Obesity Facts

Systematic Review

Obes Facts 2022;15:473–486
DOI: 10.1159/000524995

Received: January 6, 2022
Accepted: May 4, 2022
Published online: June 2, 2022

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

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Keywords
Fluoxetine · Weight loss · Adverse events · Obesity

Abstract

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. ***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. ***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; $p < 0.001$) 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. ***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.

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; $p < 0.001$), osteoarthritis, metabolic syndrome, type 2 diabetes mellitus (HR 1.86; 95% CI

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0.99–3.50; $p = 0.053$), and depression (OR 1.57; 95% CI 1.23–2.01; $p < 0.001$), which reduce the quality of life and increase the costs derived from their complications [2–6]. Therefore, different pharmacological strategies to reduce weight have been investigated to decrease the prevalence of obesity such as pancreatic lipase inhibitors (orlistat), GLP-1 analogues (liraglutide, semaglutide), MC4R agonists (setmelanotide), and appetite suppressants (phentermine-topiramate, naltrexone-bupropion), among others [7, 8].

Another pharmacological strategy is fluoxetine; it is a selective serotonin reuptake inhibitor with the capacity to treat major depression, obsessive behaviors, panic disorders, and bulimia, which also favors the hunger inhibition signals produced by the neuropeptide "Y" in the paraventricular hypothalamic nucleus, operating on appetite, altering food selection, and leading to a reduction in food intake [9–12]. Although fluoxetine has been documented to promote weight loss, currently, the only indications approved by the Food and Drug Administration are for the treatment of depression and obsessive behaviors, among others, as some studies have reported that its use may lead to adverse effects, such as headache, nausea, drowsiness, diarrhea, insomnia, sweating, and decreased libido in 5–30% of the users [13–15].

However, based on the evidence, it has been considered whether fluoxetine could be used alone or in combination with other pharmacological or behavioral changes interventions as a strategy to treat depression in adults with overweight or obesity who would also benefit from weight loss; however, the benefit-risk ratio (RR) of this drug is unclear in this regard, so we performed a systematic review to assess the efficacy and safety of fluoxetine in reducing weight in adults with overweight or obesity.

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/OR 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/m^2) or obesity (BMI ≥30 kg/m^2) 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 χ^2 test with a significance level of 0.1 and I^2 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%

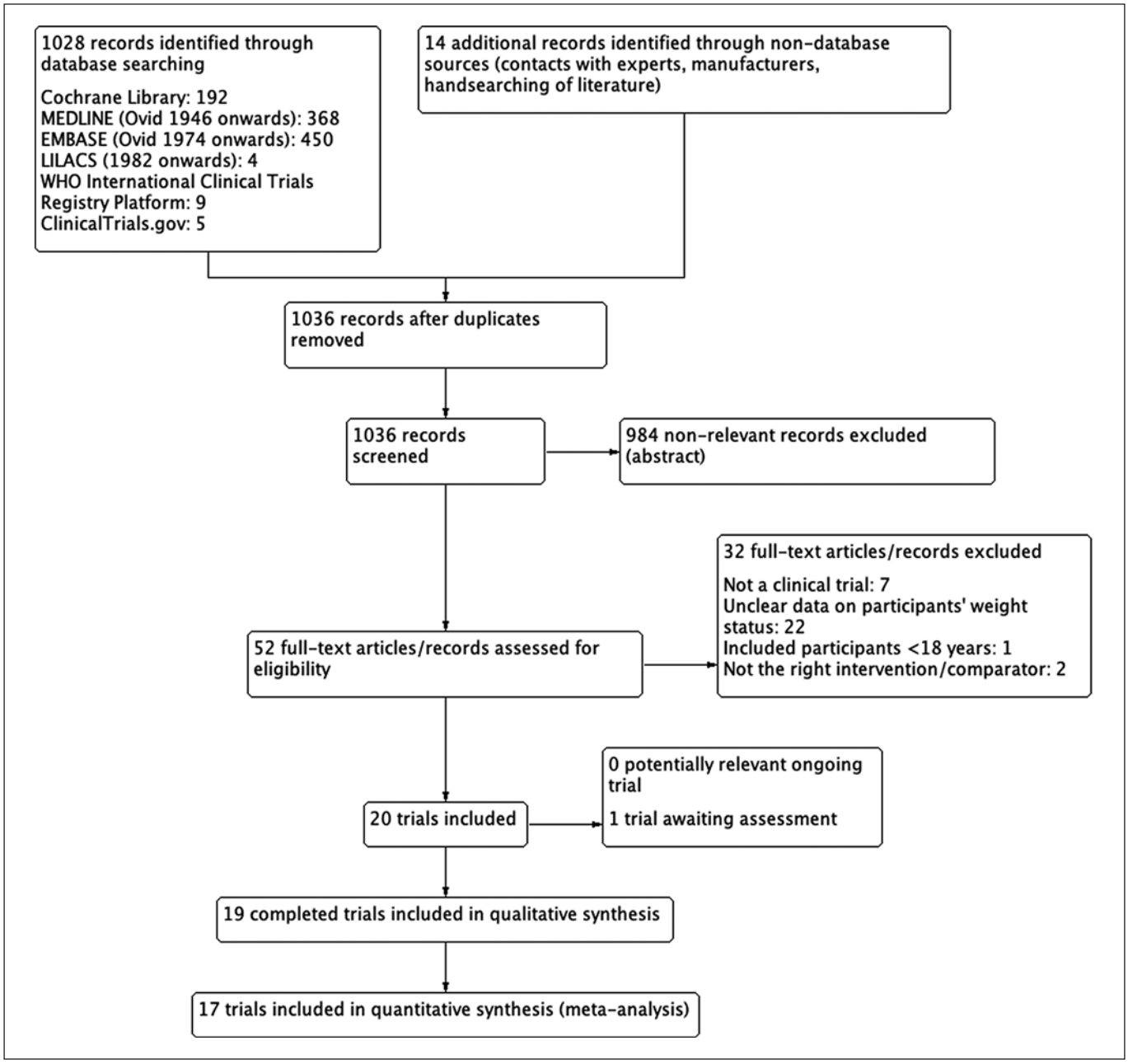

Fig. 1. Flow diagram to show the process of trial selection (PRISMA).

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/m^2 (95% CI

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Table 1. Characteristics of included trials

Author/year	Sex (female), %	Age (range), years	BMI (mean or range), kg/m^2	Intervention *N*/dose	Comparator *N*/dose	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 Omega-3 gel (1 g) orally twice a day for 2 months *N* = 12 Fluoxetine 20 mg + omega-3 gel (1 g) orally daily 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* = 31 Fenproporex 25 mg orally, once per day for 52 weeks *N* = 29 Mazindol 2 mg orally, once per day for 52 weeks *N* = 31 Fluoxetine 20 mg orally, once per day for 52 weeks *N* = 30 Sibutramine 15 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* = 8 Metformin 1.7 g orally, once per day for 90 days *N* = 8 Fluoxetine 60 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 Fluoxetine 60 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/m^2	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 Fluoxetine 20 mg orally, once per day for 40 weeks	*N* = 107 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 Dexfenfluramine mg orally, once per day for 12 weeks	*N* = 29 Placebo orally, once daily 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	–

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Table 1 (continued)

Author/year	Sex (female), %	Age (range), years	BMI (mean or range), kg/m^2	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.

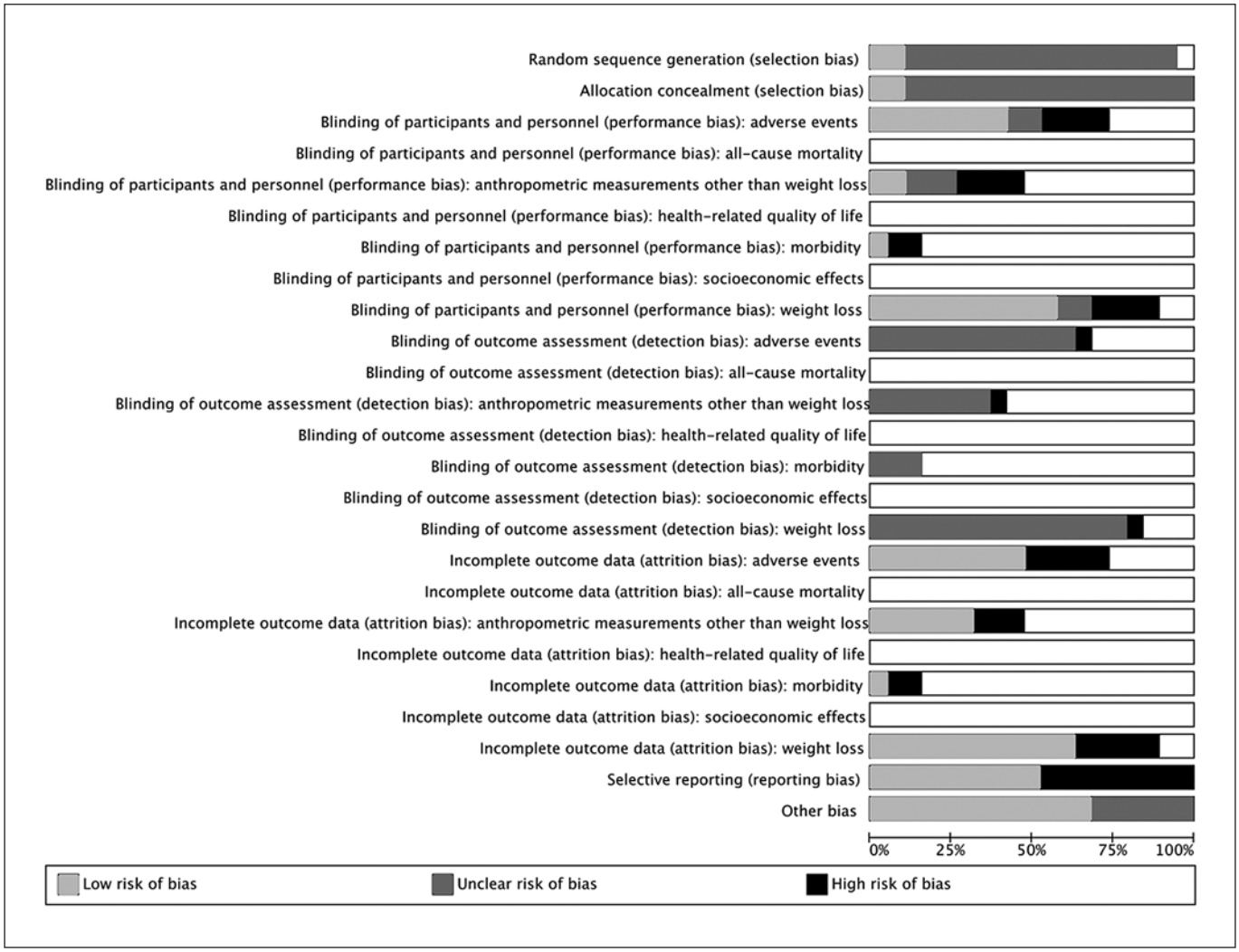

Fig. 2. Risk of bias graph.

−7.3 to 0.7; $p = 0.10$; 1 trial) and who received fluoxetine 40 mg/day showed −2.8 kg/m^2 (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/m^2 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/m^2 (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).

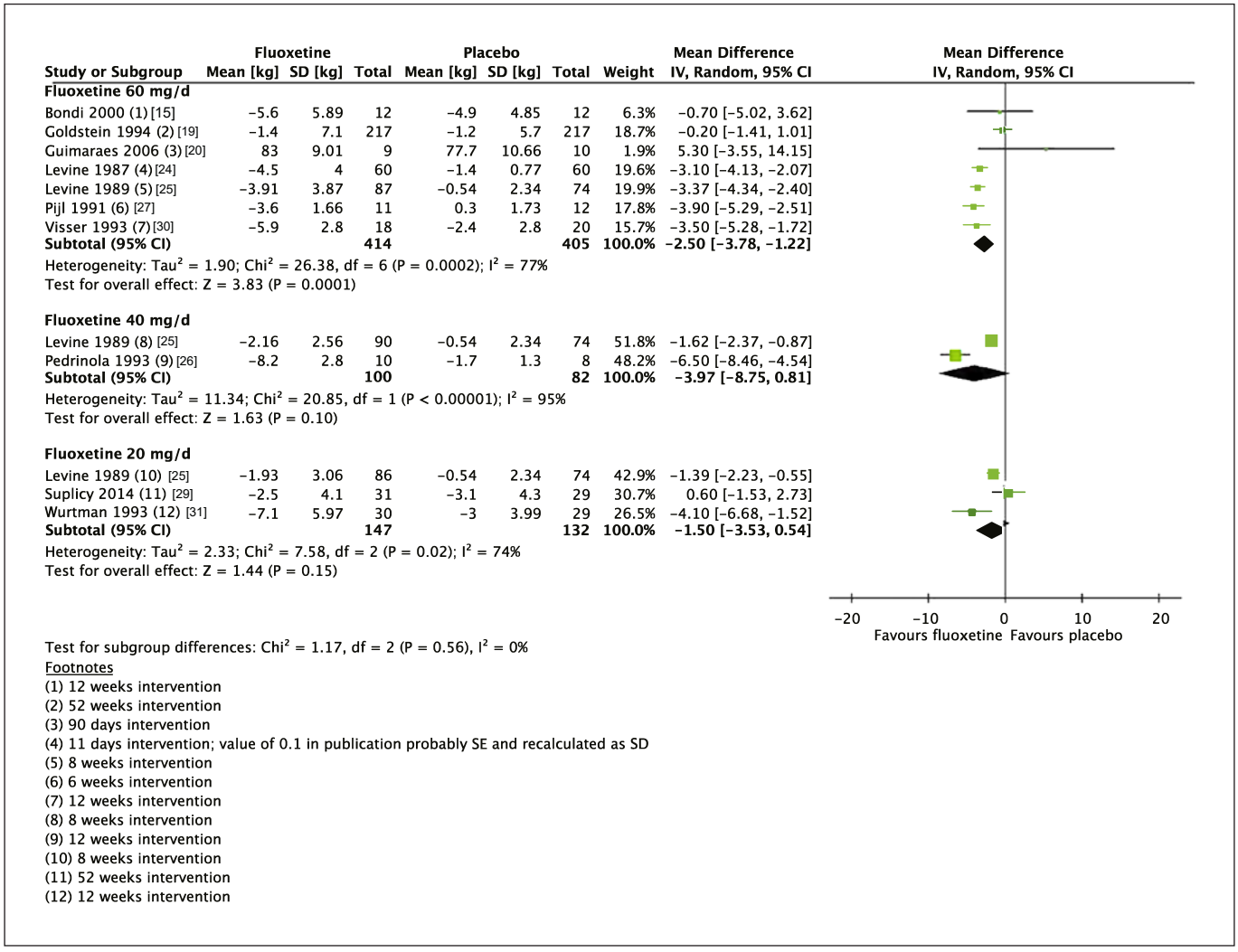

Fig. 3. Forest plot of fluoxetine versus placebo for weight loss in kg. MD, mean difference.

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/m^2 (95% CI −0.6 to −0.3; $p = 0.0001$, 60 adults) to −2.2 kg/m^2 (95% CI −8.4 to 4; $p = 0.48$; 1 trial, 17 adults) compared to no treatment and

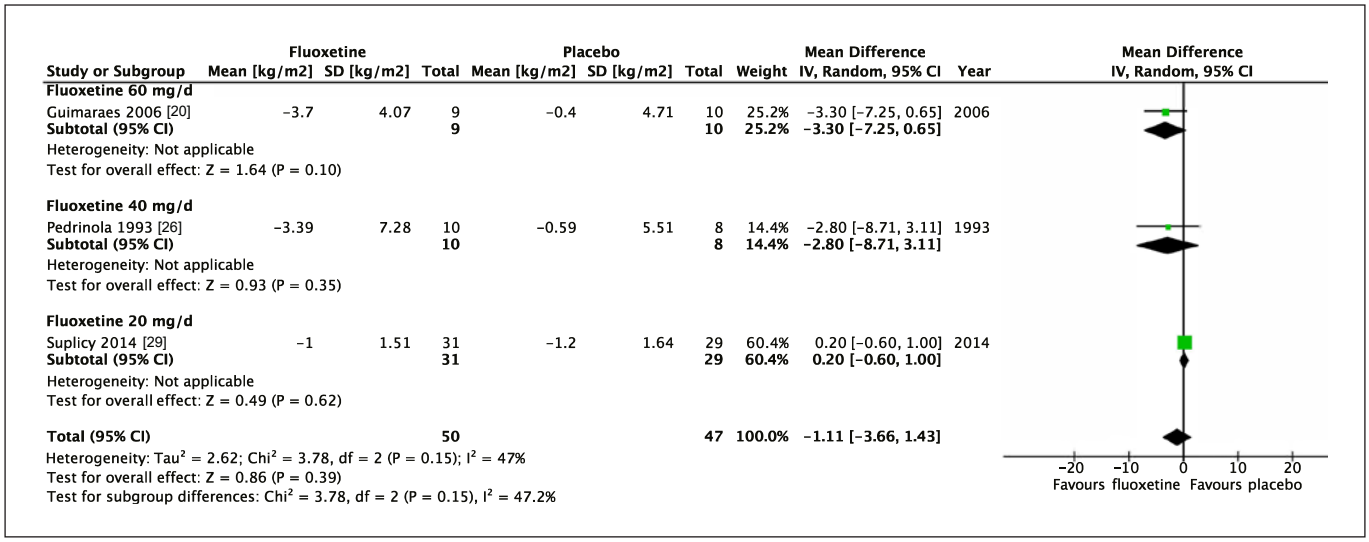

Fig. 4. Forest plot of fluoxetine versus placebo for BMI reduction. MD, mean difference.

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
Amnesia	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	1.41 (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.

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/m^2 (95% CI 0.9–3.1; $p = 0.0001$; 1 trial, 62 adults) to 2.9 kg/m^2 (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-

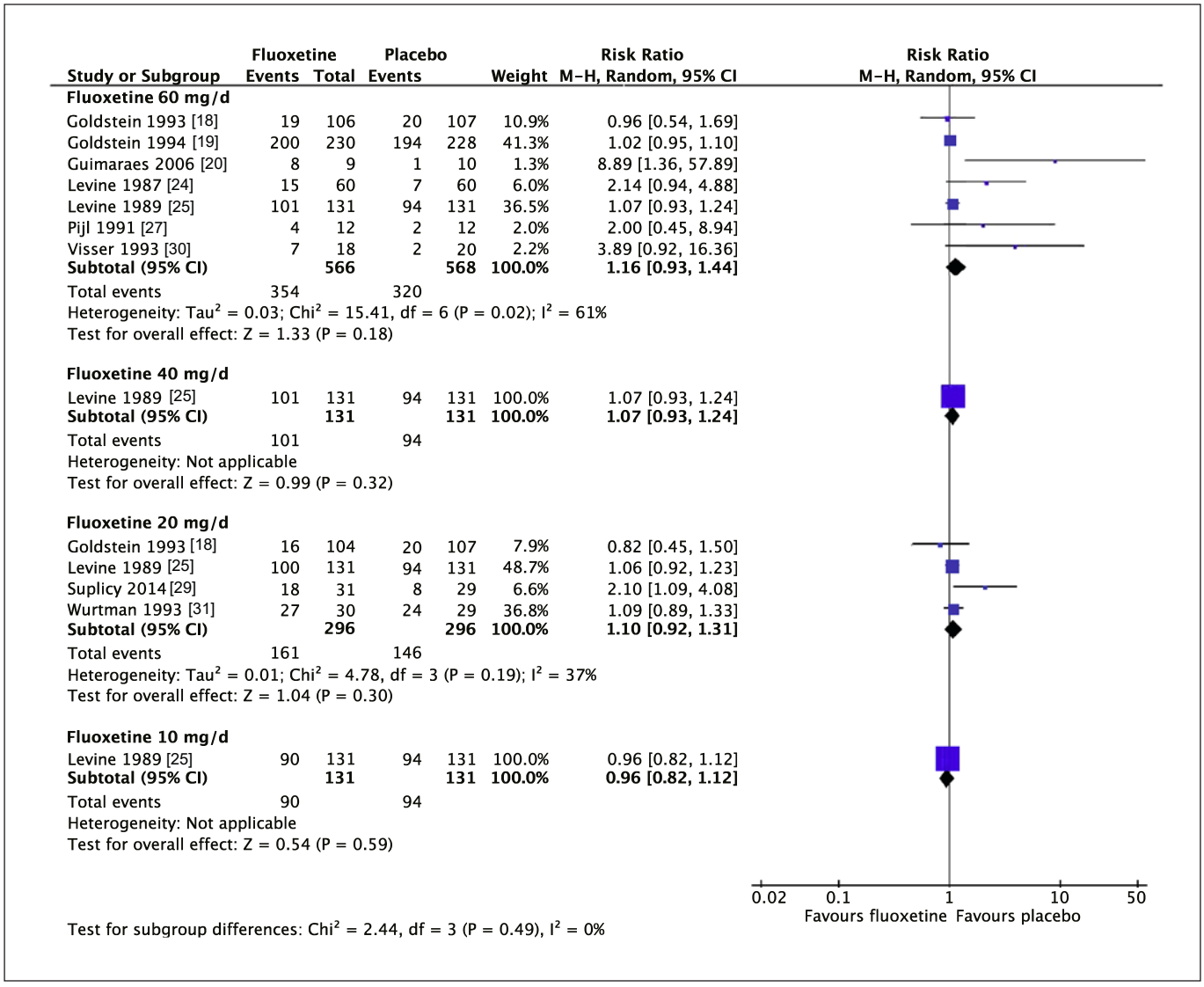

Fig. 5. Forest plot of fluoxetine versus placebo for any adverse event (per dose).

quence 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/m^2 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/m^2) 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-

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
	Mean difference (95% CI)		
BMI reduction			
Fluoxetine 60 mg/day versus sibutramine	−1.5 kg/m^2 (−5.2–2.2); $p = 0.42$	1	17
Fluoxetine 60 mg/day versus metformin	−2.2 kg/m^2 (−8.4–4); $p = 0.48$	1	17
Fluoxetine 20 mg/day versus sibutramine	2.4 kg/m^2 (1.4–3.4); $p = 0.0001$*	1	61
Fluoxetine 20 mg/day versus diethylpropion	2.9 kg/m^2 (1.8–4); $p = 0.0001$*	1	61
Fluoxetine 20 mg/day versus fenproporex	2 kg/m^2 (0.9–3.1); $p = 0.0006$*	1	62
Fluoxetine 20 mg/day versus mazindol	2 kg/m^2 (1.1–2.9); $p = 0.0001$*	1	60
Fluoxetine 60 mg/day versus no treatment	−0.5 kg/m^2 (−0.6 to −0.3); $p = 0.0001$*	1	60
	Relative risk (95% CI)		
Adverse events			
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.

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.

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

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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