

The placebo response rate and nocebo events in obesity pharmacological trials. A systematic review and meta-analysis

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Summary

Background There is a growing number of trials examining the effectiveness of pharmacotherapies for obesity, however, little is known about placebo and nocebo effect in these trials. Hence, we sought to examine the effect of placebo in obesity trials, to better understand the potential factors affecting clinical endpoints in them.

Methods Medline, Embase, and Cochrane CENTRAL were searched for articles examining weight-loss RCTs examining patients with overweight or obesity in placebo-controlled arms from inception till 25 June 2022. This paper was registered online with PROSPERO (CRD42022302482). A single arm meta-analysis of proportions was used to estimate the primary outcomes, $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ total weight loss – and the adverse effects that patients experienced during the trial. A meta-analysis of means was used to estimate the pooled mean differences of the secondary outcomes including, body weight measurements, lipid levels, glycemic indices, and blood pressure over time.

Findings A total of 63 papers involving 20,454 patients and 69 trials were included. The proportion of patients that had $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ weight loss was 20.4% (CI:16.1% to 25.0%), 8.3% (CI:6.1% to 10.9%), and 6.2% (CI:3.8% to 9.7%), respectively. Analysis by duration of trials showed stepwise increase in proportion of patients with $\geq 5\%$ and $\geq 10\%$ weight loss with increasing duration of study. Analysis of secondary outcomes found modest improvement in all analyses. The pooled average rate of overall AEs, serious AEs, and discontinuation was 73.7% (CI:68.0% to 79.0%), 3.4% (CI:2.4% to 4.5%), and 5.2% (CI:4.0% to 6.5%), respectively. In psychiatric complications, the pooled rates of anxiety and depression were 2.7% (CI:1.8% to 3.7%) and 2.5 (CI:1.7% to 3.3%).

Interpretation Our meta-analysis of placebo-treated participants in weight-loss RCTs indicate a significant placebo and nocebo effect. These findings are important to quantify their effect and may inform the design of future RCTs.

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Keywords: Placebo effect; Hawthorne effect; Obesity; Weight loss

Research in context

Evidence before study

Placebo and nocebo effects of placebo arm of placebo-controlled trials is not well understood. Previous studies examining its effect on lipid lowering therapies and other metabolic diseases have been done, however, little to none have been done for weight-loss trials. We searched Medline, Embase and Cochrane for systematic reviews and meta-analyses examining the placebo and nocebo effects of weight-loss trials on 26 December 2021. We identified no previous meta-analyses examining the placebo and nocebo effects of patients with overweight or obesity.

Added value of this study

Our study is the first systematic review and meta-analysis examining the placebo and nocebo effects of weight-loss randomized controlled trials (RCTs). We found that 20.4% (CI:16.1% to 25.0%) and 8.3% (CI:6.1% to 10.9%) of patients with overweight or obesity in the placebo arms were recorded experiencing the primary outcome of $\geq 5\%$ and of $\geq 10\%$ weight loss, respectively. Trials conducted in populations without diabetes had a higher proportion of participants that had $\geq 5\%$ and $\geq 10\%$ total weight loss as compared to patients with diabetes. Modest improvement in lipid levels, glycaemic indices and blood pressure readings were also noted in our review. However, a significant proportion of patients also experienced adverse events (73.7%), with a smaller proportion of patients experiencing systemic adverse events such as, upper respiratory tract infections, neoplasm and psychiatric complications.

Implications of all the available evidence

Our study shows that the placebo effect in weight loss RCTs is significant, and clinicians should be reassured that patients undergoing these trials would experience substantial improvements in weight. Additionally, clinicians and researchers should be cognizant that not all adverse effects may be due to the drug itself, and appropriate counselling of patients should be performed to reduce the dropout rates of these trials. Future research can look to examine the potential impact the placebo effect has on their behaviour change towards weight loss and clinical improvement of psychiatric issues of patients in weight loss RCTs.

Introduction

Obesity is a major global pandemic. In 2016, the World Health Organization estimated that up to 39% and 13% of the world's adult population were overweight or with obesity respectively.¹ Global estimates suggest that upwards of 2.8 million human deaths annually are attributed to overweight or obesity.² The cost of obesity is large, estimated to be approximately US\$149.4 billion in annual medical spending in the United States (US) alone.³ Visceral adiposity has epidemiological links to major preventable causes of death and disability, including type 2 diabetes, cardiovascular diseases, stroke, non-alcoholic fatty liver disease, malignancy, and many other metabolic diseases.^{4–6}

Current US Food and Drug Administration approved medical treatments for obesity include orlistat, phentermine-topiramate, naltrexone-bupropion, liraglutide, and semaglutide.^{7,8} With substantial investments into anti-obesity therapeutics, it is imperative to better characterize the placebo effect in randomized clinical trials of pharmacotherapies for obesity. Importantly, the placebo effect and the "Hawthorne" effect describe a phenomenon where patients manifest a positive behavioral change from the awareness of being observed,⁹ while the nocebo effect encompasses the phenomenon where patients experience 'side effects' despite being on placebo, due to the expectation or anticipation of these side effects arising.¹⁰ Placebo and nocebo effects have been found to significantly affected randomized trials in other metabolic diseases such as hyperlipidaemia, non-alcoholic fatty liver disease and inflammatory bowel disease.^{11–14} Notably, the SAMSON trial showed that adverse events associated with statin use could not be differentiated from those experienced by patients taking placebo, which complicates the planning of future trials.¹¹ However, not much is known about how the placebo and nocebo effect weighs in for weight loss trials.

Participants in the control arms of placebo-controlled randomized trials represent a subset of patients recruited based on well-defined eligibility criteria, with accurately captured information on subsequent interventions and protocol deviations, and detailed follow-up by trial researchers. Hence in theory, placebo-controlled trials provide valuable opportunities to understand the

natural history of diseases, which may enable better appraisal of the true treatment effect of candidate obesity drugs.¹⁵ We therefore endeavoured to critically appraise the outcomes of placebo-treated participants in randomized studies of pharmacotherapies for obesity.

Methods

Search strategy

We conducted a systematic review and meta-analysis with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),¹⁶ Medline, Embase, and Cochrane CENTRAL databases were accessed, and relevant papers were identified from inception to 25 June 2022. Keywords and MeSH terms synonymous with “obesity”, “overweight”, “weight loss”, “placebo-controlled arms”, and “clinical trials” were utilised. The search terms were compiled based upon the analysis of previous similar reviews conducted on placebo studies,¹³ previous reviews on obesity drugs,¹⁷ and with consideration of the current literature. The complete search strategy can be found in the Supplementary Material 1. Citations were imported into EndNote X9 for the initial sieve with the removal of duplicates. References of related reviews and included articles were also hand-screened to ensure a comprehensive search.^{18,19} The protocol of this paper was registered online with PROSPERO (Registration ID: CRD42022302482).

Study selection and extraction

Four authors in pairs (YHC and NWSC, and CHN and GK) independently screened articles located with the initial search, and articles meeting the inclusion criteria were selected for analysis. A third independent author was involved in the resolution of disputes (MM), where authors discussed their reasons for inclusion or exclusion until a general consensus was met. The following criteria were used for the inclusion of studies: (1) clinical trials that were randomized, double-blinded, parallel studies, because these are considered the gold standard for judging benefits and costs of treatments²⁰; (2) studies evaluating adults (aged 18 and above) with overweight or obesity (with or without diabetes mellitus) randomised into placebo treatment for weight loss; (3) no use of any weight loss or weight gain medications in the placebo arms (4) reported weight change of participants. Only randomized controlled trials written in or translated into English by the journals were considered. All observational studies, case-control studies, reviews, meta-analyses, editorials, commentaries, conference abstracts, and non-English language articles were excluded. Background diabetes mellitus treatment medications such as metformin, sulfonylureas, insulin, and other medications deemed not to affect weight gain or loss were allowed. Duplicated studies that obtained results from the same databases were removed, where

the latest or the most comprehensive publication was retained.

Overweight was defined as a body mass index (BMI) of 23-24.9 kg/m² for Asians,²¹ and a BMI of 25-29.9 kg/m² for Europeans,¹ while obesity was defined as a BMI value of ≥ 25 kg/m² for Asians and ≥ 30 kg/m² for Europeans.^{1,21} Data were extracted independently by four authors (YHC, NWSC, CHN and GK) into a pre-determined datasheet. This includes information on study characteristics (country, region, clinical trial registration number/code, year of study, phase, funding, multi/single centre trials and duration of follow-up), baseline information (total sample size, mean age, gender, BMI, waist circumference, weight, glycated haemoglobin [HbA1c], fasting blood glucose [FBG], and presence of other comorbidities), outcomes (5%, 10%, and 15% total weight loss, change in BMI, weight, waist circumference, lipids profile, glucose profile) and adverse events (AEs). When they were not provided, estimated values of the mean and standard deviation were derived using formulas devised by Wan *et al.*²² The units for cholesterol, triglycerides and glucose were millimoles per litre (mmol/l). The primary study outcome was the proportion of patients with overweight or obesity who experienced $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ total weight loss at the end of each trial. The three weight loss goal targets were chosen as, (1) it was the most commonly studied end points of weight loss RCTs, and (2) it has been proven to be realistic initial weight loss goals that are associated with health benefits of participants with overweight or obesity.^{23,24} Secondary outcomes included the change in BMI, body weight, waist circumference, lipid profile (including total cholesterol [TC], high-density lipoproteins [HDL], low-density lipoproteins [LDL] and triglycerides [TG]), glucose profile (HbA1c and FBG) and blood pressure (systolic and diastolic). Additionally, we examined the possible AEs that people experienced through the course of the trial.

Statistical analysis

All analyses were performed in RStudio (version 4.0.3). A generalized linear mixed model (GLMM) with Clopper-Pearson intervals to stabilise the variance was used for the analysis of pooled proportions and mean differences of the primary and secondary study outcomes of participants in the trials.^{25,26} Statistical heterogeneity was measured using I², tau, Cochran Q test. An I² value of 25%, 50%, and 75% equated to small moderate and large amounts of heterogeneity respectively,²⁷ while a Cochran Q test value of ≤ 0.10 was deemed statistically significant. Hartung-Knapp adjustments were employed to adjust for confidence intervals by controlling for heterogeneity arising from between-study estimations.²⁸ The random effects model was used regardless of heterogeneity scores.²⁹ Analyses were only conducted when sufficient data could be extracted for the outcome of interest and publication bias was not

conducted due to lack of a suitable assessment tool for single-arm meta-analyses.³⁰ Where possible, a sensitivity analysis was conducted for articles that only included patients with obesity, and for articles with low-moderate risk-of-bias. Additional analyses were performed on both primary and secondary outcomes according to the duration of intervention and follow up (<6 months, 6-12 months, 12-24 months, >24 months), diabetes status of included patients (studies only with patients who either had or did not have diabetes), single-centre versus multicentre studies, differing geographical regions (i.e. North America, Europe, Asia, and multinational), route of administration, and government/institutional funded trials versus pharmaceutical company funded trials. Associated risk factors (age, BMI, weight, waist circumference, baseline HbA1c and FBG, gender, race, history of dyslipidaemia or hypertension) for primary outcomes were analysed using a mixed-model meta-regression to account for study level predictors with the Hartung-Knapp estimator to stabilize the variance.³¹ In brief, a negative coefficient describes the inverse relationship between the outcome variable and the unit increase of the independent variable. A p-value of <0.05 was considered as statistically significant.

Quality and risk-of-bias assessment

Four authors (YHC, CHN, NWSC, and GK) independently assessed the risk-of-bias of the included trials using the Cochrane Risk-of-Bias 2 tool for randomized trials (RoB2) in pairs.³² All disagreements were resolved through consensus with discussion with a third independent author (MM). The RoB2 tool evaluates bias of included trials across five dimensions, namely the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The final assessment of the included trials was presented using the Robvis visualisation tool.

Role of the funding source

This research did not receive additional support from organizations beyond the authors' academic institutions.

Results

A total of 6,249 publications were identified in the initial search strategy, among which 3,799 were excluded as duplicates. Another 2,235 papers were then excluded after the initial sieve, with a full-text review being conducted for 215 papers. The overall Cohen's Kappa statistic was 0.80, and the most common reasons for disputes that required an independent author for consensus was for the confirmation on whether background medications in both arms could affect weight loss or gain ($n = 15$), and whether the participants met the overweight or obesity criteria ($n = 3$). Finally, 65

articles involving 20,555 patients and 70 trials were included in this meta-analysis (Figure 1). Of the trials included, 30 were international, 26 were conducted in the USA, four in Germany, three in Denmark, two in Sweden, one each in Australia, China, France, Japan, and the Netherlands. Most of the studies were multicentre trials ($n = 57$), and 41 trials examined patients without diabetes mellitus. A total of 59 trials elaborated on the diet and exercise regime provided to their participants. In most studies, a general advice of 500 kcal deficit a day and increase in moderate exercise (brisk walking or cycling) of up to 150mins/day was given, and only 2 trials had some form of enforcement of these recommendations (reporting to an exercise venue or daily reporting of diet and exercise). Most participants were female (66.1%), and 62.8% and 65.7% of patients had a history of hypertension and hyperlipidaemia, respectively.

At baseline, the mean age, BMI, weight, and waist circumference of included patients were 49.1 (CI:47.5 to 50.6) years old, 35.6 (CI:34.9 to 36.2) kg/m², 100.0 (CI:98.1 to 101.9) kg, and 110.6 (CI:108.3 to 112.8) cm. The baseline mean lipid profiles for TC, LDL, HDL, and TG were 4.8 (CI:4.7 to 5.0) mmol/L, 2.9 (CI:2.8 to 3.0) mmol/L, 1.3 (CI:1.2 to 1.4) mmol/L, and 1.6 (CI:1.5 to 1.7) mmol/L, respectively. Baseline mean HbA1c was 6.8% (CI:6.3% to 7.2%), and serum blood glucose was 6.9 (CI:6.3 to 7.5) mmol/L. A summary of the included publications and baseline characteristics of participants can be found in Supplementary Material 2, and a summary of the dietary and exercise recommendations can be found in Supplementary Material 3. Most of the included studies were assessed to have low to moderate risk of bias, and the detailed RoB2 assessment can be seen in Supplementary Material 4.

Primary outcomes

A total of 18,886 and 18,495 participants in placebo groups were examined for $\geq 5\%$ and $\geq 10\%$ weight loss, respectively. Among them, 20.4% (CI:16.1% to 25.0%, $I^2 = 94.0\%$) had the primary outcome of $\geq 5\%$ weight loss. A subgroup analysis by the duration of studies found a stepwise increase in proportion of placebo participants experiencing $\geq 5\%$ weight loss with increasing duration of study (Figure 2). Trials conducted in populations without diabetes had a significantly higher proportion of $\geq 5\%$ weight loss compared to those with diabetes (23.7%, CI:17.8% to 30.1%, $I^2 = 93.6\%$ vs 14.6%, CI:9.3% to 20.9%, $I^2 = 93.0\%$, $p = 0.036$). Next, 8.3% (CI:6.1% to 10.9%, $I^2 = 92.0\%$) of the 18,495 placebo participants had $\geq 10\%$ weight loss during their trial. Similarly, a subgroup analysis by the duration of studies found a stepwise increase in proportion of patients with $\geq 10\%$ weight loss with an increasing duration of study, albeit without significant differences (Figure 3). There was also a larger proportion of placebo

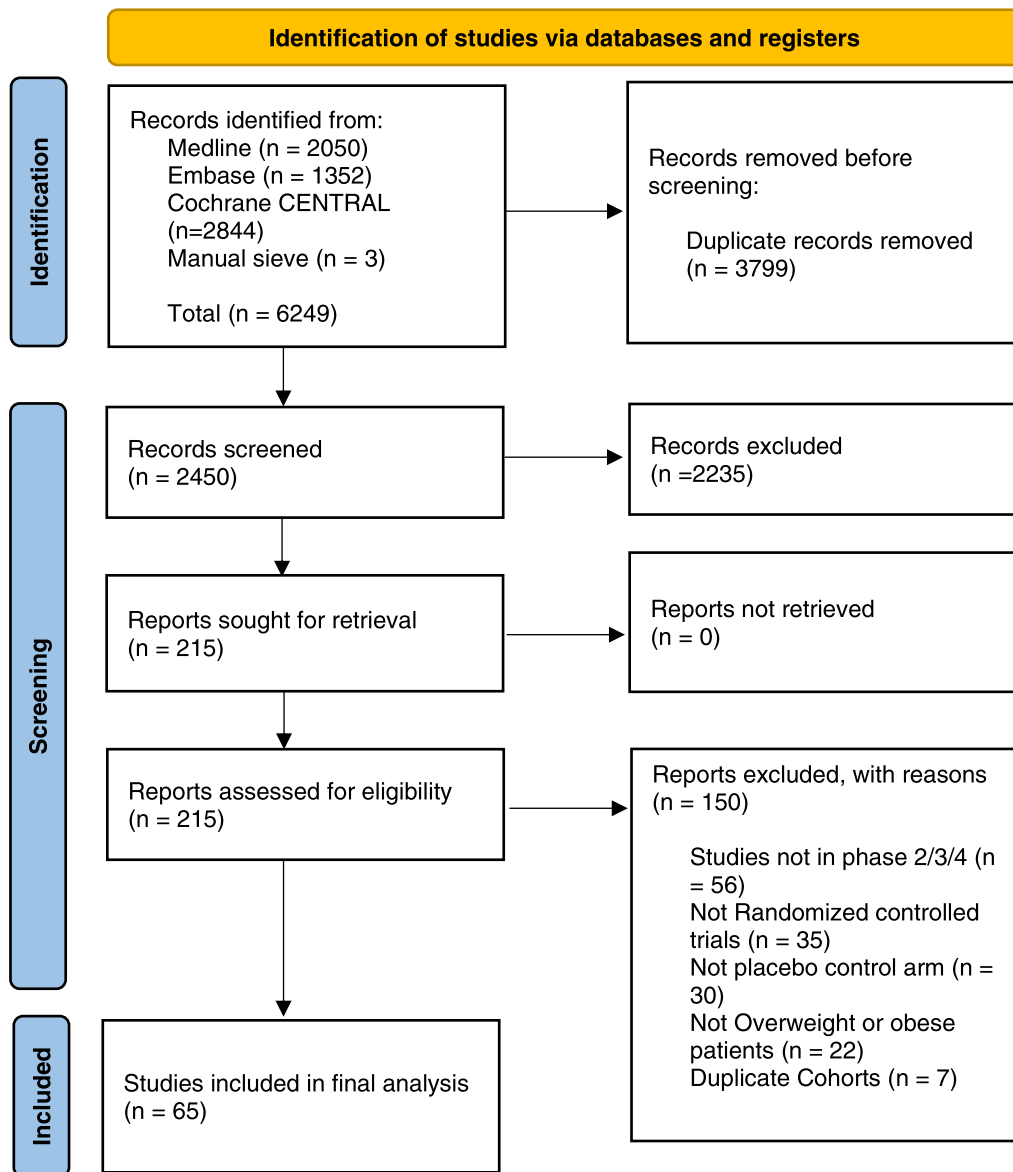


Figure 1. PRISMA diagram.

groups experiencing $\geq 10\%$ weight loss among those without diabetes compared to those with diabetes (11.4%, CI:8.2% to 15.1%, $I^2 = 89.2\%$ vs 3.9% CI:2.1% to 6.2%, $I^2 = 82.7\%$, $p < 0.0001$). Subgroup analysis of study-level factors for the analysis of $\geq 5\%$ and $\geq 10\%$ weight loss, including but not limiting to the location of study, funding, route of administration, single vs multi-centre can be found in [Table 1](#). Meta-regression for factors including weight, BMI, age, and gender, was conducted and can be found in Supplementary Material 5. For both $\geq 5\%$ and $\geq 10\%$ total weight loss, increased age ($\beta = -0.06$; CI: -0.12 to -0.00 ; $p = 0.020$ and β

$= -0.086$; CI: -0.13 to -0.01 ; $p = 0.015$, respectively), and presence of diabetes ($\beta = -0.85$; CI: -1.54 to -0.16 ; $p = 0.016$ and $\beta = -1.14$; CI: -1.81 to -0.48 ; $p = 0.00073$, respectively) were associated with reduced proportions of patients experiencing those weight loss thresholds. There were 3,343 patients with reported data on $\geq 15\%$ weight loss, among whom 6.2% (CI: 3.8% to 9.7%, $I^2 = 86.6\%$) experienced that outcome. There were insufficient studies for a comprehensive subgroup analysis, but the effect was similarly larger in people without diabetes (Supplementary Material 6).

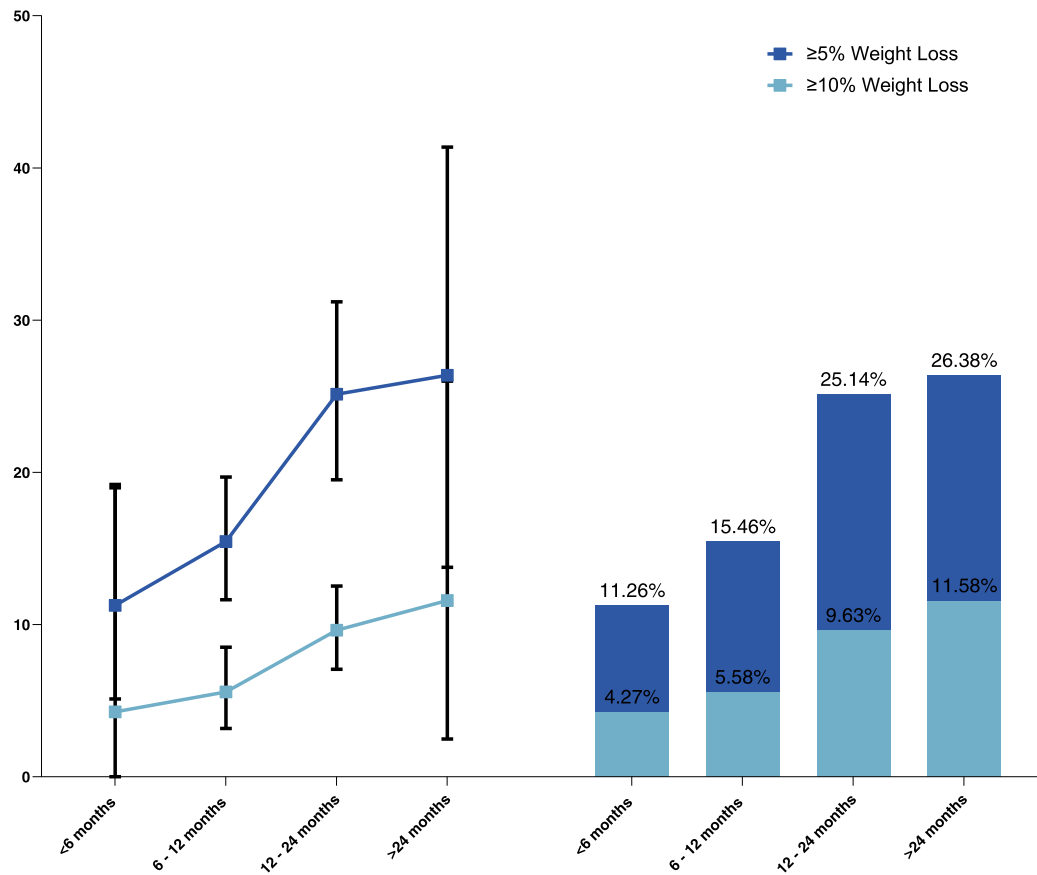


Figure 2. Proportion of patients with $\geq 5\%$ and $\geq 10\%$ weight loss by duration of trial.

Secondary outcomes

Full results of subgroup analyses conducted for waist circumference, BMI, weight reduction, LDL, TG, HDL, TC, blood pressure, and glycaemic indices can be found in Supplementary Material 7 and Table 2. Mean change in BMI was reported among 6,671 placebo participants, with an average -1.0 (CI: -1.5 to -0.4 , $I^2 = 96.2\%$) kg/m². Average weight reduction in a pooled analysis of 19,048 patients was -1.4 (CI: -2.0 to -0.9 , $I^2 = 94.6\%$) kg. The average reduction in waist circumference was -2.7 (CI: -3.4 to -2.1 , $I^2 = 95.0\%$) cm in a pooled analysis of 17,176 patients. There were small changes with placebo in LDL, TG, HDL, TC. The magnitude of change in glycaemic indices including HbA1c and FBG was significantly larger in placebo groups with diabetes compared to those without diabetes (Supplementary Material 8). Placebo patients experienced an average reduction in systolic and diastolic blood pressure of -1.7 (CI: -2.8 to -0.6 , $I^2 = 91.1\%$) mmHg and -1.0 (CI: -1.6 to -0.5 , $I^2 = 88.7\%$) mmHg in a pooled analysis of 11,477 individuals. Meta-regression analyses were conducted and can be found in Supplementary Material 9. For change in body weight, a higher baseline BMI ($\beta = -0.22$; CI: -0.43 to -0.01 ; $p = 0.039$), weight ($\beta =$

-0.08 ; CI: -0.15 to -0.02 ; $p = 0.017$), and waist circumference ($\beta = -0.14$; CI: -0.25 to -0.03 ; $p = 0.011$) was associated with a greater decrease in body weight. Lastly, for change in waist circumference, a higher baseline BMI ($\beta = -0.43$; CI: -0.63 to -0.24 ; $p < 0.0001$), weight ($\beta = -0.13$; CI: -0.19 to -0.07 ; $p < 0.0001$), waist circumference ($\beta = -0.18$; CI: -0.28 to -0.09 ; $p < 0.0001$), and the female gender ($\beta = -4.59$; CI: -8.09 to -1.10 ; $p = 0.011$) were associated with a greater decrease in waist circumference. Additionally, the presence of hyperlipidaemia ($\beta = 3.03$; CI: 0.53 to 5.53 ; $p = 0.021$) and hypertension ($\beta = 2.89$; CI: 0.28 to 5.50 ; $p = 0.032$) were associated with smaller decrease in waist circumference.

Adverse events

A detailed summary of overall AEs can be found in Supplementary Material 10 and Table 3. The overall rate of reported AEs among 9,408 placebo participants was 73.7% (CI: 68.0% to 79.0%, $I^2 = 95.4\%$). The reported rates of serious AEs and discontinuations were 3.4% (CI: 2.4% to 4.5%, $I^2 = 91.8\%$) and 5.2% (CI: 4.0% to 6.5%, $I^2 = 84.2\%$) in a pooled analysis of 12,230 and

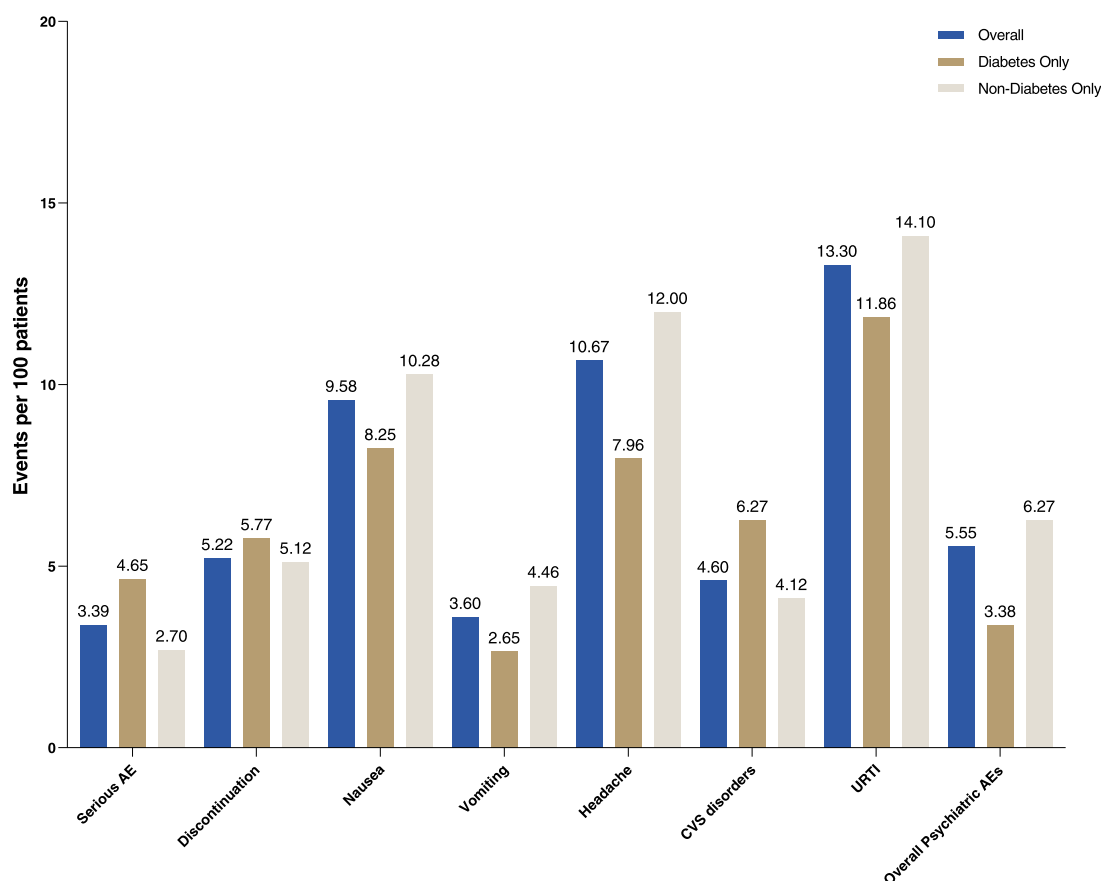


Figure 3. Adverse events reported by participants in placebo-arms in the weight-loss placebo-controlled trials.

18,648 patients, respectively. Meta-regression analyses were conducted and can be found in Supplementary Material 11. The detailed summary of systemic AEs can be found in Supplementary Material 12 and Table 3. Among reported systemic AEs, the most common was upper respiratory tract infection, which occurred in 13.3% (CI:11.1% to 15.6%, $I^2 = 87.5\%$) of placebo participants. Neoplasm occurred in 1.4% (CI:0.5% to 2.6%, $I^2 = 84.5\%$) of this group. Interestingly, 10.3% (CI:6.3% to 15.0%, $I^2 = 86.4\%$) reported symptoms of injection-site reaction, despite receiving placebo. Regarding psychiatric complications, the pooled rates of anxiety and depression were 2.7% (CI:1.8% to 3.7%, $I^2 = 71.5\%$) and 2.5% (CI:1.7% to 3.3%, $I^2 = 75.4\%$) among 5,244 and 8,758 participants, respectively, and 1.3% (CI:0.5% to 2.6%, $I^2 = 75.4\%$) had suicidal events.

Sensitivity analysis

Individuals with obesity only. A sensitivity analysis was conducted for studies including patients with obesity only (Supplementary Material 13). A total of 2,940 and 2,772 such placebo participants were examined for $\geq 5\%$ and $\geq 10\%$ weight loss, respectively. A total of

22.3% (CI:13.5% to 32.4%, $I^2 = 93.1\%$) and 8.6% (CI:4.5% to 13.9%, $I^2 = 85.8\%$) had $\geq 5\%$ and $\geq 10\%$ reduction in weight, respectively. In the secondary endpoints, the mean change in weight was -1.15 (CI:-2.4 to 0.0, $I^2 = 92.3\%$) kg, and average reduction in waist circumference was -3.0 (CI:-4.6 to -1.4, $I^2 = 90.3\%$) cm. There was a small magnitude of change in lipids, glycaemic indices, and blood pressure with placebo. In a pooled analysis of adverse events, the overall pooled rate of reported AEs was 80.3% (CI:74.4% to 85.6%, $I^2 = 83.5\%$) among 2,428 people. The pooled rates of reported serious AEs and discontinuations were 4.0% (CI:2.5% to 5.8%, $I^2 = 76.4\%$) and 5.5% (CI:4.5% to 6.5%, $I^2 = 16.5\%$) in analyses of 3,116 and 2,456 participants, respectively.

Excluding studies with high risk of bias

A sensitivity analysis was conducted removing studies with high risk-of-bias (Supplementary Material 14). A total of 18,783 and 18,392 such placebo participants were examined for $\geq 5\%$ and $\geq 10\%$ weight loss, respectively. A total of 20.5% (CI:16.1% to 25.2%, $I^2 = 94.2\%$) and 8.4% (CI:6.0% to 11.0%, $I^2 = 85.8\%$) had $\geq 5\%$ and

	Studies, n	Sample Size, n	Pooled effect size (95% CI)	I ²	Subgroup differences	Studies, n	Sample Size, n	Pooled effect size (95% CI)	I ²	Subgroup differences
			≥5% Weight Loss					≥10% Weight Loss		
Overall	45	18886	20.38 (16.09 to 25.00)	94.0%		39	18495	8.32 (6.05 to 10.91)	92.0%	
DM status					0.036					<0.0001
DM	12	8050	14.63 (9.33 to 20.85)	93.6%		11	7925	3.90 (2.12 to 6.18)	82.7%	
No DM	29	9592	23.66 (17.77 to 30.08)	93.0%		25	9393	11.41 (8.15 to 15.12)	89.2%	
Setting					0.258					0.049
Multicentre	40	18690	19.05 (15.60 to 22.76)	93.5%		35	18359	7.39 (5.57 to 9.44)	91.6%	
Single Centre	5	197	35.61 (8.80 to 68.27)	96.3%		4	137	23.75 (6.63 to 46.55)	88.8%	
Funding					0.204					0.470
Pharmaceutical	38	17366	21.71 (17.15 to 26.62)	93.2%		33	17039	8.85 (6.54 to 11.46)	91.9%	
Company-Funded										
Government-Funded	7	1520	13.52 (4.74 to 25.54)	96.7%		6	1456	5.62 (0.45 to 14.88)	93.9%	
Phase					0.002					0.001
2	16	1152	12.73 (8.33 to 17.83)	81.2%		10	743	3.20 (1.1 to 6.1)	72.0%	
3	24	11521	21.79 (17.17 to 26.79)	94.8%		24	11539	9.04 (6.77 to 11.59)	90.8%	
4	4	6113	50.58 (24.87 to 76.13)	97.7%		4	6113	24.88 (9.24 to 44.73)	96.5%	
Route					0.034					0.079
Oral	26	15102	16.91 (13.08 to 21.12)	93.0%		21	14737	6.91 (4.87 to 9.27)	91.6%	
Subcutaneous	17	3660	27.81 (18.47 to 38.2)	93.3%		16	3634	11.69 (6.67 to 17.8)	90.3%	
Duration of study					0.015					0.324
<6 months	11	738	11.26 (5.12 to 19.20)	87.8%		4	269	4.27 (0 to 18.99)	92.1%	
6-12 months	5	328	15.46 (11.63 to 19.69)	15.0%		5	328	5.58 (3.18 to 8.52)	1.3%	
12-24 months	27	11577	25.14 (19.19 to 31.61)	95.6%		27	11555	9.63 (6.84 to 12.54)	93.3%	
>24 months	2	6243	26.38 (13.76 to 41.37)	15.0%		2	6243	11.58 (2.48 to 26.00)	1.3%	
Region					0.016					<0.0001
North America	17	5349	21.00 (15.14 to 27.52)	92.7%		16	5323	10.07 (6.58 to 14.17)	89.2%	
Europe	5	223	31.97 (6.62 to 64.73)	96.6%		4	163	15.90 (2.25 to 37.15)	91.2%	
Multinational	22	13286	19.16 (15.06 to 23.64)	95.1%		19	13009	6.19 (4.09 to 8.67)	93.0%	

Table 1: Summary of findings of patients that achieved ≥5% and ≥10% weight loss.

Legend: N, Number of Studies; CI, Confidence Interval; DM, Diabetes Mellitus.

*bolded *p*-value < 0.05 denotes statistical significance.

	Studies, n	Sample Size, n	Pooled effect size (95% CI)	I ²
Body weight indicators				
Change in BMI	20	6671	MD -0.96 (-1.51 to -0.41) kg/m ²	96.2%
Change in Weight	60	19048	MD -1.42 (-1.99 to -0.85) kg	94.6%
Change in Waist Circumference	46	17176	MD -2.71 (-3.36 to -2.07) cm	95.0%
Lipid Profile				
Change in Total Cholesterol	46	17176	MD -2.71 (-3.36 to -2.07) cm	95.0%
Change in LDL	41	10677	MD 0.08 (-0.00 to 0.17) mmol/L	98.4%
Change in HDL	41	10686	MD 0.03 (0.01 to 0.05) mmol/L	94.0%
Change in TG	39	10557	MD -0.01 (-0.09 to 0.07) mmol/L	98.3%
Glycaemic indices				
Change in HbA1c	35	15017	MD -0.13 (-0.20 to -0.06)%	95.6%
Change in FBG	40	15688	MD -0.10 (-0.20 to 0.00) mmol/L	87.7%
Blood Pressure				
Change in SBP	43	11718	MD -1.71 (-2.82 to -0.59) mmHg	91.1%
Change in DBP	42	11477	MD -1.03 (-1.61 to -0.46) mmHg	88.7%

Table 2: Summary of secondary outcomes findings.

Legend: n, Number of Studies; CI, Confidence Interval; DBP, Diastolic Blood Pressure; FBG, Fasting Blood Glucose; HDL, High-Density Lipoprotein; HbA1c, Glycated hemoglobin; LDL, Low-Density Lipoprotein; SBP, Systolic Blood Pressure.

≥10% reduction in weight, respectively. In the secondary endpoints, the mean change in weight was -1.3 (CI: -1.8 to -0.8, I² = 94.8%) kg, and average reduction in waist circumference was -2.6 (CI: -3.3 to -2.0, I² = 95.3%) cm. The summary of the change in lipids, glycaemic indices, and blood pressure with placebo, and the adverse events can be found in Supplementary Material 14.

Discussion

A randomized, double-blinded trial with reference to placebo remains the fundamental building block in the assessment for clinical investigations. Despite an estimated \$1.28 billion invested for pharmaceutical studies of obesity in 2022 in the US,³³ a comprehensive analysis of placebo effects among such clinical trials has yet to be systematically examined. These effects should not be underestimated, as approximately one fifth and one tenth of participants receiving placebo had ≥5% and ≥10% weight loss, respectively, with associated reductions in weight, BMI, and waist circumferences, despite receiving no active medication. In a pooled analysis of ≥5% weight loss, 11.3%, 15.5%, 25.1%, and 26.4% reached that primary endpoint at <6 months, 6-12 months, 12-24 months, and >24 months of follow-up, respectively. Similar effects were seen in a pooled analysis of ≥10% weight loss. These findings are of particular interest because volitional weight loss through lifestyle interventions is typically unsustainable with increasing duration of follow-up.^{34,35}

The observed findings in primary weight-loss outcomes, and improvements in the secondary ancillary weight-loss and metabolic markers show that placebo effects can lead to improvements in the overall

metabolic milieu of participants with overweight or obesity in these placebo-controlled trials. These findings could be attributed to the lifestyle programs advocated by the trials or the Hawthorne and placebo effects that result from desirable changes in behaviour, with increased attention by physicians.³⁶ Patients enrolled in clinical trials have been shown to be more regularly followed-up by physicians, which may potentially lead to implicit bias due to the increased quality time spent relative to conventional care.^{37,38} Famously, McCarney et al demonstrated that patients who received more intensive and regular follow-up experienced greater improvement in dementia compared to individuals with minimal follow-up, despite receiving the same pharmaceutical treatment.⁹ In the context of obesity studies, where calorie restriction and physical activity are often emphasised as cornerstones of treatment,⁴ the unmeasured Hawthorne effect can significantly influence outcomes in both treated and untreated groups. Participants in the included long-term trials (>12 months) generally had mandated follow-up of varying durations from once a week to once a month, more frequent than the recommendations of follow-ups by the American Diabetes Association of at least once a month to once every three months.³⁹ These could explain why patients had sustainable volitional weight loss despite the longer duration of follow-up. Importantly, double-blinded trials also potentially expose patients to the placebo effect, which describes a psychological phenomenon attributed to learning mechanisms in the mind, where pharmacologically inert treatment exposure results in clinical improvement.⁴⁰

However, the use of placebo is not without its own set of problems. Undesirable nocebo events can arise among study participants not receiving active

	Studies, n	Sample Size, n	Pooled effect size (95% CI)	I ²
General Adverse Events				
Overall Adverse Events	46	9408	73.66 (67.99 to 78.96)	95.4%
Serious Adverse Events	51	18648	3.39 (2.45 to 4.46)	91.8%
Discontinuation	45	12230	5.22 (4.02 to 6.54)	84.2%
Other Generalised Adverse Events				
Fatigue	24	9473	4.20 (3.54 to 4.91)	54.6%
Dizziness	30	10374	3.64 (2.64 to 4.78)	70.2%
Systemic Adverse Events				
Allergy Adverse Events				
Injection site reactions	17	2370	10.32 (6.35 to 15.04)	86.4%
Allergies	12	3743	3.83 (1.79 to 6.49)	94.7%
Gastrointestinal Adverse Events				
Abdominal Pain	22	4674	5.60 (3.49 to 6.86)	69.4%
Nausea	55	13852	9.58 (7.58 to 11.77)	89.7%
Vomiting	32	7666	3.60 (2.70 to 4.62)	66.6%
Constipation	37	10723	7.79 (6.14 to 9.59)	83.9%
Diarrhea	51	13402	8.81 (7.15 to 10.61)	85.4%
Dyspepsia	16	3020	2.73 (2.11 to 3.41)	2.5%
Dry Mouth	18	6958	1.95 (1.61 to 2.32)	36.1%
Hepatobiliary Adverse Events				
Gallbladder Disorder	10	3255	0.76 (0.43 to 1.15)	0.9%
Hepatic Disorder	8	3268	2.61 (1.25 to 4.39)	89.3%
Cholelithiasis	8	2882	0.32 (0.10 to 0.63)	0.0%
Cardiovascular and Kidney Adverse Events				
Cardiovascular disorders	15	5339	4.60 (2.08 to 7.93)	96.0%
Acute Kidney Injury	4	1346	0.23 (0.01 to 0.64)	0.0%
Infections				
Upper Respiratory Tract Infection	34	12064	13.3 (11.15 to 15.61)	87.5%
Nasopharyngitis	36	12533	11.39 (9.29 to 13.67)	89.2%
Sinusitis	20	9669	6.74 (5.85 to 7.69)	59.2%
Bronchitis	11	5963	3.21 (1.98 to 4.73)	90.9%
Urinary Tract Infections	18	6218	5.11 (3.21 to 7.40)	81.1%
Psychiatric Adverse Events				
Overall Psychiatric Adverse Events	17	5677	5.55 (3.52 to 7.99)	93.3%
Insomnia	20	6894	4.99 (4.19 to 5.85)	45.7%
Sleep Disorder	18	3758	4.18 (2.89 to 5.67)	75.3%
Anxiety	15	5244	2.69 (1.85 to 3.66)	71.5%
Depression	19	8758	2.46 (1.70 to 3.34)	75.4%
Suicidal	4	3196	1.35 (0.47 to 2.62)	75.4%
Pain/Sensory Adverse Events				
Headache	45	12684	10.67 (8.85 to 12.62)	80.0%
Back Pain	25	9691	5.39 (4.17 to 6.75)	74.9%
Arthralgia	16	5432	4.66 (2.81 to 6.92)	82.1%
Paraesthesia	6	895	1.76 (1.15 to 2.46)	24.6%
Cancer				
Neoplasm	11	5061	1.42 (0.55 to 2.62)	84.5%

Table 3: Summary of overall adverse events.

Legend: n, Number of Studies; CI, Confidence Interval; *bolded p-value denotes statistical significance.

medication, due to those individuals' perceived expectations of adverse effects. Approximately three-quarters of patients experienced any AEs and 3.4% experienced serious adverse effects, with another 5% of patients discontinuing placebo medications due to adverse events.

The SAMSON trial famously showed that the onset, severity, and duration of adverse events associated with statin use could not be differentiated from those experienced by patients taking placebo.¹¹ However, these symptoms could also be by-products from the natural

course of the disease. Additionally, though these placebo arms were assumed to be inert, they potentially could be irritative and lead to adverse events experienced by participants of these trials. Nevertheless, although it might prove difficult to ascertain and attribute subjective events to the course of disease versus nocebo effects, pooled analysis of AEs can provide detailed references for future clinical trials. Current evidence about the natural history of obesity has been derived from longitudinal population cohorts that have dissimilar baseline characteristics, and hence pooled analyses may offer insights to more accurately gauge expected rates of complications from obesity. An additional observation of interest made in the current analysis relates to the lower-than-expected incidence of psychological complications. Current estimates suggest that the global prevalence of depression and anxiety are 12.9% and 7.3%, respectively.^{41,42} However, only 2.5% and 2.7% developed depression and anxiety, respectively, in our meta-analysis. These lower rates of depression and anxiety might relate to the following reasons. First, there could be a lack of probing during clinical consultations, potentially exposing an underestimation of reported psychological complications. Second, it could be due to the potential placebo effect of undergoing these trials, where patients undergoing these trials experience weight loss, which alleviates their source of stress and poor mental health, thus experiencing improvement in their mental health.⁴³ Last, clinical trials usually exclude patients with severe psychiatric disorders for safety concerns,⁴⁴ and studies have also shown that patients with depression and other psychiatric disorders are less likely to join clinical trials.⁴⁵ Importantly, there was a lack of information regarding the participants mental health in included trials, and future trials should take into consideration these complications as they are important for adherence and compliance to weight loss therapies.

This is the first and most comprehensive study examining the impact of placebo and nocebo effects in obesity RCTs on weight loss, metabolic markers (weight, BMI, waist circumference, glucose and lipid markers), and adverse events among participants. However, we note some limitations to our study. First, we were unable to quantify or account for potential effects that exercise and diet interventions could have exerted on participants in the placebo arms of the included trials due to lack of reporting of these regimes. Similar improvements in weight, glycemic indices and lipid markers have been observed in open-label trials with moderate-intensity lifestyle programs, and the improvements we reported could be also due to these lifestyle programs. However, many trials did not track or report the exercise or diet regimes suggested to participants of the trials. Thus, we were unable to analyse whether patients who adhered to the behavioural change requirements lost more weight compared to those who did not.

This limits the generalisability of our findings. Second, we were unable to analyse possible dose-dependent placebo effects because there were no available data on the dose-related outcomes. Third, adverse events could be confounded by the concomitant medications or co-morbidities of the study population, and such studies are often unable to differentiate the impact of the placebo compared with these confounders. Fourth, there is significant heterogeneity among trials and patients, although we attempted to control for these differences through subgroup and meta-regression analyses. This limits the generalisability of our findings, however, we do note that the I^2 can be influenced by sample sizes and thus can be misleading,^{46,47} this can be seen where many single-arm meta-analyses of large sample sizes depicting substantial heterogeneity of more than 90%.^{48,49} Last, most studies came from North America and Europe, which may have affected the generalisability of our findings. However, we suspect that these effects may be substantially different due to genetic differences, varying socio-demographic index scores, as well as availability of trials by region. Future studies can be done to quantify these differences to help improve the generalisability of our findings.

Our meta-analyses showed that there is substantial placebo effect in weight-loss RCTs. Up to 26% of participants in placebo groups experience at least 5% weight loss at >24 months of follow-up, with modest improvements in all lipid levels, glycemic indices, and blood pressure readings. We also showed and quantified the presence of significant nocebo effects, with up to 74% of study subjects experiencing adverse events while taking pharmacologically inert pills. These findings may inform the design of future RCTs examining weight-loss medications.

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All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

All articles in this manuscript are available from Medline and Embase.

Declaration of interests

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Vincent Wong: V.W. has served as an advisory board member or consultant for 3 V-BIO, AbbVie, Allergan, Boehringer Ingelheim, Echosens, Gilead Sciences, Inventiva, Merck, Novartis, Novo Nordisk, Pfizer, ProSciento, Sagimet Biosciences, TARGET PharmaSolutions, and Terns and is on the speaker's bureau for Abbott, AbbVie, Echosens, Gilead Sciences, and Novo Nordisk; he has received a grant from Gilead Sciences for fatty liver research and is a cofounder of Illuminatio Medical Technology Limited.

Mazen Noureddin: M.N. has been on the advisory board for 89BIO, Gilead, Intercept, Pfizer, Novo Nordisk, Blade, EchoSens, Fractyl, Terns, Siemens and Roche diagnostic; he has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Pfizer, Shire, Viking and Zydus; he is a minor shareholder or has stocks in Anaetos, Rivus Pharma and Viking.

Arun Sanyal: A.J.S. is President of Sanyal Biotechnology and has stock options in Genfit, Akarna, Tiziana, Indalo, Durect and Galmed. He has served as a consultant to Astra Zeneca, Nitto Denko, Enyo, Ardelyx, Conatus, Nimbus, Amarin, Salix, Tobira, Takeda, Janssen,

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Supplementary materials

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