Supplementary Online Content

Khera R, Murad MH, Chandar AK, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA*. doi:10.1001/jama.2016.7602

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Additional Methods

Study Selection

Studies were selected for review through a two-step process. First, through a systematic literature search of multiple electronic databases (OVID Medline, Embase, Cochrane databases, Web of Science and Scopus), we identified 3616 unique articles which were exported an EndNote file. Then, two study investigators (SS, PSD) independently reviewed the title and abstract of these studies, to exclude 3454 studies that did not address the research question of interest, based on pre-specified inclusion and exclusion criteria. In the second step, two authors (SS, PSD) independently reviewed the full texts of the remaining 162 articles to determine whether they met inclusion criteria and contained relevant information. Conflicts in study selection at this stage were resolved by consensus, referring back to the original article in consultation with a third reviewer (RK). In the end, we selected 28 studies in our meta-analysis. A detailed flow sheet summarizing study identification and selection is shown in **eFigure 1**.

Data Abstraction

Data on the following characteristics were abstracted by two sets of authors independently (RK, AKC, PSD, SS): (a) study characteristics – primary author, time period of study/year of publication, geographic location and centers where study was conducted, duration of follow-up; (b) patient characteristics – age, sex, race, weight and BMI at baseline; (c) obesity-associated comorbidities – proportion of patients with DM, impaired glucose tolerance, hypertension, hyperlipidemia, cardiovascular disease, obstructive sleep apnea; (d) treatment characteristics – dose, duration and schedule of primary intervention; (e) co-interventions – dietary therapy, lifestyle interventions and behavioral modifications recommended and strategies used for implementing them; (f) outcome assessment – total number of patients in intervention and comparator group, and proportion achieving the outcome of interest (as dichotomous variable), mean weight loss (in kgs), with respective standard deviation from baseline; and (f) adverse effects – proportion of patients with serious adverse events, and discontinuation due to adverse

events. Discrepancies were resolved by consensus, referring back to the original article, in consultation with a third reviewer.

Quality Assessment

In the Cochrane Risk of Bias tool, studies were deemed to be at high, low or unclear risk of bias based on adequacy of sequence generation, allocation concealment, blinding, method of addressing incomplete data, selective reporting, and other biases.

Statistical Analysis – Network Meta-analysis

To incorporate indirect comparisons with direct comparisons, we conducted random-effects Bayesian network meta-analyses using Markov chain Monte Carlo methods in WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) using methods described by Lu and Ades,[1] and the statistical model suggested by Dias et al.[2]

As a reference for interested readers we summarize the statistical basis for the analysis for both categorical (all are dichotomous) and continuous outcomes, and also provide the actual study data and the corresponding WinBUGS codes, first for the categorical outcome (at least 5% weight loss), and then for the continuous outcome (weight loss in kg).

Categorical Outcome:

Our analysis uses a contrast-based approach, wherein study data abstracted for each arm (as treatment type, number of events and the sample size) are incorporated as log-odds ratio for each comparison in the included studies for our analysis. We used the statistical outline and WinBUGS code by Dias et al[2] as a primer for our analysis. The data is organized in the following format for each arm of study:

t[1,] r[1,] n[1,]

where,

't' is treatment arm, with each treatment-type assigned a number. The placebo arm is assigned the number 1.

'r' the number of events in the treatment or control arm

'n' is the total number of patients in the particular treatment or control arm

As previously suggested by Dias et al,[2] we assumed that the number of events in each study arm are defined by the binomial likelihood:

No. of events in study arm 'k' of the i^{th} study (r_{ik}) ~ Binomial (p_{ik},n_{ik})

where,

p_{ik} – probability of an event in k^{th} arm of i^{th} study

n^{ik} – number of patients in k^{th} arm of i^{th} study

i – whole number values corresponding to the study number

k – whole number values corresponding to number of arms for each study

Since, p_{ik} is the probability of interest; we used a logit link to estimate its value. This can be presented as a function of the odds of the event in the control arm of the i^{th} study, μ_i and the log-odds ratio of the odds of success in intervention (2) compared to to control arm (1) in trial 'i', denoted as $\delta_{i,12}$ using the following relation:

$$\text{logit}(p_{i2}) = \mu_i + \delta_{i,12} \qquad \text{(for a two comparison study)}$$

or, more generally as,

$$\text{logit}(p_{ik}) = \mu_i + \delta_{ik} I_{(k\neq 1)} \qquad \text{(for a k comparison study)}$$

where,

$I_{(c)}$ *= 1 if c is true, and 0 otherwise*

In our random effects model, the study specific log-odds ratios (δ_{ik}) are presumed to be drawn from a common distribution for each comparison, $\delta_{1k} \sim N(d_{1k}, \sigma^2)$, σ^2 representing between trial heterogeneity.

Further, to define the posterior probability distribution for our probabilities of interest, we modelled our Markov chain Monte Carlo model with 100,000 simulated draws after a burn in of 10,000 iterations. Multiple chains (i.e., multiple initial values) were evaluated for each analysis. To account for between-arm correlations for multi-arm trials, a correction was performed in estimating the random effect for each multi-arm trial study using a conditional univariate distribution, as described by Dias et al.[2] Model fit was evaluated using the total residual deviance, which indicated good fit if it approximated the number of data points.

To generate summary statistics in our analysis, the use of the logit link function allowed for assessment of pairwise log-odds ratios for all treatment comparisons on the linear logit scale, as the difference of probability of the event on the treatment-arm 'k'

and a control-arm, 'c', as described on the logit scale. Similarly, odds ratio were estimable as exponential of the corresponding log-odds ratios.

The use of Bayesian probability distributions allowed for direct estimation of OR with their 95% credible intervals (CrI).[2] The point estimates for the OR were derived from the median of the posterior distribution for their respective functions (as described above), and the corresponding 95% CrI were obtained using the 2.5th and 97.5th percentiles of the respective posterior distribution. We estimated the posterior distribution of all parameters using non-informative priors to limit inference of data derived from the trials at hand (i.e., made no assumptions about the efficacy of these drugs from data external to the trials included in this systematic review); several vague priors (uniform distributions, normal distributions, and gamma distributions with different means and variances) were tested in sensitivity analyses, to assure robustness of the analysis. We tested the adequacy of burn-in and convergence (reaching a stable equilibrium distribution) using visual inspection of parameter fluctuation depicted in trace plots, monitoring the Monte Carlo error, and by estimating the values of the Brooks-Gelman-Rubin statistic.[3]

The above commonly used model for network meta-analysis assumes "consistency" of treatment effects across trials, such that both direct and indirect treatment effects are assumed to be equivalent. This is an extension of the exchangeability assumption that states that the data for our network meta-analysis composed of '*i*' trials with '*k*' treatment effects are derived from '*i*' trials - all with *k*-arms - among which some of the arms are missing at random. This assumption of network consistency was evaluated by comparing the direct estimates to the indirect estimates for each comparison, using a node-splitting technique. In addition, as a sensitivity analysis, we adopted a frequentist approach using the contrast-based "inconsistency" model developed by White et al., using the network meta package in Stata to conduct the analyses.[4] This model made no assumptions about equivalence between direct and indirect estimates, and differentiated the two by including trial design as an additional covariate in the analysis (eTable 7). Next, we assessed the probability that each intervention was the most efficacious in achieving weight loss, the second best, the third best, and so on, comparing each drug with an arbitrary common control group,

and counting the proportion of iterations of the Markov chain in which each drug had the probability of being ranked highest, the second highest, and so on. The probability of each agent being ranked are presented as their surface under the cumulative ranking (SUCRA) score.[5] The SUCRA is presented as a value between 0 and 1, with 1 representing an imaginary agent that is the best without uncertainty.[5] In this study, for all weight loss outcomes a higher number is consistent with more frequent weight loss for categorical outcomes, and higher magnitude of weight loss for the continuous outcomes. For the adverse event outcome, the agent associated with the lowest rate of discontinuation due to adverse events received a higher score.

Finally, we generated estimates of absolute event rates (or absolute risk) by calculating the estimated risk difference (RD, also known as absolute risk reduction) by combining the odds ratio (OR) for each intervention against placebo and the median placebo response rate for the respective outcome across trial as the assumed control risk (ACR), by using the formula: Risk difference = 100 X (ACR-OR X ACR) / (1-ACR+OR X ACR).[6] The risk difference, which represents the difference between the event rates in the intervention and control group, was added back to the assumed control risk to generate an estimate of the absolute risk for each intervention. 95% confidence intervals for the estimates were generated using the 95% credible intervals of the odds ratios in the above calculations. Estimates of absolute risk were generated using the GRADEpro version 3.6.1 (McMaster University, 2014).

Bayesian network meta-analysis code (with data) for categorical outcome

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                  # LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0           # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
```

```
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LOR distributions
       delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
       md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
       taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
       w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
       sw[i,k] <- sum(w[i,1:k-1])/(k-1)
     }
  }
totresdev <- sum(resdev[])          # Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }

# Extra code for all odds ratios and log odds ratios, ranking, and absolute effects, and relative
effects
# on alternative scales: Numbers Needed to Treat, Risk Difference, Relative Risks

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1))                    {
for (k in (c+1):nt)          {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
                                                                    }
                                                          }

# ranking on relative scale
for (k in 1:nt) {
rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
# rk[k] <- rank(d[],k) # assumes events are “bad”
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
}
```

Data
# ns= number of studies; nt=number of treatments
list(ns=27, nt=6, meanA=0, precA=0.001)

t[,1]	r[,1]	n[,1]	t[,2]	r[,2]	n[,2]	t[,3]	r[,3]	n[,3]	na[]	# StudyName
2 29	67	1	19	67	6	53	72	3	#	Astrup 2012
2 51	111	1	12	109	NA	NA	NA	2	#	Berne 2005
2 1194	1640	1	738	1637	NA	NA	NA	2	#	Torgerson 2004
2 171	346	1	102	350	NA	NA	NA	2	#	Krempf 2003
2 97	250	1	40	254	NA	NA	NA	2	#	Miles 2002
2 97	189	1	57	180	NA	NA	NA	2	#	Hanefeld 2002
2 147	265	1	65	266	NA	NA	NA	2	#	Broom 2002
2 122	267	1	60	265	NA	NA	NA	2	#	Bakris 2002
2 87	266	1	35	269	NA	NA	NA	2	#	Kelley 2002
2 151	242	1	102	237	NA	NA	NA	2	#	Rossner 2000
2 103	190	1	76	186	NA	NA	NA	2	#	Lindgrade 2000
2 106	210	1	65	212	NA	NA	NA	2	#	Hauptman 2000
2 38	110	1	23	108	NA	NA	NA	2	#	Finer 2000
2 432	657	1	97	223	NA	NA	NA	2	#	Davidson 1999
2 235	343	1	167	340	NA	NA	NA	2	#	Sjostrom 1998
2 79	162	1	36	159	NA	NA	NA	2	#	Hollander 1998
3 94	251	1	40	248	NA	NA	NA	2	#	O'Neil 2012
3 737	1561	1	385	1541	NA	NA	NA	2	#	Fidler 2011
3 731	1538	1	304	1499	NA	NA	NA	2	#	Smith 2010
4 417	826	1	78	456	NA	NA	NA	2	#	Apovian 2013
4 118	265	1	30	159	NA	NA	NA	2	#	Hollander 2013
4 320	482	1	82	193	NA	NA	NA	2	#	Wadden 2011
4 226	471	1	84	511	NA	NA	NA	2	#	Greenway 2010
5 332	498	1	86	498	NA	NA	NA	2	#	Allison 2012
5 687	981	1	204	979	NA	NA	NA	2	#	Gadde 2011
6 205	412	1	29	211	NA	NA	NA	2	#	Davies 2015
6 1540	2437	1	332	1225	NA	NA	NA	2	#	Pi-Sunyer 2015

END

Initial Values
#chain 1
list(d=c(NA, 0, 0, 0, 0, 0), sd=1, mu=c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0))
#chain 2
list(d=c(NA, -1), sd=4, mu=c(-3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3))
#chain 3
list(d=c(NA, 2), sd=2, mu=c(-3, 5, -1, -3, 7, -3, -4, -3, -3, 0, -3, -3,0, 3, 5, -3, -3, -1, -3, -7, -3, -3))

Continuous Outcome:

The analysis of our continuous outcome uses the same basic statistical model, however, as suggested by Dias et al,[2] we use a generalized linear model with a 'normal' likelihood and an 'identity' link function to allow for its analysis. For our continuous outcome of mean weight loss, we extracted the mean difference (weight change in kilogram [kg]) and standard error for the change from each study arm as an input for the model. Similar to prior studies, we ensured that since our sample sizes were not small,[2] the central limit theorem was valid, which allows us to assume that the means of the different studies (sample means) are approximately normally distributed, and can be represented as:

$$y_{ik} \sim N(\theta_{ik}, se_{ik}^2)$$

where, y_{ik} is a sample mean with a standard error, se_{ik}, drawn from a population with true mean θ_{ik}, unconstrained on the real line. We preferentially used the standard error for the mean difference (i.e. change in weight) rather than the standard error of the study arm, our analysis accounted for any within-patient correlation arising due to repeated measures. We used the analytical approach suggested by Dias et al,[2] which accounted for within study correlation in multi-arm studies.

Next, using an 'identity' link function, θ_{ik}, which was the variable of interest, could be presented as:

$$\theta_{ik} = \mu_i + \delta_{ik} I_{(k \neq 1)} \qquad \text{(similar notation as above)}$$

Using a random effects Bayesian model as above, we estimated the posterior distribution of the weighted mean difference (WMD) using non-informative priors.

Bayesian network meta-analysis code (with data) for continuous outcome

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials

model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
var[i,k] <- pow(se[i,k],2) # calculate variances
```

```
prec[i,k] <- 1/var[i,k] # set precisions
y[i,k] ~ dnorm(theta[i,k],prec[i,k])
theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
}
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# All pairwise comparisons
for (c in 1:(nt-1)) { for (k in (c+1):nt) { diff[c,k] <- (d[c] - d[k] )}}
for (k in 1:nt) {
#rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
rk[k] <- rank(d[],k) # assumes events are “bad”
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
}
} # *** PROGRAM ENDS
```

Data

```
# ns= number of studies; nt=number of treatments
list(ns=22, nt=6)
t[,1]   y[,1]   se[,1]   t[,2]   y[,2]   se[,2]   t[,3]   y[,3]   se[,3]   na[]   #
        StudyName
1       -2      0.475239139  2       -3.9    0.449583555  6       -7.8    0.474940055
        3       #       Astrup 2012
1       -0.9    0.323076923  2       -4.7    0.590563041  NA      NA      NA      2
        #       Swinburn 2005
1       -3.6    0.502451135  2       -6.3    0.499971097  NA      NA      NA      2
        #       Krempf 2003
1       -1.8    0.301178786  2       -4.7    0.2972541    NA      NA      NA      2
        #       Miles 2002
```

```
1       -3.4    0.395038676  2       -5.3    0.370970413  NA      NA      NA      2
        #       Hanefeld 2002
1       -2.3    0.392409177  2       -5.8    0.522150849  NA      NA      NA      2
        #       Broom 2002
1       -2.7    0.393148875  2       -5.4    0.391673639  NA      NA      NA      2
        #       Bakris 2002
1       -1.27   0.28046695   2       -3.89   0.269781309  NA      NA      NA      2
        #       Kelley 2002
1       -6.4    0.435211768  2       -9.4    0.411407582  NA      NA      NA      2
        #       Rossner 2000
1       -4.3    0.432608989  2       -5.6    0.37724765   NA      NA      NA      2
        #       Lindgrade 2000
1       -4.14   0.563178312  2       -7.94   0.572754414  NA      NA      NA      2
        #       Hauptman 2000
1       -1.31   0.82    2       -3.29   0.82    NA      NA      NA      2       #
        Finer 2000
1       -5.8    0.66964953   2       -8.8    0.370630299  NA      NA      NA      2
        #       Davidson 1999
1       -4.3    0.570997142  2       -6.2    0.502831489  NA      NA      NA      2
        #       Hollander 1998
1       -1.6    0.4000504    3       -4.7    0.397652474  NA      NA      NA      2
        #       O'Neil 2012
1       -2.9    0.163034177  3       -5.8    0.161986388  NA      NA      NA      2
        #       Fidler 2011 (BLOSSOM)
1       -2.2    0.10073115   3       -5.8    0.198891597  NA      NA      NA      2
        #       Smith 2010 (BLOOM)
1       -1.2    0.29970746   4       -6.4    0.29923227   NA      NA      NA      2
        #       Apovian 2013 (COR II)
1       -1.4    0.30081429   4       -6.1    0.29950419   NA      NA      NA      2
        #       Greenway 2010 (COR I)
1       -1.4    0.310013344  5       -10.2   0.280962377  NA      NA      NA      2
        #       Gadde 2011 (CONQUER)
1       -2.2    0.040617275  6       -6.4    0.354225876  NA      NA      NA      2
        #       Davies 2015 (SCALE-DM)
1       -2.8    0.185714286  6       -8.4    0.135720996  NA      NA      NA      2
        #
        Pi-Sunyer 2015 (SCALE Obesity)


END

Initial Values
#chain 1
list(d=c( NA, 0,0,0,0, 0), mu=c(0,0, 0, 0, 0, 0, 0, 0, 0,0,0,0,0,0,0,0,0,0,0,0))
#chain 2
list(d=c( NA, -1, -1,-3,-1,1), mu=c(-3, -3, -3, -3, -3, -3,   -3, -3))
```

#chain 3
list(d=c(NA, 2,2,2,2,2), mu=c(-3, 5, -1, 7, -3, -4, -3, -4))

Sensitivity Analyses – Post-hoc

During the peer review process, based on comments from the reviewers and Editors, additional post-hoc sensitivity analyses were performed to verify the stability of results. These included: (a) worst-case scenario analysis, in which all patients who were randomized but did not undergo assessment of outcomes at the end of study, were considered treatment failures for efficacy outcomes; (b) complete-case analysis, limited analysis to patients who completed the entire study and underwent assessment at end of the trial for efficacy outcomes; (c) frequentist analysis using the inconsistency model for all outcomes; (d) after trials in which behavioral modification was the primary intervention; (e) use of Hartnug-Knapp methods for direct meta-analysis; and (f) use of vague priors (uniform distributions, normal distributions, and gamma distributions with different means and variances) in Bayesian random effect network meta-analysis.

Detailed Search Strategy

Ovid

Database(s): Embase 1988 to 2016 Week 12, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials February 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 16, 2016
Search Strategy:

#	Searches	Results
1	exp Obesity/	473031
2	exp Weight Loss/	146900
3	exp Overweight/	475908
4	(obes* or "body mass ind*" or adipos* or overweight or "over weight" or "overload syndrom*" or overeat* or "over eat*" or overfeed* or "over feed*" or overfed or "over fed" or "weight cycling" or ((weight or fat) adj3 (gain* or reduc* or los* or maint* or decreas* or watch* or control*)) or "skinfold thickness" or antiobesity or "anti- obesity" or obesitas or bodyweight or "body weight").mp.	1616090
5	1 or 2 or 3 or 4	1640485
6	tetrahydrolipstatin/	5091
7	(alli or orlipastat or orlistat or "ro 18 0647" or "ro 180647" or ro180647 or tetrahydrolipstatin or xenical).mp.	7300
8	lorcaserin/	545
9	("apd 356" or apd356 or belviq or lorcaserin or lorqess).mp.	806

10	phentermine plus topiramate/	331
11	((phentermine and topiramate) or phenterminetopiramate or qnexa or qsiva or qsymia or topiramatephentermine).mp.	894
12	amfebutamone plus naltrexone/	158
13	((amfebutamone and naltrexone) or (bupropion and naltrexone) or contrave).mp.	992
14	liraglutide/	3752
15	(liraglutide or "nn 2211" or nn2211 or "nnc 90 1170" or "nnc90 1170" or Saxenda or victoza).mp.	5221
16	or/6-15	13639
17	5 and 16	9710
18	exp meta analysis/	154618
19	exp Meta-Analysis as Topic/	35884
20	exp "systematic review"/	92205
21	exp controlled study/	4796474
22	exp Randomized Controlled Trial/	769004
23	exp triple blind procedure/	97
24	exp Double-Blind Method/	354701
25	exp Single-Blind Method/	54294
26	exp latin square design/	299
27	exp Placebos/	282973
28	exp Placebo Effect/	8097
29	((meta adj analys*) or (systematic* adj3 review*) or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo*).mp,pt.	6519934
30	or/18-29	6519984
31	17 and 30	4377
32	from 17 keep 7036-9138	2103
33	limit 32 to (controlled clinical trial or randomized controlled trial or pragmatic clinical trial or systematic reviews) [Limit not valid in Embase,CCTR,CDSR; records were retained]	512
34	31 or 33	4430
35	exp animals/ or exp nonhuman/	36059600
36	exp humans/	27999176
37	34 not (35 not 36)	4228
38	limit 37 to (editorial or erratum or letter or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical	137

	index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	
39	37 not 38	4091
40	from 17 keep 9139-9710	572
41	39 or 40	4233
42	limit 41 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	3902
43	limit 42 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	1579
44	limit 41 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	3645
45	limit 44 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	684
46	45 not 43	73
47	41 not 46	4160
48	remove duplicates from 47	3132

Scopus

1 TITLE-ABS-KEY(obes* or "body mass ind*" or adipos* or overweight or "over weight" or "overload syndrom*" or overeat* or "over eat*" or overfeed* or "over feed*" or overfed or "over fed" or "weight cycling" or ((weight or fat) W/3 (gain* or reduc* or los* or maint* or decreas* or watch* or control*)) or "skinfold thickness" or antiobesity or "anti- obesity" or obesitas or bodyweight or "body weight")

2 TITLE-ABS-KEY(alli OR orlipastat OR orlistat OR "ro 18 0647" OR "ro 180647" OR ro180647 OR tetrahydrolipstatin OR xenical OR "apd 356" OR apd356 OR belviq OR lorcaserin OR lorqess OR "phentermine hydrochloride plus topiramate" OR "phentermine plus topiramate" OR phenterminetopiramate OR "phentermine-topiramate" OR qnexa OR qsiva OR qsymia OR "topiramate plus phentermine" OR "topiramate plus phentermine hydrochloride" OR topiramatephentermine OR "topiramate-phentermine" OR (phentermine and topiramate) OR phenterminetopiramate OR qnexa OR qsiva OR qsymia OR topiramatephentermine OR (amfebutamone and naltrexone) OR (bupropion and

naltrexone) OR contrave OR liraglutide OR "nn 2211" OR nn2211 OR "nnc 90 1170" OR "nnc90 1170" OR Saxenda OR victoza)

3 TITLE-ABS-KEY((meta W/1 analys*) or (systematic* W/3 review*) or (control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo*)

4 1 and 2 and 3

5 TITLE-ABS-KEY((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR "c elegans" OR "Caenorhabditis elegans" OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR "D melanogaster" OR "dairy calf" OR "dairy calves" OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR "Drosophila melanogaster" OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR "fruit flies" OR "fruit fly" OR "G mellonella" OR "Galleria mellonella" OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR "orang-utan" OR orangutans OR "orang-utans" OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR "zebra fish" OR zebrafish) AND NOT (human OR humans))

6 4 and not 5

7 TITLE-ABS-KEY(newborn* or neonat* or infant* or toddler* or child* or adolescent* or paediatric* or pediatric* or girl or girls or boy or boys or teen or teens or teenager* or preteen or preteens or "pre-teen" or "pre-teens") AND NOT TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" or elderly or geriatric*)

8 6 and not 7

9 DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
10 8 and not 9
11 PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
12 10 and not 11

Web of Science

1 TOPIC: ((obes* or "body mass ind*" or adipos* or overweight or "over weight" or "overload syndrom*" or overeat* or "over eat*" or overfeed* or "over feed*" or overfed or "over fed" or "weight cycling" or ((weight or fat) NEAR/3 (gain* or reduc* or los* or maint* or decreas* or watch* or control*)) or "skinfold thickness" or antiobesity or "anti- obesity" or obesitas or bodyweight or "body weight")) *AND* TOPIC: ((alli OR orlipastat OR orlistat OR "ro 18 0647" OR "ro 180647" OR ro180647 OR tetrahydrolipstatin OR xenical OR "apd 356" OR apd356 OR belviq OR lorcaserin OR lorqess OR "phentermine hydrochloride plus topiramate" OR "phentermine plus topiramate" OR phenterminetopiramate OR "phentermine-topiramate" OR qnexa OR qsiva OR qsymia OR "topiramate plus phentermine" OR "topiramate plus phentermine hydrochloride" OR topiramatephentermine OR "topiramate-phentermine" OR (phentermine and topiramate) OR phenterminetopiramate OR qnexa OR qsiva OR qsymia OR topiramatephentermine OR (amfebutamone and naltrexone) OR (bupropion and naltrexone) OR contrave OR liraglutide OR "nn 2211" OR nn2211 OR "nnc 90 1170" OR "nnc90 1170" OR Saxenda OR victoza)) *AND* TOPIC: (((meta NEAR/1 analys*) or (systematic* NEAR/3 review*) or (control* NEAR/3 study) or (control* NEAR/3 trial) or (randomized NEAR/3 study) or (randomized NEAR/3 trial) or (randomised NEAR/3 study) or (randomised NEAR/3 trial) or "pragmatic clinical trial" or (doubl* NEAR/1 blind*) or (doubl* NEAR/1 mask*) or (singl* NEAR/1 blind*) or (singl* NEAR/1 mask*) or (tripl* NEAR/1 blind*) or (tripl* NEAR/1 mask*) or (trebl* NEAR/1 blind*) or (trebl* NEAR/1 mask*) or "latin square" or placebo* or nocebo*)) Indexes=SCI-EXPANDED Timespan=All years

2 TS=((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR "c elegans" OR "Caenorhabditis elegans" OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR "D melanogaster" OR "dairy calf" OR "dairy calves" OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR "Drosophila melanogaster" OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR "fruit flies" OR "fruit fly" OR "G mellonella" OR "Galleria mellonella" OR geese OR gerbil OR gerbils OR goat OR goats OR

goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR "orang-utan" OR orangutans OR "orang-utans" OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR "zebra fish" OR zebrafish) NOT (human OR humans)) Indexes=SCI-EXPANDED Timespan=All years

3 #1 NOT #2 Indexes=SCI-EXPANDED Timespan=All years

4 TS=(newborn* or neonat* or infant* or toddler* or child* or adolescent* or paediatric* or pediatric* or girl or girls or boy or boys or teen or teens or teenager* or preteen or preteens or "pre-teen" or "pre-teens") NOT TS=(adult or adults or "middle age" or "middle aged" or elderly or geriatric*) Indexes=SCI-EXPANDED Timespan=All years

5 #3 NOT #4 Indexes=SCI-EXPANDED Timespan=All years

6 (#5) AND DOCUMENT TYPES: (Article OR Abstract of Published Item OR Meeting Abstract OR Proceedings Paper OR Review)Indexes=SCI-EXPANDED Timespan=All years

eTable 1. Baseline Patient Characteristics in Included Randomized Clinical Trials Comparing Different Pharmacological Interventions for Long-term Weight Loss

Study and year	Intervention, No.	Control, No.	Age, mean (SD), y	Male, No. (%)	Race/ethnicity (White), No. (%)	Weight, mean (SD), kg	BMI, mean (SD), kg/m^2	Diabetes Mellitus, No. (%)	Pre-diabetes[#] or IGT, No. (%)	Hypertension, No. (%)	Dyslipidemia, No. (%)
Orlistat vs. Placebo											
Astrup 2012[7]	95	98	I: 45.9 (9.1) C: 45.9 (10.3)	I: 22 (23) C: 25 (25)	NR	I: 96.0 (11.7) C: 97.3 (12.3)	I: 34.1 (2.6) C:34.9 (2.8)	I: 3 (3) C: 4 (4)	I: 27 (28) C: 32 (33)	I: 16 (17) C: 27 (28)	I: 2 (2) C: 4 (4)[a]
Swinburn 2005[8]	170	169	I: 52.0 (7.5) C: 52.5 (7.4)	I: 66 (38.8) C: 80 (47.3)	NR	I: 103.3 (17.8) C: 106.9 (17.8)	I: 37.6 (5.1) C: 38 (4.9)	I: 14 (8.2) C: 14 (8.3)	-	I: 26 (15.3) C: 31 (18.3)	I: 51 (30) C: 49 (29)
Berne 2005[9]	111	109	I: 59.8 (9.1) C: 59.3 (8.5)	I: 61 (55) C: 59 (54)	I: 111 (100) C: 109 (100)	I: 95.3 (12.6) C: 95.7 (12.5)	I: 32.6 (3.1) C: 32.9 (3)	I: 111 (100) C: 109 (100)	-	NR	NR
Torgerson 2004 (XENDOS)[10]	1650	1655	I: 43 (8) C: 43.7 (8)	I: 735 (44.8) C: 732 (44.7)	NR	I: 110.4 (16.3) C: 110.6 (16.5)	I: 37.3 (4.2) C: 37.4 (4.5)	-	I: 350 (21.3) C: 344 (21)	NR	NR
Krempf 2003[11]	346	350	I: 40 (11.1) C: 42 (11.2)	I: 44 (12.7) C: 51 (14.6)	NR	I: 97 (16.7) C: 97.5 (16.8)	I: 36 (5.6) C: 36.2 (5.6)	I: 0 (0) C: 0 (0)	-	NR	NR
Miles 2002[12]	255	261	I: 52.5 (6.3) C: 53.7 (6.4)	I: 130 (52) C: 132 (52)	I: 211 (84) C: 201 (79)	I: 102.1 (17.4) C: 101.1 (16)	I: 35.6 (4.7) C: 35.2 (3.2)	I: 255 (100) C: 261 (100)	-	NR	NR
Hanefeld 2002[13]	195	188	I: 56.6 (8.6) C: 55.8 (8.9)	I: 91 (48) C: 90 (50)	NR	I: 99.4 (17.5) C: 98.4 (18.5)	I: 34.5 (5.6) C: 33.7 (5.2)	I: 195 (100) C: 188 (100)	-	NR	NR

Study and year	Intervention, No.	Control, No.	Age, mean (SD), y	Male, No. (%)	Race/ethnicity (White), No. (%)	Weight, mean (SD), kg	BMI, mean (SD), kg/m^2	Diabetes Mellitus, No. (%)	Pre-diabetes[#] or IGT, No. (%)	Hypertension, No. (%)	Dyslipidemia, No. (%)
Broom 2002[14]	265	266	I: 46.7 (11.4) C: 45.3 (11.5)	I: 57 (22) C: 56 (21.3)	NR	I: 100.9 (20.5) C: 101.8 (19.8)	I: 37.1 (6.4) C: 37 (6.2)	-	I: 11 (4.2) C: 15 (5.6)	I: 54 (20.4) C: 59 (22.2)	I: 114 (43) C: 120 (45.1)
Bakris 2002[15]	278	276	I: 53.2 (0.5) C: 52.5 (0.5)	I: 98 (36.7) C: 109 (41.1)	I: 226 (85) C: 228 (86)	I: 101.2 (1) C: 101.5 (1)	I: 35.8 (3.9) C: 35.4 (4)	I: 23 (8) C: 22 (8)	-	I: 278 (100) C: 276 (100)	-
Kelley 2002[16]	274	276	I: 57.8 (8.1) C: 58.0 (8.2)	I: 116 (44) C: 118 (44)	I: 189 (71) C: 196 (73)	I: 102.0 (16.3) C: 101.8 (16.4)	I: 35.8 (3.3) C: 35.6 (4.9)	I: 274 (100) C: 276 (100)	-	NR	NR
Rossner 2000[17]	244	243	I: 43.6 (11.4) C: 44.3 (10.8)	I: 40 (16.5) C: 31 (15)	NR	I: 96.7 (13.8) C: 97.7 (14.6)	I: 34.7 (3.7) C: 35.3 (4.1)	NR	NR	NR	I: 20 (8.3) C: 24 (10.1)
Lindgarde 2000[18]	190	186	I: 53.7 (9.4) C: 53.2 (9.9)	I: 66 (34.7) C: 71 (38.2)	NR	I: 96.1 (13.7) C: 95.9 (13.5)	I: 33.2 (3) C: 33.2 (3.1)	I: 17 (8.9) C: 13 (7)	-	I: 74 (38.9) C: 81 (43.8)	I: 75 (39) C: 75 (40)
Hauptman 2000[19]	210	212	I: 43.2 (10.1) C: 41.6 (10.2)	I: 44 (21) C: 47 (22.2)	I: 184 (87.6) C: 193 (91)	I: 100.5 (14.2) C: 101.8 (14.6)	I: 36.0 (2.9) C: 36.1 (4.4)	NR	NR	NR	NR
Finer 2000[20]	114	114	I: 41.5 (10.5) C: 41.1 (10)	I: 12 (10.9) C: 13 (12)	I: 103 (93.6) C: 104 (96.3)	I: 97.9 (12.9) C: 98.4 (15)	I: 36.8 (3.6) C: 36.8 (3.7)	I: 0 (0) C: 0 (0)	-	I: 6 (5.5) C: 2 (2)	I: 59 (52) C: 60 (53)
Davidson 1999[21]	668	224	I: 43.3 (0.6) C: 44 (0.7)	I: 113 (17.2) C: 26 (11.6)	I: 534 (81.3) C: 77 (79.4)	I: 100.7 (0.6) C: 100.6 (0.9)	I: 36.2 (0.1) C: 36.5 (0.9)	I: 26 (4) C: 10 (4.5)	I: 40 (6.1) C: 13 (5.8)	I: 54 (8.2) C: 20 (9)	I: 69 (10.5) C: 12 (5.4)
Sjostrom 1998[22]	345	343	I: 45·2 (20·0–76·0) C: 44·3 (18·0–77·0)c	I: 59 (17·2) C: 57 (16·8)	NR	I: 99·1 (61·0–148·6) C: 99·8 (64·2–137·2)[c]	I: 36·0 (28·3–47·2) C: 36·1 (29·2–43·5)[c]	NR	NR	NR	NR

Study and year	Intervention, No.	Control, No.	Age, mean (SD), y	Male, No. (%)	Race/ethnicity (White), No. (%)	Weight, mean (SD), kg	BMI, mean (SD), kg/m^2	Diabetes Mellitus, No. (%)	Pre-diabetes[#] or IGT, No. (%)	Hypertension, No. (%)	Dyslipidemia, No. (%)
Hollander, 1998[23]	162	159	I: 55.4 (8.8) C: 54.7 (9.7)	I: 79 (48.8) C: 85 (53.4)	I: 141 (87) C: 140 (88)	I: 99.6 (14.5) C: 99.7 (15.4)	I: 34.5 (3.2) C: 34 (3.4)	I: 162 (100) C: 159 (100)	-	NR	NR
Loracaserin vs. Placebo											
O'Neil 2012 (BLOOM-DM)[24]	256	252	I: 53.2 (8.3) C: 52 (9.3)	I: 119 (46.5) C: 115 (45.6)	I: 150 (58.6) C: 166 (65.9)	I: 103.7 (17) C: 102.6 (18.1)	I: 36.1 (4.5) C: 35.9 (4.5)	I: 256 (100) C: 252 (100)	-	NR	NR
Fidler 2011 (BLOSSOM)[25]	1602	1601	I: 43.8 (11.8) C: 43.7 (11.8)	I 312 (19.5) C: 352 (22)	I: 1080 (67.4) C: 1064 (66.5)	I: 100.1 (15.6) C: 100.5 (16.2)	I: 36.0 (4.3) C: 35.9 (4.1)	-	I: 29 (1.8) C: 18 (1.1)	I: 388 (24.2) C: 382 (23.9)	I: 455 (28.4) C: 438 (27.4)
Smith 2010 (BLOOM)[26]	1595	1587	I: 43.8 (0.3) C: 44.4 (0.3)	I: 272 (17.1) C: 253 (16)	I: 1081 (67.9) C: 1046 (66)	I: 100.4 (0.4) C: 99.7 (0.4)	I: 36.2 (0.1) C: 36.2 (0.1)	NR	NR	NR	NR
Naltrexone-Bupropion vs. Placebo											
Apovian 2013 (COR II)[27]	1001	495	I: 44.4 (11.4) C: 44.3 (11.2)	I: (15.4) C: (15.2)	I: (83) C: (84)	I: 99.2 (15.9) C: 100.3 (16.6)	I: 36.1 (4.3) C: 36.2 (4.5)	I: 0 (0) C: 0 (0)	-	I: (21.2) C: (21.4)	I: (55.9) C: (53.1)
Hollander 2013 (COR-DM)[28]	333	169	I: 54.0 (9.1) C: 53.5 (9.8)	I: 140 (41.8) C: 80 (47.1)	I: 261 (77.9) C: 140 (82.4)	I: 104.2 (18.9) C: 105.1 (17)	I: 36.4 (4.8) C: 36.4 (4.5)	I: 333 (100) C: 169 (100)	-	NR	I: 280 (83.6) C: 145 (85.3)
Wadden 2011 (COR-BMOD)[29]	591	202	I: 45.9 (10.4) C: 45.6 (11.4)	I: 63 (10.7) C: 17 (8.4)	I: 405 (68.5) C: 149 (73.8)	I: 100.2 (15.4) C: 101.9 (15)	I: 36.3 (4.2) C: 37.0 (4.2)	I: 0 (0) C: 0 (0)	-	NR	NR
Greenway 2010 (COR I)[30]	583	581	I: 44.4 (11.1) C: 43.7 (11.1)	I: 87 (15) C: 85 (15)	I: 440 (75) C: 440 (76)	I: 99.7 (15.9) C: 99.5 (14.3)	I: 36.1 (4.4) C: 36.2 (4)	I: 0 (0) C: 0 (0)	-	I: 130 (22) C: 113 (19)	I: 284 (49) C: 288 (50)

Study and year	Intervention, No.	Control, No.	Age, mean (SD), y	Male, No. (%)	Race/ethnicity (White), No. (%)	Weight, mean (SD), kg	BMI, mean (SD), kg/m^2	Diabetes Mellitus, No. (%)	Pre-diabetes[#] or IGT, No. (%)	Hypertension, No. (%)	Dyslipidemia, No. (%)
Phentermine-Topiramate vs. Placebo											
Allison 2012 (EQUIP)[31]	512	514	I: 41.9 (12.2) C:43.0 (11.8)	I: 88 (17.2) C: 89 (17.3)	I: 408 (79.7) C: 413 (80.4)	I: 115.2 (20.7) C: 115.8 (21.5)	I: 41.9 (6) C: 42.0 (6.2)	I: 0 (0) C: 0 (0)	I: 0 (0) C: 0 (0)	NR	NR
Gadde 2011 (CONQUER) [32]	995	994	I: 51 (10.6) C: 51.2 (10.2)	I: 302 (30) C: 299 (30)	I: 850 (85) C: 861 (87)	I: 103.0 (17.6) C: 103.3 (18.1)	I: 36.6 (4.5) C: 36.7 (4.6)	I: 664 (67)[d] C: 675 (68)		I: 520 (52) C: 524 (53)	I: 363 (36)[b] C: 354 (36)
Liraglutide vs. Placebo											
Davies 2015 (SCALE-DM)[33]	423	212	I: 55 (10.8) C: 54.7 (9.8)	I: 202 (52) C: 95 (45.8)	I: 353 (83.5) C: 175 (82.5)	I: 105.7 (21.9) C: 106.5 (21.3)	I: 37.1 (6.5) C: 37.4 (7.1)	I: 423 (100) C: 212 (100)	-	I: 293 (69.3) C: 145 (68.4)	I: 295 (69.7) C: 126 (59.4)
Pi-Sunyer 2015 (SCALE Obesity)[34]	2487	1244	I: 45.2 (12.1) C: 45 (2)	I: 530 (21.3) C: 273 (21.9)	I: 2107 (84.7) C: 1061 (85.3)	I: 106.2 (21.2) C: 106.2 (21.7)	I: 38.3 (6.4) C: 38.3 (6.3)	I: 0 (0) C: 0 (0)	I: 1528 (61.4) C: 757 (60.9)	I: 850 (34.2) C: 446 (35.9)	I: 737 (29.6) C: 359 (28.9)
Astrup 2012[7]	93	98	I: 45.9 (10.7) C: 45.9 (10.3)	I: 23 (25) C: 25 (25)	NR	I: 97.6 (13.7) C: 97.3 (12.3)	I: 34.8 (2.8) C: 34.9 (2.8)	I: 4 (4) C: 4 (4)	I: 27 (29) C: 32 (33)	I: 11 (12) C: 27 (28)	I: 7 (8) C: 4 (4)
Liraglutide vs. Orlistat											
Astrup, 2012[7]	93	95	I: 45.9 (10.7) C: 45.9 (9.1)	I: 23 (25) C: 22 (23)	NR	I: 97.6 (13.7) C: 96 (11.7)	I: 34.8 (2.8) C: 34.1 (2.6)	I: 4 (4) C: 3 (3)	I: 27 (29) C: 27 (28)	I: 11 (12) C: 16 (17)	I: 7 (8) C: 2 (2)

Agents presented in chronological order of first trial; individual trials presented from most recent to oldest

[Abbreviations: BMI-Body mass index; C-Control; I-Intervention; IGT-Impaired glucose tolerance; NR-Not reported; Pre-Diabetes (study defined – impaired fasting glucose, impaired glucose tolerance); SD-Standard deviation]

Pre-Diabetes (study defined – impaired fasting glucose, impaired glucose tolerance)

a - study reports patients on anti-hypertensives and cholesterol-lowering medications

b - only hypertriglyceridemia reported

c - means and range

d - Pre-diabetes and Diabetes Mellitus combined

eTable 2. Sensitivity Analysis: Hartung-Knapp Direct Meta-analysis

Pharmacological Intervention	(A) ≥5% weight loss	(B) ≥10% weight loss	(C) Weight change (in excess of comparator) in Kg	(D) Adverse events
Compared with Placebo				
Orlistat	2.69 (2.32, 3.12)	2.41 (2.05, 2.83)	-2.63 (-3.05, -2.21)	1.87 (1.55, 2.26)
Loracaserin	3.09 (1.96, 4.86)	3.17 (1.90, 5.28)	-3.23 (-4.37, -2.09)	1.39 (0.61, 3.17)
Naltrexone-Bupropion	3.90 (2.43, 6.26)	4.11 (2.22, 7.63)	-4.95 (-8.76, -1.14)	2.60 (1.92, 3.53)
Phentermine-Topiramate	9.10 (3.03, 27.29)	11.34 (2.72, 47.25)	-8.80 (-9.62, -7.98)	2.32 (0.55, 9.76)
Liraglutide	5.19 (2.95, 9.15)	4.57 (2.43, 8.58)	-5.15 (-7.36, -2.94)	2.82 (1.49, 5.34)
Compared with Orlistat				
Liraglutide	3.66 (1.79, 7.46)	3.87 (1.65, 9.04)	-3.90 (-5.18, -2.62)	3.50 (0.70, 17.49)

Pooled odds ratio of achieving **(A) at least 5% weight loss**, **(B) at least 10% weight loss, (C)** weighted mean difference of **overall weight loss** (in excess of comparator, at 1 year) and **(D) discontinuation of therapy due to adverse events** in direct comparisons, using Hartung-Knapp estimator. Numbers in parentheses indicate 95% confidence. All comparisons are significant, unless shaded in gray.

eTable 3. Secondary Outcomes

Pharmacological Intervention	(A) Weight change (in excess of comparator) in Kg (95% CrI)	(B) ≥10% weight loss, OR (95% CrI)
Compared with Placebo		
Orlistat	-2.60 (-3.04, -2.16)	2.42 (2.03, 2.86)
Loracaserin	-3.22 (-3.97, -2.46)	3.20 (2.41, 4.38)
Naltrexone-Bupropion	-4.95 (-5.94, -3.96)	4.19 (3.08, 5.72)
Phentermine-Topiramate	-8.80 (-10.20, -7.42)	11.40 (7.91, 16.50)
Liraglutide	-5.27 (-6.06, -4.52)	4.99 (3.67, 7.48)
Compared with Orlistat		
Loracaserin	-0.63 (-1.49, 0.26)	1.32 (0.96, 1.90)
Naltrexone-Bupropion	-2.36 (-3.43, -1.28)	1.74 (1.22, 2.47)
Phentermine-Topiramate	-6.21 (-7.67, -4.75)	4.72 (3.16, 7.08)
Liraglutide	-2.68 (-3.55, -1.83)	2.07 (1.48, 3.20)
Compared with Loracaserin		
Naltrexone-Bupropion	-1.73 (-2.98, -0.49)	1.31 (0.84, 1.98)
Phentermine-Topiramate	-5.58 (-7.17, -4.00)	3.56 (2.19, 5.65)
Liraglutide	-2.05 (-3.16, -1.00)	1.56 (1.02, 2.56)
Compared with Naltrexone-Bupropion		
Phentermine-Topiramate	-3.85 (-5.56, -2.14)	2.72 (1.68, 4.40)
Liraglutide	-0.32 (-1.59, 0.92)	1.20 (0.77, 2.00)
Compared with Phentermine-Topiramate		
Liraglutide	3.53 (1.91, 5.11)	0.44 (0.28, 0.76)

Pooled weighted mean difference of **(A) overall weight loss** (in excess of comparator, at 1 year) and odds ratio of **(B) achieving at least 10% weight loss** (over baseline, at 1 year) based on combined direct and indirect evidence from random-effects Bayesian network meta-analysis. Numbers in parentheses indicate 95% credible interval. All comparisons are significant, unless shaded in gray.

eTable 4. Estimated Absolute Rate of Outcomes With Intervention

Pharmacological Intervention	(A) ≥5% weight loss[a]	(B) ≥10% weight loss[b]	(C) Adverse events[c]
Orlistat	45% (42%-49%)	20% (17%-23%)	8% (7%-10%)
Lorcaserin	49% (42%-55%)	25% (20%-31%)	6% (5%-8%)
Naltrexone-Bupropion	55% (48%-61%)	30% (24%-37%)	12% (9%-14%)
Liraglutide	63% (56%-71%)	34% (27%-43%)	13% (9%-17%)
Phentermine-Topiramate	74% (67%-80%)	54% (45%-63%)	10% (8%-13%)

Estimated absolute event rate of (A) proportion of patients achieving **≥5% weight loss**, (B) proportion of patients achieving **≥10% weight loss**, and **(**C) proportion of patients with **discontinuation of therapy due to adverse events**, derived from odds ratios for the comparison of each agent against placebo in network meta-analysis. Median of placebo event rate was used as assumed control risk (ACR). Median placebo event rates for each outcome are included in the footnote. Numbers in parenthesis represent 95% confidence intervals derived by replacing the odds ratios in the calculation with the lower and upper limits of their respective 95% credible intervals.

[a]Based on assumed control risk of 23% (corresponding to median 23% of placebo-treated patients achieving ≥5% weight loss)

[b]Based on assumed control risk of 9% (corresponding to median 9% of placebo-treated patients achieving ≥10% weight loss)

[c]Based on assumed control risk of 5% (corresponding to median 5% of placebo-treated patients who discontinued therapy due to adverse events)

eTable 5. Sensitivity Analysis

Pharmacological Intervention	(A) Only Non-diabetics	(B) Standard dose of Phentermine-Topiramate	(C) Excluding behavioral therapy
Compared with Placebo			
Orlistat	2.58 (2.12, 3.08)	2.69 (2.33, 3.10)	2.70 (2.37, 3.07)
Loracaserin	3.09 (2.20, 4.35)	3.09 (2.34, 4.10)	3.09 (2.43, 3.94)
Naltrexone-Bupropion	4.06 (2.94, 5.54)	3.95 (3.00, 5.16)	4.50 (3.39, 5.92)
Phentermine-Topiramate	9.64 (5.58, 16.74)	6.23 (3.85, 10.11)	9.19 (6.82, 12.49)
Liraglutide	5.34 (3.70, 8.38)	5.56 (4.13, 7.93)	5.42 (4.19, 7.44)
Compared with Orlistat			
Loracaserin	1.20 (0.82, 1.79)	1.15 (0.84, 1.58)	1.15 (0.88, 1.52)
Naltrexone-Bupropion	1.57 (1.09, 2.28)	1.47 (1.08, 1.99)	1.67 (1.23, 2.26)
Phentermine-Topiramate	3.73 (2.12, 6.73)	2.32 (1.40, 3.84)	3.40 (2.47, 4.76)
Liraglutide	2.07 (1.40, 3.38)	2.07 (1.50, 3.03)	2.01 (1.52, 2.83)
Compared with Loracaserin			
Naltrexone-Bupropion	1.31 (0.82, 2.08)	1.28 (0.86, 1.87)	1.46 (1.00, 2.09)
Phentermine-Topiramate	3.12 (1.64, 5.99)	2.02 (1.15, 3.53)	2.98 (2.02, 4.38)
Liraglutide	1.73 (1.06, 3.07)	1.80 (1.21, 2.85)	1.75 (1.24, 2.63)
Compared with Naltrexone-Bupropion			
Phentermine-Topiramate	2.37 (1.27, 4.51)	1.58 (0.91, 2.78)	2.04 (1.37, 3.12)
Liraglutide	1.32 (0.82, 2.32)	1.41 (0.95, 2.22)	1.21 (0.83, 1.86)
Compared with Phentermine-Topiramate			
Liraglutide	0.56 (0.29, 1.14)	0.89 (0.51, 1.64)	0.59 (0.40, 0.92)

Outcome (A) –10 trials Orlistat vs. placebo (n=7911), 2 Lorcaserin vs.placebo (n=6139), 3 Naltrexone-Bupropion vs. placebo (n=2939), 1 Phentermine-topiramate vs. placebo (n=996), 2 Liraglutide vs. placebo (n=3853) and 1 Liraglutide vs. Orlistat (n=188)
Outcome (B) – 16 trials Orlistat vs. placebo (n=10236), 3 Lorcaserin (n=6638), 4 Naltrexone-Bupropion (n=3363), 1 Phentermine-topiramate (n=1467), 3 Liraglutide vs. placebo (n=4476) and 1 trial Liraglutide vs. Orlistat (n=188).
Outcome (C) – 16 Orlistat vs. placebo (n=10236), 3 Lorcaserin (n=6638), 4 Naltrexone-Bupropion (n=2688), 2 Phentermine-topiramate (n=2956), 3 Liraglutide vs. placebo (n=4476) and 1 trial Liraglutide vs. Orlistat (n=188).
Pooled odds ratio of achieving 5% weight loss in sensitivity analysis based on: **(A)** restricting only studies in non-diabetic adults **(B)** replacing trials of high-dose phentermine-topiramate with standard dose phentermine-topiramate (7.5mg P/46mg T once daily) and **(C)** excluding studies in which behavior modification co-intervention was particularly rigorous and was clearly stated as a primary co-intervention. Numbers in parentheses indicate 95% credible interval. All comparisons are significant, unless shaded in gray.

eTable 6. Sensitivity Analysis: Worst Case Scenario

Pharmacological Intervention	(A) ≥5% weight loss	(B) ≥10% weight loss
Compared with Placebo		
Orlistat	2.44 (1.55, 3.83)	2.72 (1.83, 4.03)
Loracaserin	2.32 (1.65, 3.49)	2.62 (1.95, 3.86)
Naltrexone-Bupropion	3.16 (2.23, 4.44)	3.95 (2.84, 5.63)
Phentermine-Topiramate	6.93 (4.41, 10.99)	11.30 (7.43, 17.10)
Liraglutide	3.80 (2.06, 7.01)	4.06 (2.40, 6.90)
Compared with Orlistat		
Loracaserin	0.95 (0.55, 1.78)	0.96 (0.60, 1.71)
Naltrexone-Bupropion	1.30 (0.73, 2.29)	1.45 (0.87, 2.48)
Phentermine-Topiramate	2.84 (1.51, 5.45)	4.16 (2.34, 7.37)
Liraglutide	1.56 (0.73, 3.36)	1.49 (0.77, 2.91)
Compared with Loracaserin		
Naltrexone-Bupropion	1.36 (0.79, 2.20)	1.51 (0.91, 2.37)
Phentermine-Topiramate	2.99 (1.61, 5.24)	4.3 (2.39, 7.05)
Liraglutide	1.64 (0.78, 3.26)	1.55 (0.79, 2.77)
Compared with Naltrexone-Bupropion		
Phentermine-Topiramate	2.20 (1.25, 3.91)	2.86 (1.65, 4.84)
Liraglutide	1.20 (0.60, 2.43)	1.03 (0.54, 1.92)
Compared with Phentermine-Topiramate		
Liraglutide	0.55 (0.26, 1.18)	0.36 (0.19, 0.71)

Outcome (A) – 2 trials Orlistat vs. placebo (n=4001), 3 Lorcaserin vs. placebo (n=6638), 4 Naltrexone-Bupropion vs. placebo (n=3363), 2 Phentermine-topiramate vs. placebo (n=2956) and 1 trial Liraglutide vs. placebo (n=3662)
Outcome (B) - 3 trials Orlistat vs. placebo (n=3945), 3 Lorcaserin vs. placebo (n=6638), 4 Naltrexone-Bupropion vs. placebo (n=3363), 2 Phentermine-topiramate vs. placebo (n=2956) and 1 trial Liraglutide vs. placebo (n=3662)
Pooled odds ratio of achieving **(A) at least 5% weight loss** and **(B) at least 10% weight loss** in sensitivity analysis based on worst case assumption (i.e. all patients who were randomized but did not undergo assessment of outcomes at the end of study – week 52 or beyond – were considered treatment failures). Numbers in parentheses indicate 95% credible interval. All comparisons are significant, unless shaded in gray.

eTable 7. Sensitivity Analysis: Complete-Case Analysis

Pharmacological Intervention	(A) ≥5% weight loss	(B) ≥10% weight loss	(C) Weight change (in excess of comparator) in Kg
Compared with Placebo			
Orlistat	2.03 (1.35, 3.20)	2.15 (1.51, 3.25)	-2.78 (-5.58, 0.16)
Loracaserin	3.64 (2.57, 5.24)	3.29 (2.35, 4.91)	-4.34 (-6.57, -1.94)
Naltrexone-Bupropion	4.67 (3.21, 6.40)	4.59 (3.19, 6.59)	-5.50 (-7.37, -3.51)
Phentermine-Topiramate	15.62 (9.93, 24.53)	15.75 (10.00, 24.67)	-11.82 (-14.27, -9.58)
Liraglutide	4.95 (2.80, 8.76)	4.04 (2.31, 7.17)	-5.76 (-8.82, -2.59)
Compared with Orlistat			
Loracaserin	1.80 (1.01, 3.11)	1.54 (0.90, 2.57)	-1.55 (-5.25, 2.10)
Naltrexone-Bupropion	2.31 (1.25, 3.79)	2.14 (1.22, 3.50)	-2.71 (-6.21, 0.74)
Phentermine-Topiramate	7.69 (4.03, 14.10)	7.35 (3.91, 12.85)	-9.05 (-12.90, -5.50)
Liraglutide	2.44 (1.16, 4.92)	1.89 (0.92, 3.60)	-2.99 (-7.20, 1.21)
Compared with Loracaserin			
Naltrexone-Bupropion	1.28 (0.75, 2.02)	1.39 (0.81, 2.26)	-1.17 (-4.17, 1.84)
Phentermine-Topiramate	4.28 (2.39, 7.53)	4.77 (2.59, 8.25)	-7.48 (-10.96, -4.37)
Liraglutide	1.36 (0.69, 2.65)	1.23 (0.61, 2.36)	-1.42 (-5.35, 2.40)
Compared with Naltrexone-Bupropion			
Phentermine-Topiramate	3.34 (1.96, 6.10)	3.43 (1.91, 6.13)	-6.32 (-9.53, -3.43)
Liraglutide	1.05 (0.57, 2.13)	0.88 (0.46, 1.74)	-0.26 (-3.94, 3.41)
Compared with Phentermine-Topiramate			
Liraglutide	0.32 (0.15, 0.66)	0.26 (0.13, 0.54)	6.06 (2.30, 10.10)

Outcome (A) – 2 trials Orlistat vs. placebo (n=1833), 3 Lorcaserin vs. placebo (n=3256), 4 Naltrexone-Bupropion vs. placebo (n=1969), 2 Phentermine-topiramate vs. placebo (n=1718) and 1 trial Liraglutide vs. placebo (n=2579)
Outcome (B) – 4 trials Orlistat vs. placebo (n=1946), 3 Lorcaserin vs. placebo (n=3256), 4 Naltrexone-Bupropion vs. placebo (n=1969), 2 Phentermine-topiramate vs. placebo (n=1718) and 1 trial Liraglutide vs. placebo (n=2579)
Outcome (C) – 2 trials Orlistat vs. placebo (n=539), 3 Lorcaserin vs. placebo (n=3256), 3 Naltrexone-Bupropion vs. placebo (n=1562), 2 Phentermine-topiramate vs. placebo (n=1718) and 2 trials Liraglutide vs. placebo (n=3012)
Pooled odds ratio of achieving **(A) at least 5% weight loss** and **(B) at least 10% weight loss** and **(C)** weighted mean difference of **overall weight loss** (in excess of comparator, at 1 year) in complete-case analysis (wherein we limited analysis to patients who completed the entire study and underwent assessment of outcomes at end of the trial). Numbers in parentheses indicate 95% credible interval. All comparisons are significant, unless shaded in gray.

eTable 8. Sensitivity Analysis: Frequentist Approach Using Inconsistency Model

Pharmacological Intervention	(A) ≥5% weight loss	(B) ≥10% weight loss	(C) Weight change (in excess of comparator) in Kg	(D) Adverse events
Compared with Placebo				
Orlistat	2.72 (2.39, 3.09)	2.43 (2.08, 2.85)	-2.69 (-3.11, -2.26)	1.86 (1.55, 2.24)
Loracaserin	3.09 (2.47, 3.88)	3.18 (2.47, 4.11)	-3.22 (-3.87, -2.58)	1.32 (1.06, 1.66)
Naltrexone-Bupropion	3.94 (3.12, 4.97)	4.11 (3.12, 5.41)	-4.95 (-5.83, -4.08)	2.61 (2.13, 3.21)
Phentermine-Topiramate	9.17 (6.90, 12.20)	11.31 (8.26, 15.50)	-8.80 (-10.03, -7.57)	2.31 (1.80, 2.96)
Liraglutide	7.05 (3.13, 15.85)	5.14 (1.95, 13.53)	-5.80 (-7.40, -4.20)	3.50 (0.70, 17.61)

Outcome (A) –16 trials Orlistat vs. placebo (n=10363), 3 Lorcaserin vs. placebo (n=6893), 4 Naltrexone-Bupropion vs. placebo (n=3952), 2 Phentermine-topiramate vs. placebo (n=3015), 3 Liraglutide vs. placebo (n=4557) and 1 Liraglutide vs. Orlistat (n=188)
Outcome (B) –14 trials Orlistat vs. placebo (n=9426), 3 Lorcaserin vs. placebo (n=6893), 4 Naltrexone-Bupropion vs. placebo (n=3952), 2 Phentermine-topiramate vs. placebo (n=3015), 3 Liraglutide vs. placebo (n=4557) and 1 Liraglutide vs. Orlistat (n=188)
Outcome (C) –14 trials Orlistat vs. placebo (n=6489), 3 Lorcaserin vs. placebo (n=6893), 2 Naltrexone-Bupropion vs. placebo (n=2264), 1 Phentermine-topiramate vs. placebo (n=1960), 3 Liraglutide vs. placebo (n=6893) and 1 Liraglutide vs. Orlistat (n=188)
Outcome (D) –16 trials Orlistat vs. placebo (n=10381), 3 Lorcaserin vs. placebo (n=6893), 4 Naltrexone-Bupropion vs. placebo (n=3952), 2 Phentermine-topiramate vs. placebo (n=3015), 3 Liraglutide vs. placebo (n=4557) and 1 Liraglutide vs. Orlistat (n=188)
Pooled odds ratio of achieving **(A) at least 5% weight loss**, **(B) at least 10% weight loss, (C)** weighted mean difference of **overall weight loss** (in excess of comparator, at 1 year) and **(D) discontinuation of therapy due to adverse events,** in direct comparisons, using frequenstist approach. Numbers in parentheses indicate 95% confidence. All comparisons are significant, unless shaded in gray. This analysis uses all trials from the original analyses in the respective groups.

eTable 9. Description of Serious Adverse Events and Rates/Reasons of Drop-out in Individual Trials

Study, Year	Serious adverse events (SAE)		Rates of dropout	
	Intervention	Control	Intervention - n/N	Control - n/N
Orlistat vs. Placebo				
Astrup 2012[7]	2.1% SAE	3.1% SAE	40/95	36/98
	Not clearly specified	Not clearly specified	3 adverse events	2 adverse events
			12 withdrew consent	12 withdrew consent
			3 non-compliance	3 non-compliance
			1 lack of efficacy	4 lack of efficacy
			21 others	15 others
Swinburn 2005[8]	(16) 9.4%	(12) 7.1%	38/170	32/169
	5 (2.9%) withdrew due to GI related AEs	2 (1.2%) withdrew due to GI related AEs)	16 adverse events	12 adverse events
			12 lost to follow-up	6 lost to follow-up
			10 withdrew consent	11 withdrew consent
				3 insufficient therapeutic response
Berne 2005[9]	None (all side effects were mild to moderate)	None (all side effects were mild to moderate)	15/111	15/109
			5 adverse events	4 adverse event
			2 intercurrent illness	1 intercurrent illness
			4 withdrew consent	7 withdrew consent
			2 loss to follow-up	1 loss to follow-up
			2 other reasons	2 other reasons
Torgerson 2004 (XENDOS)[10]	15% had at least 1 SAE over the course of 4 years; 8% withdrew due to AEs	13% had at least 1 SAE over the course of 4 years; 4% withdrew due to AEs	230/1640 refused treatment	327/1637 refused treatment
			131/1640 discontinued due to insufficient therapeutic response	311/1637 discontinued due to insufficient therapeutic response
Krempf 2003[11]	5	4	122/346	149/350
	(thrombotic thrombocytopenic purpura, anal abscess, pain hypocondrium and liver disorder)	(abdominal pain, breast cancer and ulcerative colitis)	38 withdrew consent	53 withdrew consent
			21 treatment failures	36 treatment failures
			24 adverse events	12 adverse events
			4 lost to follow-up	10 lost to follow-up

Study, Year	Serious adverse events (SAE)		Rates of dropout	
	Intervention	Control	Intervention - n/N	Control - n/N
Miles 2002[12]	None (all side effects were mild or moderate)	None (all side effects were mild or moderate)	90/255	115/261
			36 refused treatment	57 refused treatment
			25 lost to follow-up	35 lost to follow-up
			25 adverse events	12 adverse events
				5 protocol violations
				2 treatment failures
Hanefeld 2002[13]	6	5	62/195	57/188
	(GI related severe side effect)	(GI related severe side effect)	16 adverse events	12 adverse events
			13 withdrew consent	22 withdrew consent
			9 protocol violations	5 protocol violations
			13 lost to follow-up	11 lost to follow-up
Broom 2002[14]	13	17	79/265	105/266
	(investigators did not deem them to be related to the study medication)	(investigators did not deem them to be related to the study medication)	20 adverse events	11 adverse events
			40 withdrew consent	49 withdrew consent
	1 death (carcinomattosis which was deemed to be unrelated to the study medication)		16 lost to follow-up	18 lost to follow-up
Bakris 2002[15]	14	15	116/278	168/276
	(necessitated hospitalization or prolonged hospitalization); 1 withdrew due to SAE	(necessitated hospitalization or prolonged hospitalization); 4 withdrew due to SAE	18 adverse events	20 adverse events)
			40 refused treatment	91 refused treatment
			48 lost to follow-up	47 lost to follow-up
			8 other	9 other
			2 excluded	1 excluded

Study, Year	Serious adverse events (SAE)		Rates of dropout	
	Intervention	Control	Intervention - n/N	Control - n/N
Kelley 2002[16]	1 Hypoglycemia (necessitating medical intervention)	3 Hypoglycemia (necessitating medical intervention)	137/274	148/276
			35 adverse events	22 adverse events
	Most other side effects were mild to moderate	Most other side effects were mild to moderate	102 non-safety	126 non-safety
			1 insufficient therapeutic response	1 insufficient therapeutic response
			3 protocol violations	7 protocol violations
			55 refused treatment	79 refused treatment
			36 failed to return for follow-up	35 failed to return for follow-up
			7 other	4 other
Rossner 2000[17]	2	0	63/244 (year 1)	85/243 (year 1)
	1 cholelithiasis	(most side effects were mild to moderate)	19 adverse events	6 adverse events
	1 diverticulitis		6 treatment failures	5 treatment failures
	(most side effects were mild to moderate)		20 refused treatment	23 refused treatment
			5 lost to follow-up	21 lost to follow-up
			11 did not cooperate	19 did not cooperate
			2 protocol violations	5 protocol violations
			2 administrative	1 entry violation
				5 administrative
Lindgarde 2000[18]	19 + 1	5	31/190	22/186
	(one death was attributed to a patient with Type 2 DM with severe atherosclerosis who died of a brain stem infarction)		10 adverse events	5 adverse events
			4 non-compliance	3 non-compliance
			6 withdrew consent	4 withdrew consent
			4 loss to follow-up	
Hauptman 2000[19]	None (all side effects were mild or moderate)	None (all side effects were mild or moderate)	59 withdrew from the study (1 year)	90 withdrew from the study (1 year)

Study, Year	Serious adverse events (SAE)		Rates of dropout	
	Intervention	Control	Intervention - n/N	Control - n/N
Finer 2000[20]	None (all side effects were mild or moderate)	None (all side effects were mild or moderate)	41/114	48/114
			15 lost to follow-up	18 lost to follow-up
			9 adverse events	8 did not cooperate
			7 did not cooperate	7 adverse events
			5 protocol violations	5 administrative
			3 administrative	5 refused treatment
			2 refused treatment	3 protocol violations
				2 treatment failures
Davidson 1999[21]	None (all side effects were mild to moderate)	None (all side effects were mild to moderate)	210/668	86/224
			59 lost to follow-up	21 lost to follow-up
	3 breast cancer diagnoses	1 breast cancer diagnosis	42 administrative	21 administrative
			61 adverse events	9 adverse events
			26 did not cooperate	16 did not cooperate
			6 treatment failures	11 treatment failures
			13 protocol violations	5 protocol violations
			3 entry violations	1 entry violation
				2 refused treatment
Sjostrom 1998[22]	25	24	61/345	83/343
	Only 1 SAE was deemed to be related to the intervention	Only 1 SAE was deemed to be related to the intervention	23 adverse events	9 adverse events
			38 other (did not cooperate, lost to follow-up, refused treatment, administrative, treatment failure, protocol violation, entry violation, died during study)	74 other (did not cooperate, lost to follow-up, refused treatment, administrative, treatment failure, protocol violation, entry violation, died during study)
Hollander 1998[23]	None (all side effects were mild to moderate)	None (all side effects were mild to moderate)	24/163	44/159
			(Adverse events, non-compliance, loss to follow-up, administrative protocol violations, treatment failure)	(Adverse events, non-compliance, loss to follow-up, administrative protocol violations, treatment failure)

Study, Year	Serious adverse events (SAE)		Rates of dropout	
	Intervention	Control	Intervention - n/N	Control - n/N
Lorcaserin vs. Placebo				
O'Neil 2012 (BLOOM-DM)[24]	6.3% (not detailed)	6.7% (not detailed)	87/256	96/253
			22 Adverse event	11 Adverse event
	6 had new valvulopathy	1 had new valvulopathy	32 Withdrew consent	50 Withdrew consent
			20 Lost to follow up	14 Lost to follow up
			3 Noncompliance	10 Noncompliance
			3 Sponsor decision	1 Pl decision
			7 Other	5 Sponsor decision
				5 Other
Fidler 2011 (BLOSSOM)[25]	3.1% with any SAE	2.2% with any SAE	686/1602	769/1601
	3 possibly related to drug – 1 syncope, 1 moderate depression, 1 acute anxiety	1 died from asthma exacerbation;	293 Patient request	376 Patient request
			198 Lost to follow-up	234 Lost to follow-up
	2% with new valvulopathy	1 with ventricular tachycardia, syncope, 1 anaphylactic reaction	115 Adverse event	73 Adverse event
			59 Noncompliance	49 Noncompliance
		2% with new valvulopathy	20 PI/Sponsor decision	37 PI/Sponsor decision
			1 Other	
Smith 2010 (BLOOM)[26]	43 SAE;	39 SAE	712/1595	871/1587
	2 cardiac disorder, 7 Hepatic/GI, 4 Infection, 3 respiratory disorder, 27 Others	0 cardiac disorder, 5 Hepatic/GI, 2 Infection, 0 respiratory disorder, 32 Others	191 Lost to follow-up	226 Lost to follow-up
			280 Patient request	351 Patient request
	2.7% with new valvulopathy		113 Adverse event	106 Adverse event
		2.3% with new valvulopathy	27 Lack of efficacy	88 Lack of efficacy
			34 PI/Sponsor decision	32 PI/Sponsor decision
			67 Other	68 Other

Study, Year	Serious adverse events (SAE)		Rates of dropout	
	Intervention	Control	Intervention - n/N	Control - n/N
Naltrexone-Bupropion vs. Placebo				
Apovian 2013 (COR II)[27]	2.1% SAE	1..4% SAE	462/1001	226/495
	1 Myocardial Infarction; 1 Seizure		241 adverse events	68 adverse events
			75 Withdrew consent	56 Withdrew consent
			77 Lost to follow up	48 Lost to follow up
			19 Lack of efficacy	33 Lack of efficacy
			31 Non compliance	13 Non compliance
			19 Other	8 Other
Hollander 2013 (COR-DM)[28]	3.9% SAE (not specified)	4.7% SAE (not specified)	160/335	70/170
			98 Adverse events	26 Adverse events
			22 Lost to follow up	15 Lost to follow up
			21 Withdrew consent	15 Withdrew consent
			11 Non compliance	7 Non compliance
			5 Lack of efficacy	6 Lack of efficacy
			3 Other	1 Other
Wadden 2011 (COR-BMOD)[29]	2 cholecystitis (possibly drug related)	2 Suicidal ideation	249/591	84/202
	0 Suicidal ideation	0 cholecystitis	150 Adverse events	25 Adverse events
			43 Withdrew consent	24 Withdrew consent
			22 Lost to follow up	17 Lost to follow up
			17 Non-compliance	5 Non-compliance
			3 Lack of efficacy	6 Lack of efficacy
			14 Other	7 Other
Greenway 2010 (COR I)[30]	1.6% SAE	1.4% SAE	287/583	291/581
			112 adverse event	90 withdrew consent
	1 Myocardial Infarction leading to death, 1 Heart failure (both judged not drug related)	1 pericardial effusion	65 lost to follow-up	66 lost to follow-up
			60 withdrew consent	56 adverse event
			12 Lack of efficacy	40 Lack of efficacy
			26 Non-compliance	22 Non-compliance
			1 death	17 other
			11 other	

Study, Year	Serious adverse events (SAE)		Rates of dropout	
	Intervention	Control	Intervention - n/N	Control - n/N
Phenteramine/Topiramate vs. Placebo				
Allison 2012 (EQUIP)[31]	1 SAE	2 SAE	211/512	273/512
	(Myelogenous leukemia)	1 chest pain, 1 pulmonary embolism	42 Withdrew consent	93 Withdrew consent
			82 Adverse events	43 Adverse events
			53 Lost to follow-up	92 Lost to follow-up
			6 Noncompliance	11 Noncompliance
			14 Pregnancy	2 Pregnancy
			5 Lack of efficacy	20 Lack of efficacy
			9 Other	12 Other
Gadde 2011 (CONQUER)[32]	5% SAE (50)	4% SAE (40)	360/995	429/994
	7 sever acidosis, 3 Nephrolithiasis	1 cardiac arrest (died), 1 severe acidosis	62 lost to follow-up	126 lost to follow-up
			192 adverse events	89 adverse events
			69 withdrew consent	139 withdrew consent
			5 lack of efficacy	39 lack of efficacy
			10 non-compliance	6 non-compliance
			2 pregnancies	30 other reasons
			20 other reasons	
Liraglutide vs. Placebo				
Davies 2015 (SCALE-DM)[33]	8.8% SAE	6.1% SAE	99/423	72/212
	5 events of severe hypoglycemia, 1 atrial fibrillation, 1 atrial flutter	0 severe hypoglycemia, 1 medullary thyroid cancer	39 Adverse events	7 Adverse events
			32 Met withdrawal criteria	3 Lack of efficacy
			12 Nonadherence	13 Nonadherence
			16 Other	37 Met withdrawal criteria
				12 Others

Study, Year	Serious adverse events (SAE)		Rates of dropout	
	Intervention	Control	Intervention - n/N	Control - n/N
Pi-Sunyer 2015 (SCALE Obesity)[34]	6.2% SAE	5.0% SAE	708/2487	443/1244
	20 cholelithiasis,12 acute cholecystitis, 4 acute pancreatitis, 6 osteoarthritis, 4 breast cancer, 1 uterine leiomyoma	5 cholelithiasis, 1 breast cancer, 2 uterine leiomyoma, 0 acute cholecystitis, 0 acute pancreatitis, 0 osteoarthritis	246 Adverse events	47 Adverse events
			23 Lack of efficacy	36 Lack of efficacy
			264 Met withdrawal criteria	259 Met withdrawal criteria
			65 Nonadherence	38 Nonadherence
			76 Others	63 Others
Astrup 2012[7]	7.5% SAE	3.1% SAE	28/93	36/98
	1 cholelithiasis and pancreatitis, others not specified	Not clearly specified	7 adverse events	3 adverse events
			10 withdrew consent	12 withdrew consent
			2 non-compliance	3 non-compliance
			0 lack of efficacy	4 lack of efficacy
			9 others	14 others
Liraglutide vs. Orlistat				
Astrup 2012[7]	7.5% SAE	2.1% SAE	28/93	40/95
	1 cholelithiasis and pancreatitis, others not specified	Not clearly specified	7 adverse events	2 adverse events
			10 withdrew consent	12 withdrew consent
			2 non-compliance	3 non-compliance
			0 lack of efficacy	1 lack of efficacy
			9 other reasons	22 others

Abbreviations: SAE – serious adverse events, AE – adverse events, GI – gastrointestinal

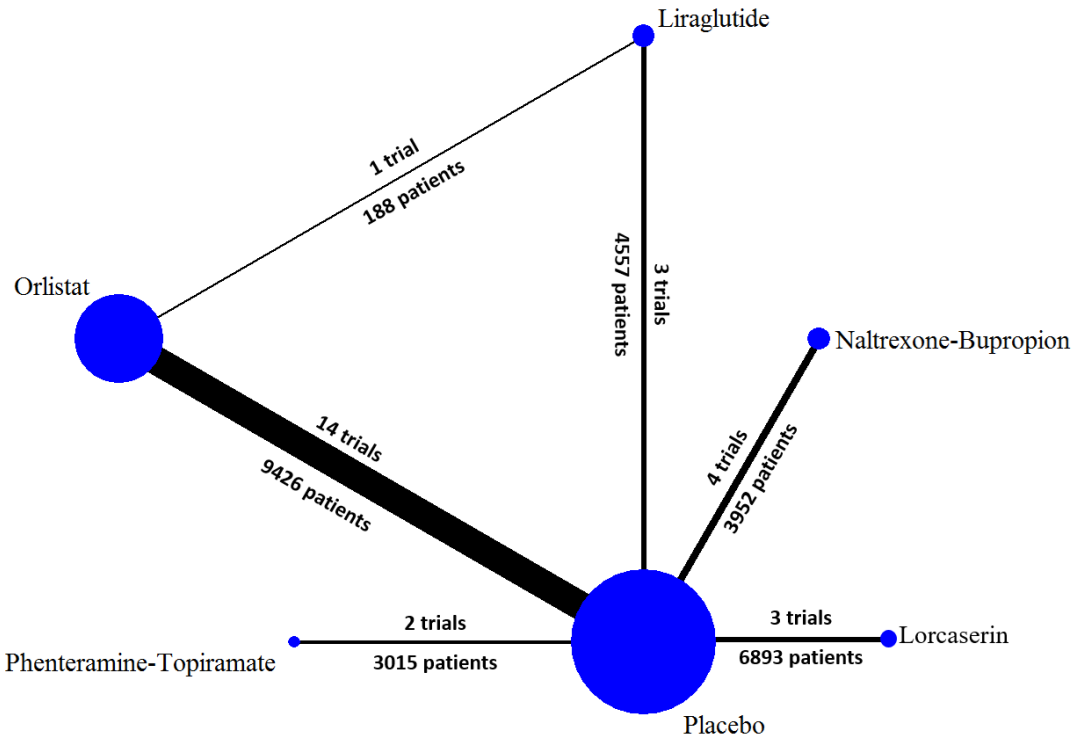
eTable 10. Overall GRADE Quality of Evidence From Network Meta-analysis

Pharmacological Intervention	≥5% weight loss
Compared with Placebo	
Orlistat	Moderate
Loracaserin	Moderate
Naltrexone-Bupropion	Moderate
Phentermine-Topiramate	Moderate
Liraglutide	Moderate
Compared with Orlistat	
Loracaserin	Low
Naltrexone-Bupropion	Moderate
Phentermine-Topiramate	Moderate
Liraglutide	Moderate
Compared with Loracaserin	
Naltrexone-Bupropion	Low
Phentermine-Topiramate	Moderate
Liraglutide	Moderate
Compared with Naltrexone-Bupropion	
Phentermine-Topiramate	Moderate
Liraglutide	Low
Compared with Phentermine-Topiramate	
Liraglutide	Moderate

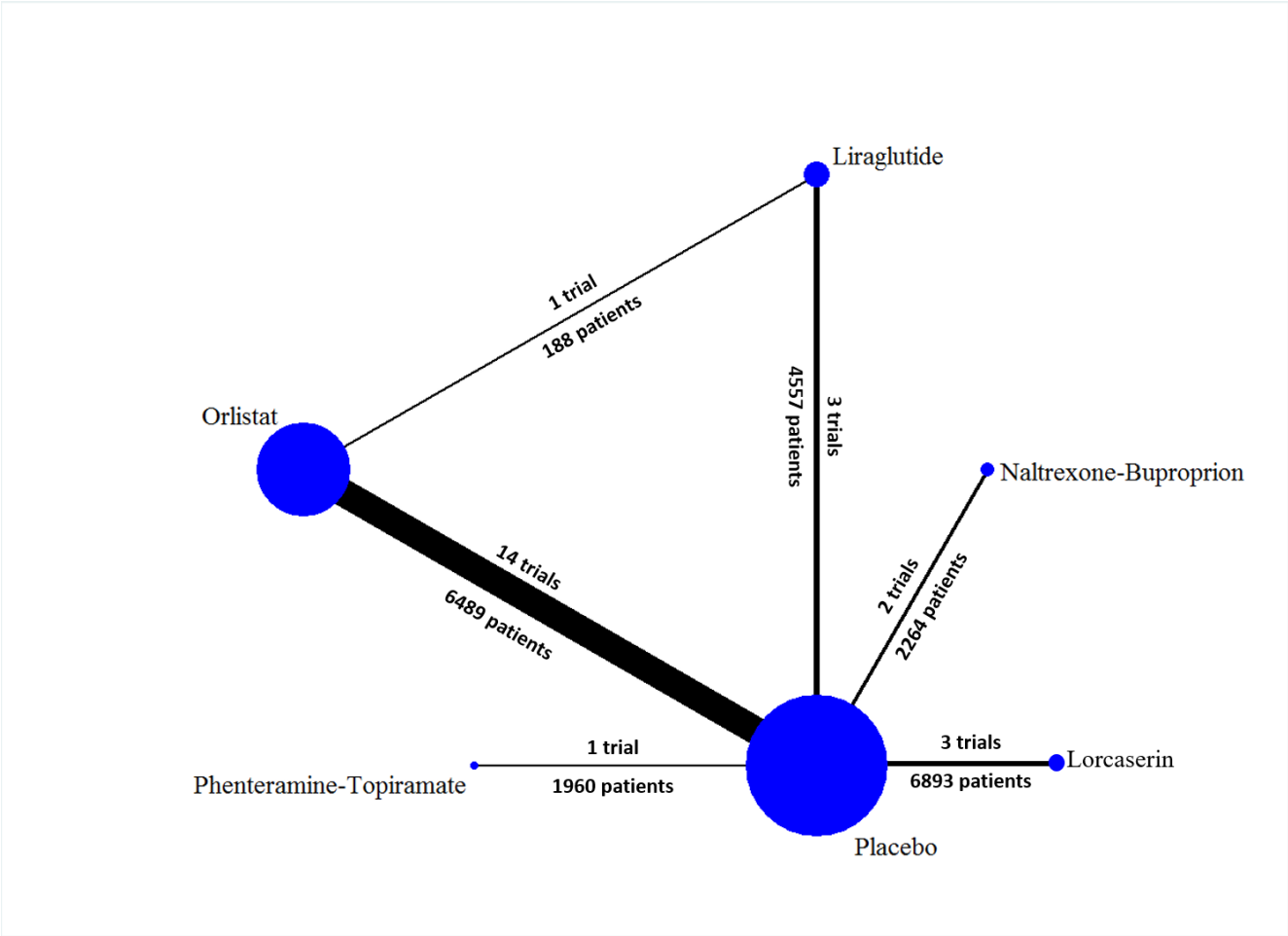
Using GRADE to rate quality of evidence from a network meta-analysis involved several steps: First, we rated quality of evidence for direct comparisons; second, we rated quality of evidence for indirect estimates (starting at the lowest rating of the two pairwise direct estimates that contribute as first-order loops to the indirect estimate, which can be rated down further for imprecision or intransitivity), and then third, rating the quality of evidence for the network combining direct and indirect estimates. In this step, if direct and indirect estimates from second-order comparisons are similar, the higher of the ratings was assigned to the network meta-analysis estimates.

eFigure 1. Network of Included Studies With the Available Direct Comparisons for All Outcomes **(A)** achieving at least 10% weight loss, **(B)** weight loss in kilograms (in excess of comparator) and **(C)** treatment discontinuation due to adverse effects. The size of the nodes and the thickness of the edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively

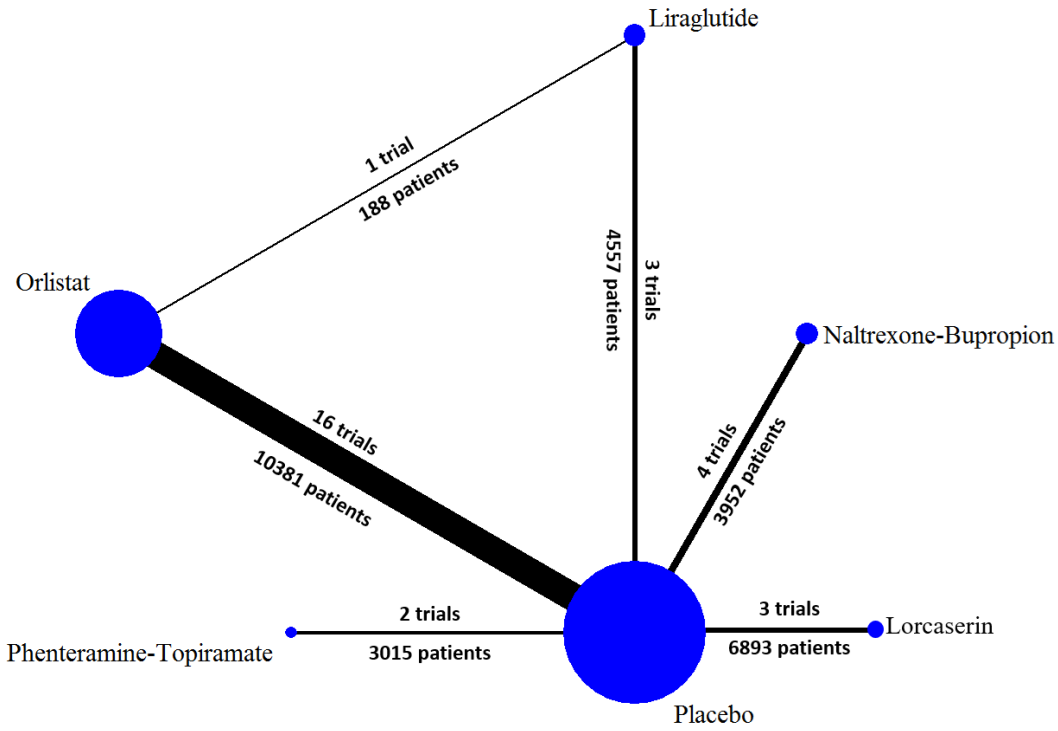
eFigure 1A



eFigure 1B

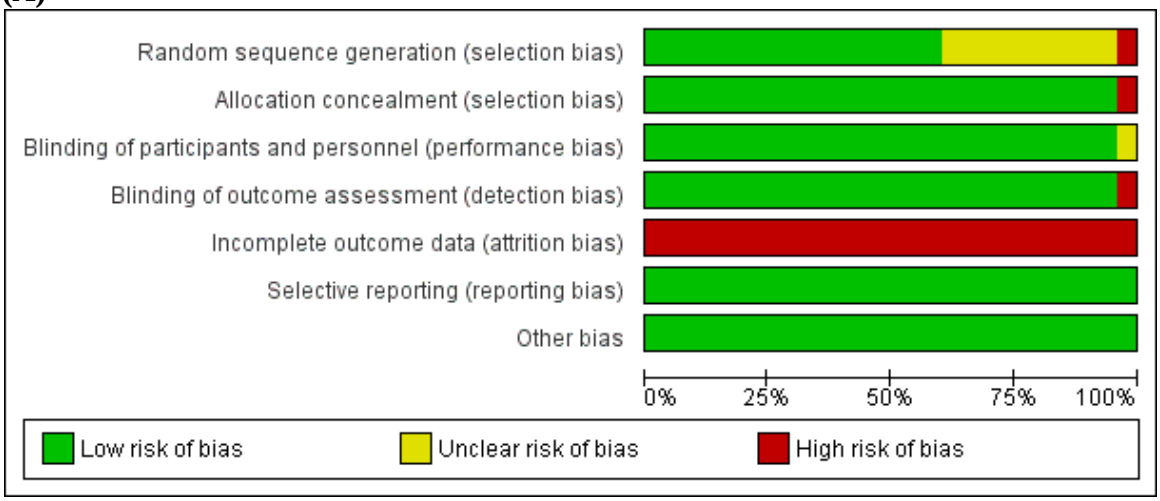


eFigure 1C

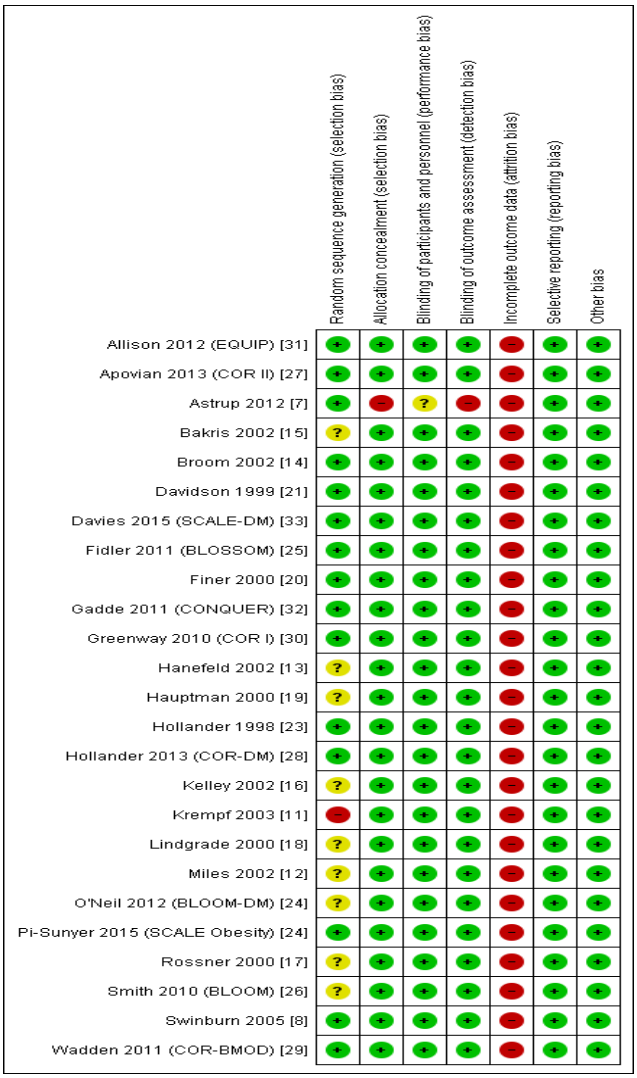


eFigure 2. Quality Assessment of 28 RCTs Included in the Analysis

(A)



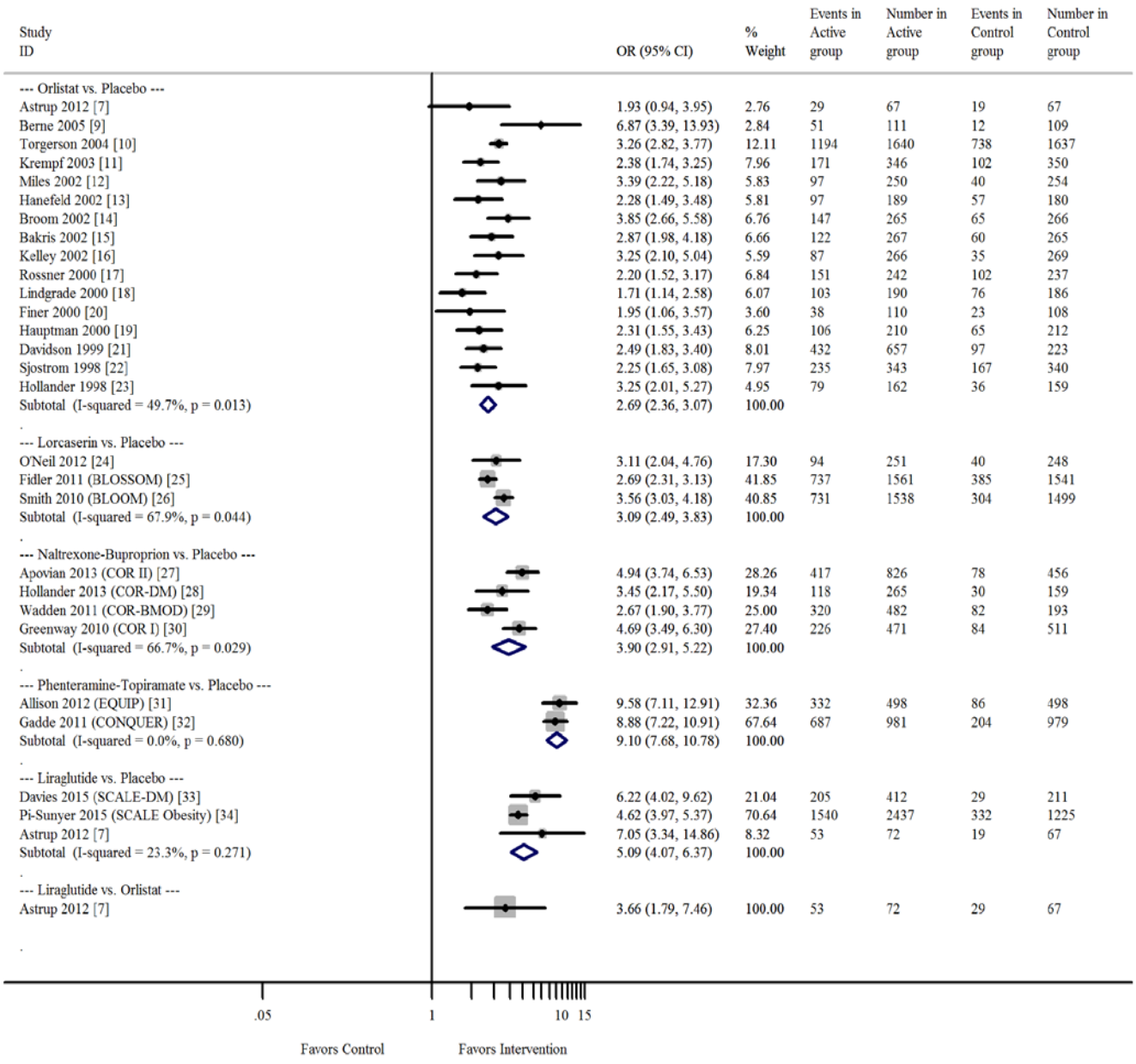
(B)



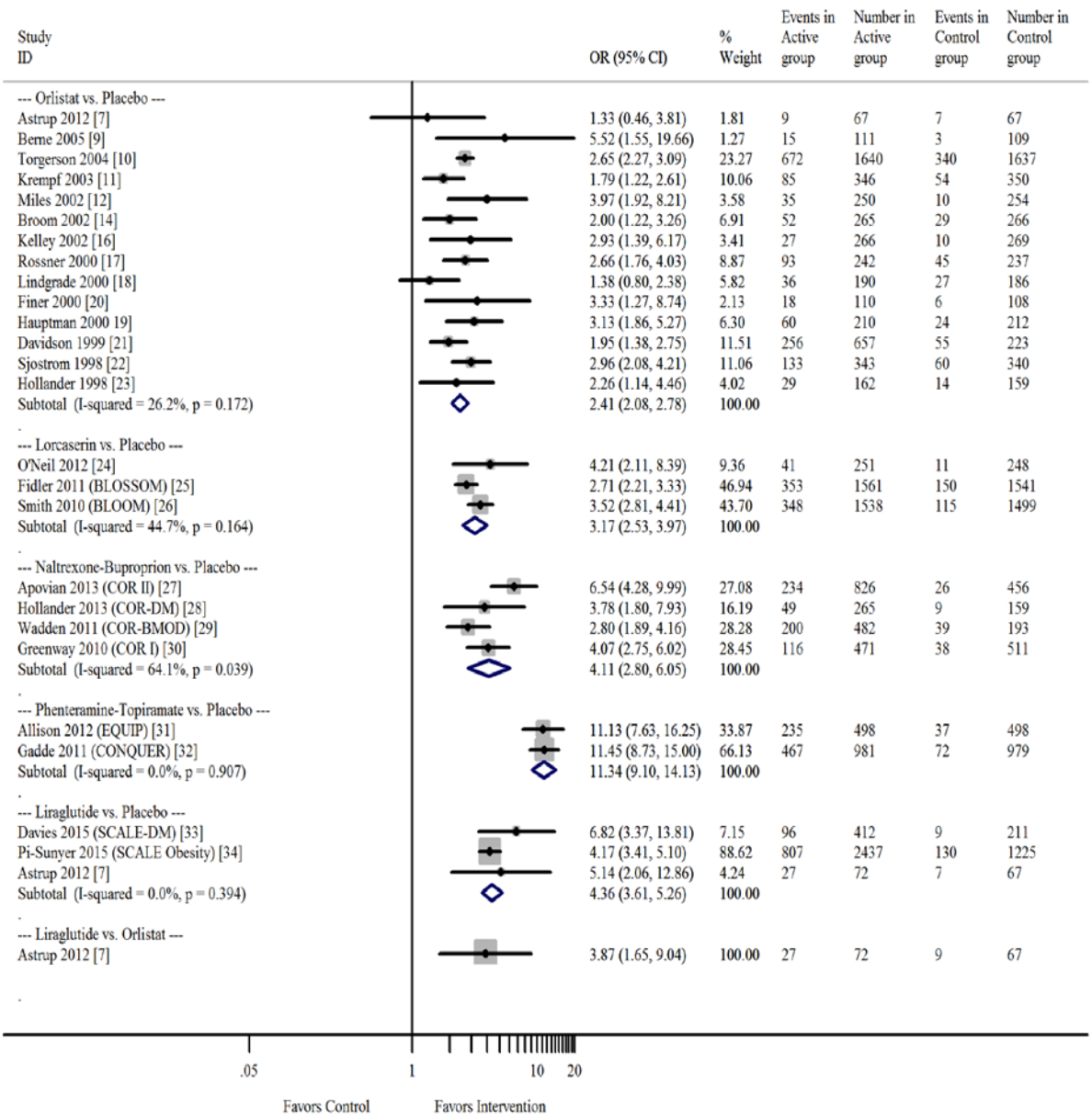
(A) Overall and (B) Study-level risk of bias, using Cochrane's risk of bias assessment tool. In this tool, studies were deemed to be at high, low or unclear risk of bias based on adequacy of sequence generation, allocation concealment, blinding, method of addressing incomplete data, selective reporting, and other biases. The review authors' judgments about each risk of bias item are presented as percentages across all included studies, and for each included study. In (B), numbers in square brackets indicate the corresponding reference numbers for each study.

eFigure 3. Direct Meta-analysis of Different Pharmacological Interventions

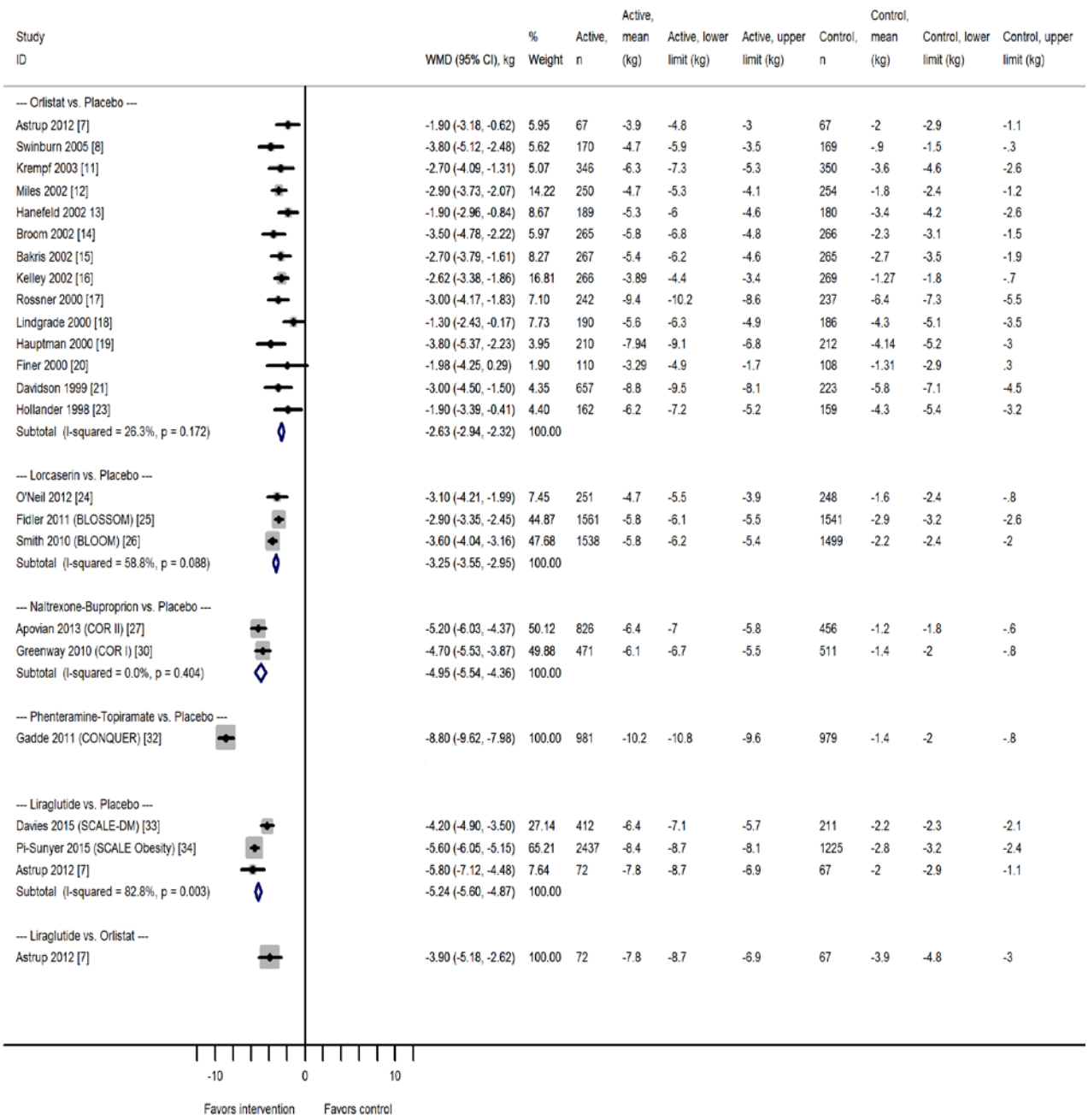
eFigure 3A. Direct Meta-analysis of 5% weight loss



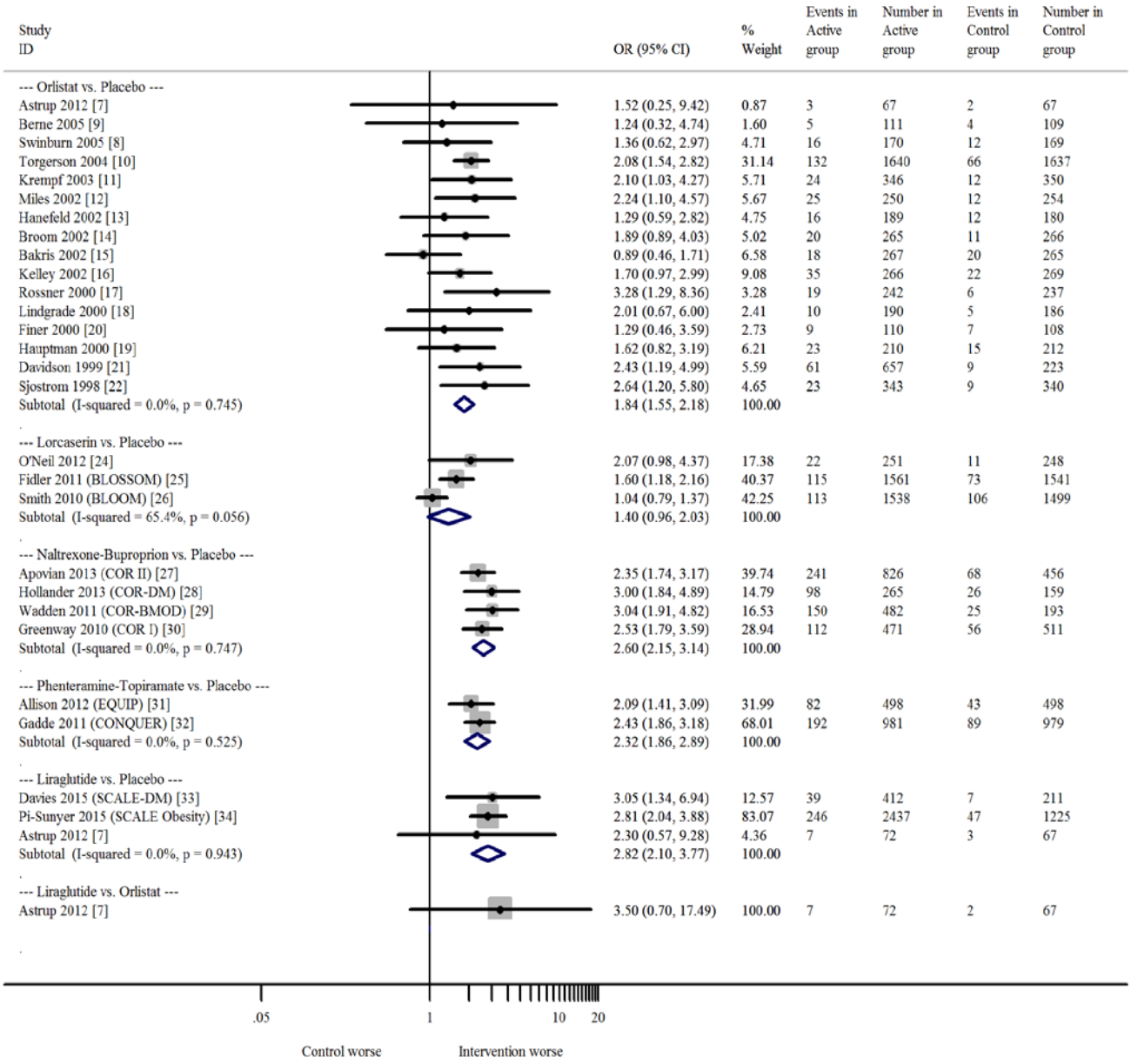
eFigure 3B. Direct meta-analysis of 10% weight loss



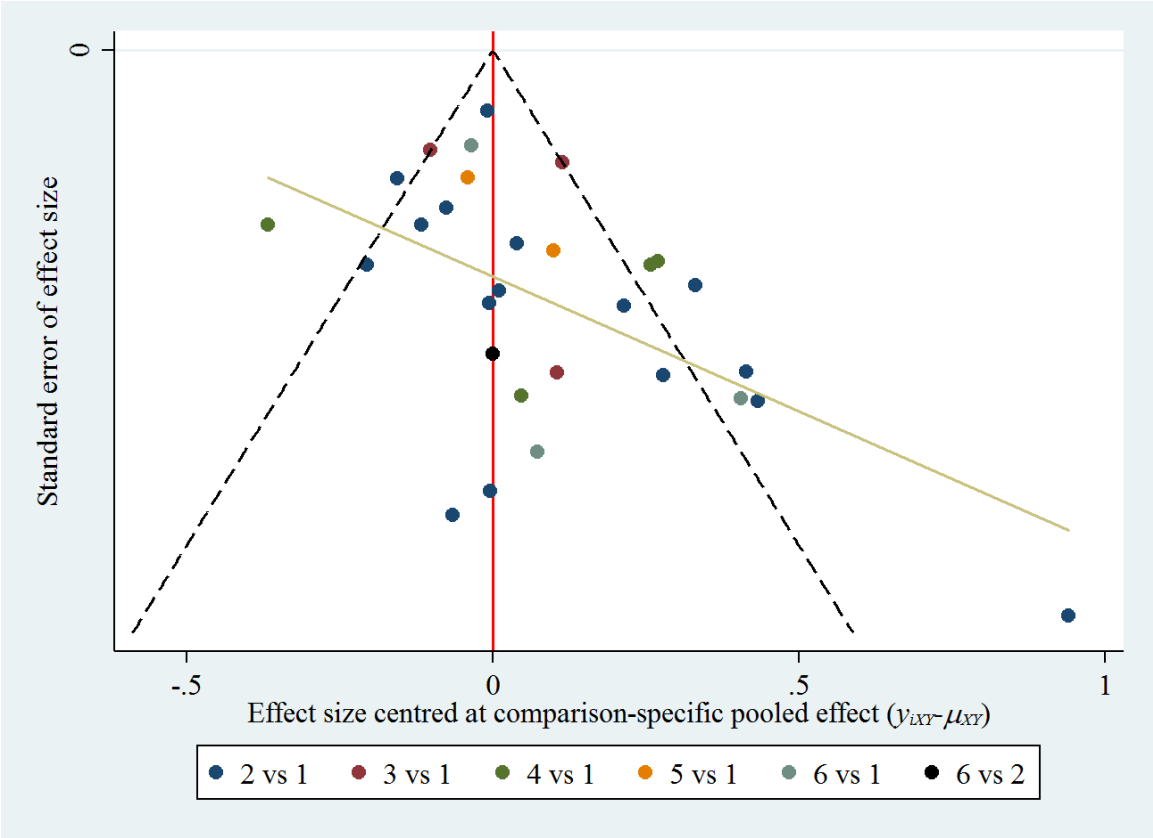
eFigure 3C. Direct meta-analysis of weight loss in kilograms



eFigure 3D. Direct meta-analysis of withdrawal from study due to drug adverse effect



eFigure 4. Publication Bias Assessed Via Funnel Plots Assessed for the 5% Weight Loss Outcome



All studies are centered on the summary effect estimate of their respective comparisons [μ_{XY} (logOR for present study)] which is represented by the vertical red line. Individual study-level effect size is represented by y_{iXY} [where X and Y are two study agents]. The yellow line represents linear regression of the comparison specific differences yi - μ_{XY} on the standard error of y_i. Outer dotted lines indicate the triangular region within which 95% of studies are expected to lie in the absence of both biases and heterogeneity (logOR ± 1.96*standard error). 16 trials for Orlistat vs. Placebo, 3 trials of Lorcaserin vs Placebo, 4 trials of Naltrexone-Bupropion vs Placebo, 2 trials of Phentermine-Topiramate vs. Placebo, 3 trials of Liraglutide vs. Placebo and 1 trial of Liraglutide vs. Orlistat are available for the 5% weight loss outcome and are included in this figure.
Key, Placebo is 1, Orlistat is 2, Lorcaserin is 3, Naltrexone-Bupropion is 4, Phentermine-Topiramate is 5 and Liraglutide is 6.

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