 weeks N = – Fenfluramine 15 mg orally, once per day for 12 weeks N = – Fluoxetine 20 mg orally, once per day for 12 weeks N = – Fluvoxamine 50 mg orally, once per day for 12 weeks | N = – Placebo 1 capsule orally, 2 or 3 times per day for 12 weeks | Cognitive and critical, behavioral, and cognitive aspects of the patient’s dietary habits | – |
| Pijl 1991 [27] The Netherlands (parallel RCT) | 100 37.3–38.1 35.2–36.4 | N = 12 Fluoxetine 60 mg orally, once per day for 6 weeks | N = 12 Placebo orally, once daily for 6 weeks | Body weight, total caloric intake, adverse events, spontaneous food choice | – |
| Levine 1989 [25] USA (parallel RCT) | 85 39–41 ≥25 | N = 131 Fluoxetine 10 mg orally, once per day for 8 weeks N = 131 Fluoxetine 20 mg orally, once per day for 8 weeks N = 131 Fluoxetine 40 mg orally, once per day for 8 weeks N = 131 Fluoxetine 60 mg orally, once per day for 8 weeks | N = 131 Placebo orally, once daily for 8 weeks | Weight loss, BMI, adverse events, heart rate | – |
| Levine 1987 [24] USA (parallel RCT) | 88 43–46 ≥25 | N = 60 Fluoxetine 60 mg orally, once per day for 11 days | N = 60 Placebo orally, once daily for 11 days | Weight loss, BMI, adverse events, blood pressure, heart rate | Advised to reduce overall calorie consumption by 20% |

BMI, body mass index; –, not reported; RCT, randomized controlled trial.
Fluoxetine to Reduce Weight in Adults with Overweight

Fluoxetine to Reduce Weight in Adults (with Overweight)

−7.3 to 0.7; \( p = 0.10; 1 \) trial) and who received fluoxetine 40 mg/day showed −2.8 kg/m² (95% CI −8.7 to 3.1; \( p = 0.35; 1 \) trial, 18 participants). On the other hand, we observed in one trial an increase in BMI of 0.2 kg/m² in 60 individuals who received fluoxetine 20 mg/day. However, overall, we observed a BMI reduction across all fluoxetine doses compared with the placebo that was −1.1 kg/m² (95% CI −3.7 to 1.4; 3 trials; 97 participants; very-low-certainty evidence) (Fig. 4) [26, 32, 35].

Adverse Events
Nine trials reported adverse events in this comparison [24–26, 30, 31, 33, 35–37]. A total of 399 out of 627 participants (63.6%) who received fluoxetine experienced an adverse event (mainly dizziness with RR 2.40; 95% CI 1.03–5.60; \( p = 0.04; \) drowsiness with RR 2.67; 95% CI 1.68–4.24; \( p = 0.0001; \) fatigue RR 2.50; 95% CI 1.62–3.85; \( p = 0.0001; \) insomnia with RR 2.23; 95% CI 1.22–4.08; \( p = 0.009; \) and nausea RR 1.99; 95% CI 1.35–2.91; \( p = 0.0004; \)) compared with 352 out of 626 participants (56.2%) who received placebo.

We observed an increase in the risk to develop at least one adverse event with RR 1.16 (95% CI 0.93–1.44; \( p = 0.18; 7 \) trials) in 1,134 participants who received fluoxetine 60 mg/day; same findings were identified in 262 adults who received fluoxetine 40 mg/day (RR 1.07; 95% CI 0.93–1.24; \( p = 0.32; 1 \) trial), fluoxetine 20 mg/day (RR 1.10; 95% CI 0.92–1.31; \( p = 0.30; 1 \) trial, 592 participants), and fluoxetine 10 mg/day (RR 0.96; 95% CI 0.82–1.12; \( p = 0.59; 1 \) trial, 262 participants) without significant subgroup differences (Fig. 5).
However, pooling the trials showed an increase in the risk of experiencing at least one adverse event in the fluoxetine groups, compared with the placebo with an RR of 1.18 (95% CI 0.99–1.42; p = 0.07; 9 trials, 1,253 participants; low-certainty evidence) [24–26, 30, 31, 33, 35–37]. The 95% prediction interval ranged between 0.74 and 1.88 (Table 2).

**Fluoxetine versus Other Therapies and No Treatment**

Weight Loss in Kilograms

Three trials (234 participants) compared different doses of fluoxetine with six types of anti-obesity agents (sibutramine, metformin, dexfenfluramine, diethylpropion, fenproporex, and mazindol) [26, 35, 37]; one trial (48 participants) used the omega-3 gel as monotherapy and in combination with fluoxetine [19]; and one trial compared with no treatment (60 participants) [27]; however, due to the great heterogeneity between the studies, it was not possible to generate the meta-analysis (Table 3).

**BMI Reduction**

Two trials compared fluoxetine with five types of anti-obesity agents (sibutramine, metformin, diethylpropion, fenproporex, and mazindol) [26, 35], and one trial compared with no treatment [27]. We identified that participants who received fluoxetine 60 mg/day showed a BMI reduction from −0.5 kg/m² (95% CI −0.6 to −0.3; p = 0.0001, 60 adults) to −2.2 kg/m² (95% CI −8.4 to 4; p = 0.48; 1 trial, 17 adults) compared to no treatment and

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**Table 3.** Forest plot of fluoxetine versus placebo for weight loss in kg. MD, mean difference.

| Study or Subgroup | Fluoxetine | Placebo | Mean Difference |
|-------------------|------------|---------|----------------|
| Mean [kg] | SD [kg] | Total [kg] | Mean [kg] | SD [kg] | Total [kg] | Weight | IV, Random, 95% CI |
| Fluoxetine 60 mg/d | -5.6 | 5.89 | 12 | -4.9 | 4.65 | 12 | 6.3% | -0.70 [-5.02, 3.62] |
| Bondi 2000 (1) [19] | -1.4 | 7.1 | 217 | -1.2 | 5.7 | 217 | 18.7% | -0.20 [-1.41, 1.01] |
| Gulnara 2006 (3) [20] | 83 | 9.01 | 9 | 77.7 | 10.66 | 10 | 1.9% | 5.30 [-3.55, 14.15] |
| Levine 1987 (4) [24] | -4.5 | 4 | 60 | -1.4 | 0.77 | 60 | 19.6% | -3.10 [-4.13, -2.07] |
| Levine 1989 (5) [25] | -3.91 | 3.87 | 87 | -0.54 | 2.34 | 74 | 19.9% | -3.37 [-4.34, -2.40] |
| Pijl 1991 (6) [27] | -3.6 | 1.66 | 11 | 0.3 | 1.73 | 12 | 17.8% | -1.90 [-5.29, -2.61] |
| Visser 1993 (7) [30] | -5.9 | 2.8 | 18 | -2.4 | 2.8 | 20 | 15.7% | -3.50 [-5.28, -2.72] |
| Subtotal (95% CI) | 414 | 405 | 100% | -2.50 [-3.78, -1.22] |

Heterogeneity: Tau² = 1.90; Chi² = 26.38, df = 6 (p = 0.0002); I² = 77%

Test for overall effect: Z = 3.43 (p = 0.0001)

Fluoxetine 40 mg/d

Levine 1989 (8) [25] | -2.16 | 2.56 | 90 | -0.54 | 2.34 | 74 | 51.8% | -1.62 [-2.37, -0.87] |
| Pedrirola 1993 (9) [28] | -8.2 | 2.8 | 10 | -1.7 | 1.3 | 8 | 48.2% | -6.50 [-8.46, -4.54] |
| Subtotal (95% CI) | 100 | 82 | 100% | -3.97 [-8.75, 0.81] |

Heterogeneity: Tau² = 11.34; Chi² = 20.85, df = 1 (p < 0.00001); I² = 95%

Test for overall effect: Z = 1.83 (p = 0.10)

Fluoxetine 20 mg/d

Levine 1989 (10) [25] | -1.93 | 3.06 | 86 | -0.54 | 2.34 | 74 | 42.0% | -1.39 [-2.23, -0.55] |
| Suppley 2014 (11) [20] | -2.5 | 4.1 | 31 | -3.1 | 4.3 | 29 | 30.7% | -0.60 [-1.53, 2.73] |
| Wurtman 1993 (12) [21] | -7.1 | 5.97 | 30 | -3 | 3.99 | 29 | 26.5% | -4.10 [-6.68, -1.52] |
| Subtotal (95% CI) | 147 | 132 | 100% | -1.50 [-3.35, 0.54] |

Heterogeneity: Tau² = 2.33; Chi² = 7.58, df = 2 (p = 0.02); I² = 74%

Test for overall effect: Z = 1.44 (p = 0.15)

Test for subgroup differences: Chi² = 1.17, df = 2 (p = 0.56), I² = 0%

Footnotes:

(1) 12 weeks intervention
(2) 52 weeks intervention
(3) 20 days intervention
(4) 11 days intervention; value of 0.1 in publication probably SE and recalculated as SD
(5) 8 weeks intervention
(6) 6 weeks intervention
(7) 12 weeks intervention
(8) 8 weeks intervention
(9) 12 weeks intervention
(10) 8 weeks intervention
(11) 8 weeks intervention
(12) 12 weeks intervention
metformin, respectively; however, on the other hand, we also observed an increase of BMI in participants who received fluoxetine 20 mg/day from 2 kg/m² (95% CI 0.9–3.1; p = 0.0001; 1 trial, 62 adults) to 2.9 kg/m² (95% CI 1.8–4; p = 0.0001; 1 trial 61 participants) compared to sibutramine, diethylpropion, fenproporex, and mazindol. As in the previous outcome analysis, we were unable to perform the meta-analysis due to the diversity of interventions and heterogeneity between the studies (Table 3).

Adverse Events

Three trials reported the development of adverse events comparing fluoxetine with six anti-obesity agents [26, 35, and 37], and one trial compared with no treatment [27]. Overall, we observed an increase in the risk to develop at least one adverse event from an RR of 1.05 (95% CI 0.68–1.65; p = 0.82; 1 trial, 60 participants) to an RR of 1.58 (95% CI 0.91–2.77; p = 0.11; 1 trial) in participants who received fluoxetine at any dose; however, the meta-analysis could not be performed due to the heterogeneity between the trials (Table 3). For mortality and socioeconomic effects, none of the included trials reported these outcomes.

Discussion

Overall, we identified a great variety of doses and durations of treatment in the intervention groups, many different groups of comparators, and variation in the diagnostic criteria and characteristics of the grade of obesity in the participants, which limited comparability and increased the heterogeneity between trials. In most trials, the risk of selection bias was unclear because their reports did not mention in detail the methods of random se-

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**Table 2. Risk of developing adverse events with fluoxetine**

| Adverse event   | Risk of adverse events, RR (95% CI) | Trials | Participants |
|-----------------|------------------------------------|--------|--------------|
| Abdominal pain  | 1.51 (0.58–3.90); p = 0.40         | 5      | 504          |
| Allergy         | 0.17 (0.03–0.98); p = 0.05*        | 3      | 780          |
| Anemia          | 12.89 (0.73–227.44); p = 0.08      | 1      | 458          |
| Anorexia        | 8.89 (1.36–57.89); p = 0.02*       | 1      | 19           |
| Anxiety         | 1.07 (0.56–2.03); p = 0.83         | 7      | 1,210        |
| Constipation    | 2.83 (0.58–13.90); p = 0.20        | 3      | 381          |
| Diarrhoea       | 1.44 (0.97–2.13); p = 0.07         | 7      | 1,191        |
| Dizziness       | 2.40 (1.03–5.60); p = 0.04*        | 5      | 693          |
| Drowsiness      | 2.67 (1.68–4.24); p = 0.0001*      | 9      | 1,253        |
| Dry mouth       | 1.23 (0.66–2.30); p = 0.52         | 6      | 896          |
| Dyspepsia       | 1.99 (0.71–5.55); p = 0.19         | 4      | 501          |
| Fatigue         | 2.50 (1.62–3.85); p = 0.0001*      | 5      | 1,112        |
| Headache        | 1.17 (0.94–1.47); p = 0.16         | 8      | 1,234        |
| Insomnia        | 2.23 (1.22–4.08); p = 0.009*       | 7      | 1,191        |
| Irritability    | 1.44 (0.63–3.15); p = 0.40         | 3      | 442          |
| Malaise         | 0.60 (0.15–2.46); p = 0.48         | 2      | 322          |
| Nausea          | 1.99 (1.35–2.91); p = 0.0004*      | 7      | 1,016        |
| Palpitations    | 2.81 (0.12–66.40); p = 0.52        | 1      | 60           |
| Rhinitis        | 0.99 (0.75–1.30); p = 0.94         | 3      | 933          |

* p value ≤0.05.
resulting generation and concealment of allocation. Blinding of outcome assessment was unclear in almost all trials. Approximately one-third of the trials had a high risk of bias due to an attrition rate of 20% of their participants, and almost half of the trials had a high risk of reporting bias.

However, although our findings had low-certainty evidence, we observed that off-label fluoxetine at any dose, especially 60 mg once a day, may cause moderate weight loss of approximately 2.7 kg and only with this dose generate a reduction of BMI of −1.1 kg/m² compared with placebo in adults with overweight or obesity; however, it may lead to approximately twice as many adverse events, such as dizziness, drowsiness, fatigue, insomnia, or nausea. These findings are similar to other systematic reviews which reported that the participants who received fluoxetine at least for 4 months showed a weight loss from 1.3 kg in adults with overweight or obese (BMI of 26–39 kg/m²) to 5.1 kg in participants with type 2 diabetes compared with placebo [38–40].

Based on the above, although there are FDA-approved pharmacological therapies effective for weight reduction in adults with overweight or obesity, such as pancreatic lipase inhibitors, GLP-1 analogues, MC4R agonists, and appetite suppressants, the only therapeutic strategy that includes a weak antidepressant is the naltrexone-bupro-

| Study or Subgroup | Fluoxetine Events | Placebo Events | Weight M–H, Random, 95% CI | Risk Ratio M–H, Random, 95% CI |
|-------------------|------------------|----------------|---------------------------|-------------------------------|
| Fluroxetine 60 mg/d |                  |                |                           |                               |
| Goldstein 1993 [18] | 19               | 106            | 20                        | 107                           | 10.9%                        | 0.96 [0.54, 1.69] |
| Goldstein 1994 [19] | 200              | 230            | 194                       | 228                           | 41.3%                       | 1.02 [0.95, 1.10] |
| Guimaraes 2006 [20] | 8                | 9              | 1                         | 10                            | 1.3%                        | 8.89 [1.36, 57.89] |
| Levine 1987 [24]   | 15               | 60             | 7                         | 60                            | 6.0%                        | 2.14 [0.94, 4.88] |
| Levine 1989 [25]   | 101              | 131            | 94                        | 131                           | 36.5%                       | 1.07 [0.93, 1.24] |
| Pijl 1991 [27]     | 4                | 12             | 2                         | 12                            | 2.0%                        | 2.00 [0.45, 8.94] |
| Visser 1993 [30]   | 7                | 18             | 2                         | 20                            | 2.2%                        | 3.89 [0.92, 16.36] |
| Subtotal (95% CI)  | 566              | 568            | 100.0%                    | 1.16 [0.93, 1.44] |
| Total events       | 354              | 320            |                           |                               |

Heterogeneity: Tau² = 0.03; Chi² = 15.41, df = 6 (P = 0.02); I² = 61%
Test for overall effect: Z = 1.33 (P = 0.18)

| Fluroxetine 40 mg/d |                  |                |                           |                               |
|-------------------|------------------|----------------|---------------------------|-------------------------------|
| Levine 1989 [25]   | 101              | 131            | 94                        | 131                           | 100.0%                      | 1.07 [0.93, 1.24] |
| Subtotal (95% CI)  | 131              | 131            | 100.0%                    | 1.07 [0.93, 1.24] |
| Total events       | 101              | 94             |                           |                               |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)

| Fluroxetine 20 mg/d |                  |                |                           |                               |
|-------------------|------------------|----------------|---------------------------|-------------------------------|
| Goldstein 1993 [18] | 16               | 104            | 20                        | 107                           | 7.9%                        | 0.82 [0.45, 1.50] |
| Levine 1989 [25]   | 100              | 131            | 94                        | 131                           | 48.7%                       | 1.06 [0.92, 1.23] |
| Suppilly 2014 [29] | 18               | 31             | 8                         | 29                            | 6.6%                        | 2.10 [1.09, 4.08] |
| Wurtman 1993 [31]  | 27               | 30             | 24                        | 29                            | 36.8%                       | 1.09 [0.89, 1.33] |
| Subtotal (95% CI)  | 296              | 296            | 100.0%                    | 1.10 [0.92, 1.31] |
| Total events       | 161              | 146            |                           |                               |

Heterogeneity: Tau² = 0.01; Chi² = 4.78, df = 3 (P = 0.19); I² = 37%
Test for overall effect: Z = 1.04 (P = 0.30)

| Fluroxetine 10 mg/d |                  |                |                           |                               |
|-------------------|------------------|----------------|---------------------------|-------------------------------|
| Levine 1989 [25]   | 90               | 131            | 94                        | 131                           | 100.0%                      | 0.96 [0.82, 1.12] |
| Subtotal (95% CI)  | 131              | 131            | 100.0%                    | 0.96 [0.82, 1.12] |
| Total events       | 90               | 94             |                           |                               |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Chi² = 2.44, df = 3 (P = 0.49), I² = 0%

Fig. 5. Forest plot of fluoxetine versus placebo for any adverse event (per dose).
Fluoxetine to Reduce Weight in Adults with Overweight

Table 3. Fluoxetine versus another anti-obesity agents and no treatment

| Comparison                          | Mean difference (95% CI)     | Trials | Participants |
|-------------------------------------|------------------------------|--------|--------------|
| **Weight loss**                     |                              |        |              |
| Fluoxetine 60 mg/day versus sibutramine | 4.3 kg (−3.2–11.8); p = 0.26 | 1      | 17           |
| Fluoxetine 60 mg/day versus metformin | −8.9 kg (−19.9–2.1); p = 0.11 | 1      | 17           |
| Fluoxetine 20 mg/day versus sibutramine | 7 kg (4.4–9.6); p = 0.0001* | 1      | 61           |
| Fluoxetine 20 mg/day versus dexfenfluramine | −0.5 kg (−3.4–2.4); p = 0.73 | 1      | 58           |
| Fluoxetine 20 mg/day versus diethylpropion | 7.5 kg (4.7–10.3); p = 0.0001* | 1      | 61           |
| Fluoxetine 20 mg/day versus fenproporex | 5.3 kg (2.4–8.2); p = 0.0004* | 1      | 62           |
| Fluoxetine 20 mg/day versus mazindol | 4.9 kg (2.6–7.3); p = 0.0001* | 1      | 60           |
| Fluoxetine 60 mg/day versus no treatment | −2.7 kg (−3 to −2.4); p = 0.0001* | 1      | 60           |
| **BMI reduction**                   |                              |        |              |
| Fluoxetine 60 mg/day versus sibutramine | −1.5 kg/m² (−5.2–2.2); p = 0.42 | 1      | 17           |
| Fluoxetine 60 mg/day versus metformin | −2.2 kg/m² (−8.4–4); p = 0.48 | 1      | 17           |
| Fluoxetine 20 mg/day versus sibutramine | 2.4 kg/m² (1.4–3.4); p = 0.0001* | 1      | 61           |
| Fluoxetine 20 mg/day versus diethylpropion | 2.9 kg/m² (1.8–4); p = 0.0001* | 1      | 61           |
| Fluoxetine 20 mg/day versus fenproporex | 2 kg/m² (0.9–3.1); p = 0.0006* | 1      | 62           |
| Fluoxetine 20 mg/day versus mazindol | 2 kg/m² (1.1–2.9); p = 0.0001* | 1      | 60           |
| Fluoxetine 60 mg/day versus no treatment | −0.5 kg/m² (−0.6 to −0.3); p = 0.0001* | 1      | 60           |
| **Relative risk (95% CI)**          |                              |        |              |
| Fluoxetine 60 mg/day versus sibutramine | 1.19 (0.75–1.88); p = 0.47 | 1      | 17           |
| Fluoxetine 60 mg/day versus metformin | 1.78 (0.86–3.69); p = 0.12 | 1      | 17           |
| Fluoxetine 20 mg/day versus sibutramine | 1.58 (0.91–2.77); p = 0.11 | 1      | 61           |
| Fluoxetine 20 mg/day versus dexfenfluramine | 1.09 (0.89–1.33); p = 0.42 | 1      | 59           |
| Fluoxetine 20 mg/day versus diethylpropion | 1.58 (0.91–2.77); p = 0.11 | 1      | 61           |
| Fluoxetine 20 mg/day versus fenproporex | 1.20 (0.75–1.92); p = 0.45 | 1      | 62           |
| Fluoxetine 20 mg/day versus mazindol | 1.05 (0.68–1.64); p = 0.82 | 1      | 60           |
| Fluoxetine 60 mg/day versus no treatment | 8.67 (2.94–25.94); p = 0.0001* | 1      | 60           |

* p value ≤0.05.

Conclusions

We observed low-certainty evidence suggesting that off-label fluoxetine may produce a modest weight loss compared with placebo at any dose, especially when given at a dose of 60 mg/day. However, we found low-certainty evidence of a small increase in the risk for specific adverse events, such as dizziness, drowsiness, fatigue, insomnia, and nausea following fluoxetine consumption. With respect to other findings of our review, more high-certainty research is needed to exclusively determine the effects of pion combination despite the reported association between obesity and the development of depression [4]; so, although the indication for fluoxetine is for the treatment of obsessive behaviors, depression, and anxiety crises, it could be considered as another strategy for weight loss in adults with this condition since it may produce a modest weight loss as a side effect compared to the annoying adverse effects of the administration of pancreatic lipase inhibitors such as the presence of steatorrhea, flatulence, and deficits in the absorption of vitamins A, D, E, and beta-carotene or those developed by the use of GLP-1 analogues and MC4R agonists, which in addition to injection site reactions and their high cost, also favor the appearance of headache, hypoglycemia, nausea, vomiting, and diarrhea [7, 8]. In this way, health decision makers can take into consideration another therapeutic option at a lower cost, which could be an alternative to be implemented, especially in overweight or obese adults in low- and middle-income countries.
fluoxetine at different doses and whether it is useful when combined with other anti-obesity agents and non-pharmacological interventions.

Acknowledgements

We thank the Cochrane Metabolic and Endocrine Disorders Group for their assistance and their Information Specialist; Maria-Inti Metzendorf for developing the search strategy; and the Assistant Director of Scientific Information and Documentation of the Instituto Nacional de Pediatría, Cecilia Solis-Galicia, for acquiring study reports. The review authors are grateful to the following peer reviewers for their time and comments: Dr. Emma Axon, Cochrane Systematic methodologist, Cochrane Skin Group, University of Nottingham, UK, and Ian Caterson, University of Sydney.

Statement of Ethics

This manuscript did not require ethical approval by the ethics committee of the Instituto Nacional de Pediatría and was reviewed, approved, and co-published by Cochrane Database of Systematic Reviews 2019, Issue 10. Art. No.: CD011688 titled Fluoxetine for adults who are overweight or obese [18].

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This manuscript has been supported by the Instituto Nacional de Pediatría (2019/C-043 fiscal resources program E022) only for publication.

Author Contributions

A.E.S.-Z. contributed to conceptualization, investigation, supervision, validation, visualization, medical oversight, and preparing the original draft and final manuscript. A.G.G.-G. contributed to conceptualization, data curation, formal analysis, methodology, software, validation, visualization, and writing the final manuscript. Y.R.-C. contributed to investigation, conceptualization, data curation, visualization, and preparing the original draft. G.M.-M. contributed to conceptualization, supervision, validation, project administration, and critical revision of the draft and final manuscript. All the authors approved the final manuscript. Y.R.-C. and G.M.-M. contributed equally to this article and shared final authorship.

Data Availability Statement

All data generated or analyzed during this study are included in this manuscript. Further enquiries can be directed to the corresponding author.

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