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Obesity Management

Discontinuation due to adverse events in randomized trials of orlistat, sibutramine and rimonabant: a meta-analysis

K. Johansson[1], K. Neovius[2], S. M. DeSantis[3], S. Rössner[1] and M. Neovius[1,4]

[1]Department of Medicine, Obesity Unit, Karolinska Institute, Stockholm, Sweden; [2]Department of Public Health Sciences, Karolinska Institute, Stockholm, Sweden; [3]Department of Biostatistics, Bioinformatics and Epidemiology, Medical University of South Carolina, Charleston, USA; [4]Department of Medicine, Centre for Pharmacoepidemiology, Karolinska Institute, Stockholm, Sweden

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Address for correspondence: Kari Johansson, Obesity Unit, M73, Department of Medicine, Karolinska Institutet (Huddinge), SE-141 86 Stockholm, Sweden. E-mail: kari.johansson@ki.se

Summary

The objective of this article was to estimate the risk of discontinuation due to adverse events in trials of orlistat, sibutramine and rimonabant. Medline, EMBASE, the Cochrane controlled trials register and reference lists of identified articles were searched from 1990 to May 2008. All randomized placebo-controlled trials of 12–24 months of duration on adults using licensed doses were included. Studies/study arms were excluded if they evaluated weight maintenance after weight loss. Trials were identified, subjected to inclusion and exclusion criteria and reviewed. Data on participants, interventions and discontinuation were extracted and trials rated for quality based on established criteria. A random effects model was used to estimate pooled risk ratios, risk differences and number needed to harm (NNH). A total of 28 trials met the inclusion criteria (16 orlistat, 7 sibutramine and 5 rimonabant). The risk ratios for discontinuation due to adverse events were significantly elevated for rimonabant (2.00; 1.66–2.41) and orlistat (1.59; 1.21–2.08), but not sibutramine (0.98, 0.68–1.41). Compared with placebo, the risk difference was the largest for rimonabant (7%, 5–9%; NNH 14, 11–19), followed by orlistat (3%, 1–4%; NNH 39, 25–83), while no significant difference was seen for sibutramine (0.2%, –3 to 4%; NNH 500). The most common adverse events leading to withdrawal were gastrointestinal for orlistat (40%) and psychiatric for rimonabant (47%). Corresponding information was unavailable for sibutramine. In conclusion, available weight loss drugs differ markedly regarding risk of discontinuation due to adverse events, as well as in underlying causes of these events. Given the large number of patients eligible for treatment, the low NNH for rimonabant is a concern.

Keywords: Adverse events, orlistat, rimonabant, sibutramine.

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Introduction

Studies of pharmaceutical agents for weight loss are commonly afflicted by high level of attrition, with only about 60% of randomized patients completing 1 year of treatment (1,2). It is likely that patients drop out to a greater extent as a result of lack of efficacy in the placebo arm, while withdrawal from adverse events ($AE_{dropout}$) is greater in the drug arm (2,3). However, no meta-analysis has evaluated overall dropouts and $AE_{dropout}$.

Three weight loss drugs were registered in the European Union (EU) until October 2008, namely orlistat (Xenical®), sibutramine (Reductil®) and rimonabant (Acomplia®). The marketing authorization for rimonabant was suspended across the EU in October 2008 by the European Medicines Agency after they concluded that the

benefits of the drug no longer outweigh its risks. Orlistat is a lipase inhibitor, sibutramine a noradrenaline-serotonin-dopamine reuptake inhibitor and rimonabant is an endocannabinoid receptor antagonist (4). It has been reported that orlistat is mainly associated with gastrointestinal side effects, such as diarrhoea, oily stools and flatulence, sibutramine with palpitations and elevations in blood pressure, and rimonabant increases the risk of psychiatric AEs such as depression and anxiety (1–3,5,6).

Previous meta-analyses have shown increased risk in the active drug group of dropout due to psychiatric and gastrointestinal events in rimonabant and orlistat studies, respectively (2,3,7). No study has hitherto presented the risk of overall $AE_{dropout}$ for orlistat, sibutramine and rimonabant. This outcome can be interpreted as a general indicator of safety and tolerability, which is highly relevant for clinical practice for this group of patients.

The aim of this meta-analysis was to assess the risk ratio (RR), risk difference (RD) and number needed to harm (NNH) of $AE_{dropout}$ for orlistat, sibutramine and rimonabant compared with placebo.

Methods

Data sources and searches

A systematic search of three bibliographic databases (Medline, EMBASE and Cochrane controlled trials register) from 1990 to 7 May 2008 was performed using the following search string: orlistat OR xenical OR sibutramine OR meridia OR reductil OR rimonabant OR acomplia OR zimulti. The search was limited to humans, randomized controlled trials, English-language publications and adults in the databases where limitations were possible (Medline and EMBASE). The reference lists of identified articles were also searched for additional studies, as were reference lists of previously published systematic reviews.

The search was conducted in January 2008 and updated 7 May 2008. Two reviewers (KJ, MN) separately screened the abstracts for inclusion or exclusion of studies. Full-text articles were retrieved from all abstracts that were potentially relevant and were reviewed independently by the two reviewers. In case of conflicting views, a third person (SR) was asked for resolve.

Study selection

Studies/study arms were included if they were randomized controlled studies of 12–24 months of duration, used licensed doses for clinical use of orlistat (360 mg d^{-1}), sibutramine (10–15 mg d^{-1}) or rimonabant (20 mg d^{-1}), and were placebo-controlled. Studies/study arms were excluded if they evaluated weight maintenance after weight loss, or used non-standard clinical doses of orlistat (180 mg), sibutramine (>15 mg) or rimonabant (5 mg).

Data extraction and quality assessment

Data on participants, interventions, discontinuation and reason for discontinuation were extracted independently by two reviewers (KJ, KN). Disagreements were resolved through discussion. In addition to data on $AE_{dropout}$, overall attrition data were extracted, as well as information on types of AE underlying the $AE_{dropout}$.

The Verhagen Delphi list (8), a criteria list for quality assessment of randomized controlled trials, was used as a guide to assess study quality of the trials. The criteria concern description of randomization, concealment of allocation, baseline comparability, specification of eligibility criteria, blinding, outcome measure presentation, and if intention-to-treat analysis was employed (for a detailed description see Appendix Table A1). In case of important differences in study quality, sensitivity analyses were performed, stratifying by the specific quality element that differed. The quality of the included studies was assessed independently by two reviewers (KJ, KN), and any differences were resolved by a third person (MN).

Data synthesis and analysis

Pooled RRs and RDs for dropout were estimated using a random effects meta-analytic model in order to handle possible heterogeneity between studies (9). In the absence of heterogeneity, the random effects model equation defaults to a fixed effects model. Heterogeneity between studies was assessed by the I^2 statistic (10), and if this exceeded 50% or was statistically significant, the reasons for heterogeneity were explored. NNH was calculated as 1/RD and confidence interval for the NNH as $1/RD_{95\%CI}$. When treatments are not significantly different, the results of the NNH confidence interval calculations become perplexing as they include negative values, but not the point estimate. Therefore, NNH are given without confidence interval in such cases, as recommended by Altman (11). For calculation of RR in studies where both groups had zero events, 0.5 was added to each cell of the 2×2 table when a zero was encountered.

As almost all studies were either conducted or funded by pharmaceutical companies, and all studies showed a significant effect for the primary outcome (weight loss), publication bias may be suspected as trials funded by for-profit organizations are more likely to report positive findings than trials funded by not-for-profit organizations (12,13). To investigate possible publication bias, funnel plots and Egger's test were used for each drug (14).

The statistical analyses were conducted using Stata v.10 (College Station, Texas).

Results

Search results

Figure 1 summarizes the results of the systematic search, which resulted in inclusion of 28 trials: 16 studies of orlistat ($n = 7038$), seven of sibutramine ($n = 1475$) and five of rimonabant ($n = 4944$; Table 1). Some of the included studies did not separate $AE_{dropout}$ from total dropout (three sibutramine (15–17) and one orlistat study (18)). All included studies were of 12–18 months of duration, and only one (19) of the studies identified in the search was of longer duration (4 years). As it did not report dropout after 12 or 24 months, it was not included.

Description of studies

Twenty-two (79%) of the included studies declared funding from the drug manufacturer. A majority of the trials limited the enrolment to higher-risk populations. Three of the rimonabant trials included only high-risk patients with either type 2 diabetes (20), dyslipidemia (21), abdominal obesity or coronary artery disease (22). Four sibutramine studies limited their enrolment to type 2 diabetics (15,16,23,24) of which one only investigated Hispanic women (24). Nine of the orlistat studies only recruited patients with type 2 diabetes (25–28), hypertension (29), hypercholesterolemia (30) or patients with one cardiovascular risk factor (hypertension, dyslipidemia, diabetes or impaired glucose tolerance) (31–33).

Patients had similar demographic profiles across trials of all three drugs, with predominantly white patients and a greater proportion of women than men in most of the studies. The mean age ranged between 41 and 59 years and the mean body mass index ranged between 33 and 38 kg m^{-2} (Table 1).

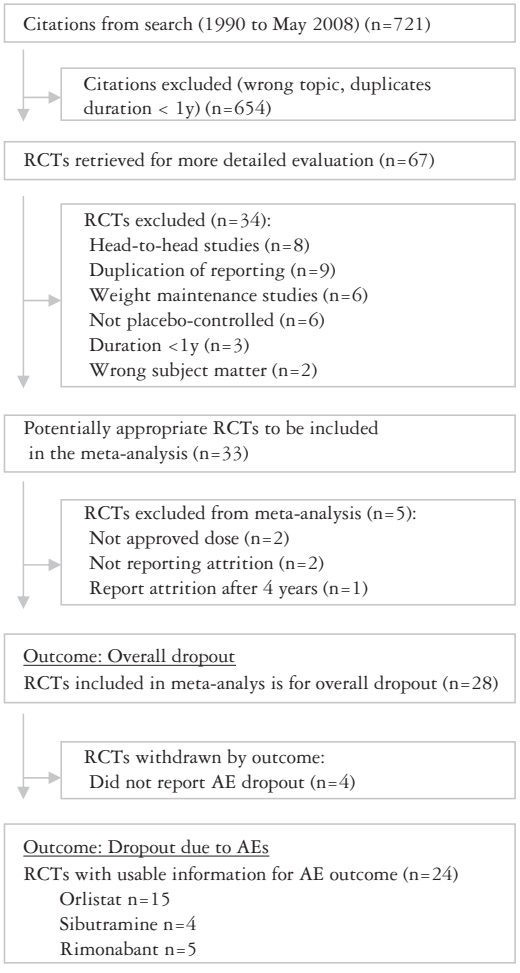

Figure 1 Flow chart of article selection process for articles reporting overall discontinuation and discontinuation due to adverse events (AE). RCT, randomized controlled trial.

Methodological quality

The majority of the studies were of similar quality and the most important limitation was the high attrition, i.e. the metameter in the current meta-analysis. Most studies did not report the randomization process, but simply stated that the patients were randomized. However, the reason for this could be that many journals have word limits and details about randomization therefore rarely described. Details on allocation concealment were also generally sparse. Three studies (17,23,34) did not specify whether they were double-blinded. These were nevertheless included in the meta-analysis, and the impact of excluding them were investigated separately in a sensitivity analysis. All studies specified the eligibility criteria and the characteristics were similar for the placebo and drug groups at baseline for all studies. All studies also reported using intention-to-treat analysis.

Absolute levels of discontinuation

The overall dropout rates were high and similar in drug and placebo groups (Table 1), with overall discontinuation rates of 30% for orlistat, 34% for sibutramine and 39% for rimonabant.

$AE_{dropout}$ showed more heterogeneity, both between study arms and between different drugs. The median $AE_{dropout}$ was highest for rimonabant (15.0%; range 12.8–17.5%), intermediate for sibutramine (9.3%; range 0–12.2%) and lowest for orlistat (7.1%; range 0–12.8%). Although the RR of $AE_{dropout}$ did not differ significantly from placebo for either orlistat or sibutramine in several studies, every single rimonabant study showed $AE_{dropouts}$ to be significantly more common in the rimonabant compared with the placebo group. Two small studies, one orlistat (34) and one sibutramine (23), reported zero $AE_{dropout}$ in both the drug and placebo arms.

Table 1 Evidence table of included studies

Study *Funding*	Follow-up (months)	Mean age (years)	Mean BMI*	Behavioural intervention (dose drug)	Run-in period	*N* randomized (drug/placebo)	Subgroup	% Attrition (AE) drug/placebo
Rimonabant (20 mg d^{-1})								
Rio-Diabetes 2006 (20) *Sanofi-Aventis*	12	56	34.2	600 kcal d^{-1} deficit diet Exercise counselling	4 weeks placebo	687 (339/348)	T2DM	32/34 (15/5)
Rio-North America 2006 (42) *Sanofi-Aventis*	12	45	37.3	600 kcal d^{-1} deficit diet Exercise counselling	4 weeks placebo	1826 (1219/607)	–	45/49 (13/7)
Rio-Lipids 2005 (21) *Sanofi-Aventis*	12	48	33.9	600 kcal d^{-1} deficit diet Exercise counselling	4 weeks placebo	688 (346/342)	Dyslipidemia	36/37 (15/7)
Rio-Europe 2005 (43) *Sanofi-Aventis*	12	45	36.0	600 kcal d^{-1} deficit diet Exercise counselling	4 weeks placebo	904 (599/305)	–	39/42 (15/9)
STRADIVARIUS (22) *Sanofi-Aventis*	18	58	35.3	Moderately reduced calorie diet	No	839 (422/417)	Abdominal obesity, CAD	28/16 (18/7)
Sibutramine (10–15 mg d^{-1})								
Wadden *et al.*, 2005 (17) *National Institute of Diabetes, Digestive and Kidney Diseases, USA*	12	44	37.9	Lifestyle modification† (15 mg, placebo)	No	115 (60/55)	–	18/15 (–/–)‡
Hauner *et al.*, 2004 (35) *Knoll Deutschland GmbH*	12	43	35.3	500–1000 kcal d^{-1} deficit diet Exercise, diet and behaviour programme (15 mg, placebo)	No	362 (180/182)	–	37/43 (12/8)
Sanchez-Reyes *et al.*, 2004 (24) *Funding? One author from Abbott*	12	44	35.1	Diet and exercise counselling (10 mg, placebo)	No	86 (44/42)	T2DM, Hispanic	45/45 (7/10)
Kaukua *et al.*, 2004 (15) *Knoll Laboratories*	12	53	35.7	700 kcal d^{-1} deficit diet (15 mg, placebo)	2 weeks placebo	236 (114/122)	T2DM	11/11 (–/–)
Redmon *et al.*, 2003 (23) *National Institute of Health, Abbott Laboratories and Slim Fast Nutrition Institute.*	12	54	38.2	500–1000 kcal d^{-1} deficit diet Exercise, diet and behaviour programme (10–15 mg, placebo)	No	59 (30/29)	T2DM	10/7 (0/0)
McNulty *et al.*, 2003 (16) *Abbott Laboratories*	12	49	36.6	Dietary counselling (15 mg, placebo)	No	132 (68/64)	T2DM	28/28
Smith *et al.*, 2001 (36) *Knoll Pharmaceuticals*	12	42	32.7	Dietary counselling (10 mg, 15 mg, placebo)	2 weeks placebo	485 (161/161/163)	–	42/49/51 (12/11/15)§

Table 1 *Continued*

Study *Funding*	Follow-up (months)	Mean age (years)	Mean BMI*	Behavioural intervention (dose drug)	Run-in period	*N* randomized (drug/placebo)	Subgroup	% Attrition (AE) drug/placebo
Orlistat (360 mg d^{-1})								
Poston *et al.*, 2006 (34) *National Institute of Health, USA*	12	41	36.0	Brief exercise, diet and behaviour counselling	No	250 (82/85)	–	34/67 (0/0)
Swinburn *et al.*, 2005 (33) *F.Hoffman-La Roche*	12	52	37.8	Fat reduced diet (25–30E%) and exercise counselling	No	339 (170/169)	Risk factor/s of CVD¶	22/19 (7/5)
Berne, 2005 (25) *F.Hoffman-La Roche*	12	59	32.7	600 kcal d^{-1} deficit diet	No	229 (111/109)	T2DM	14/14 (5/4)
Krempf *et al.*, 2003 (39) *F.Hoffman-La Roche*	18	41	36.1	Mildly reduced diet (20–30E%, never below 1200 kcal d^{-1})	15 days placebo	696 (346/350)	–	35/43 (7/3)
Derosa *et al.*, 2003 (30) *Funding?*	12	52	31.9	Controlled-energy diet programme (1500 kcal d^{-1})	No	99 (25/23)	Hypercholesterolemia	7/0 (7/0)
Bakris *et al.*, 2002 (29) *Funding? Corr. Author from Roche*	12	53	35.6	600 kcal d^{-1} deficit diet Exercise counselling	No	554 (278/276)	Hypertensive	42/61 (6/7)
Broom *et al.*, 2002 (31) *F.Hoffman-La Roche*	12	46	37.1	600–900 kcal d^{-1} deficit diet	No	531 (265/266)	Risk factor/s of CVD**	30/39 (8/4)
Miles *et al.*, 2002 (28) *F.Hoffman-La Roche*	12	53	35.4	600–800 kcal d^{-1} deficit diet and exercise counselling	No	516 (255/261)	T2DM	35/44 (10/5)
Kelley *et al.*, 2002 (27) *F.Hoffman-La Roche*	12	53	35.7	600–800 kcal d^{-1} deficit diet and exercise counselling	No	550 (274/276)	T2DM	50/54 (13/8)
Finer *et al.*, 2000 (38) *F.Hoffman-La Roche*	12	41	36.8	600–900 kcal d^{-1} deficit diet	4 weeks placebo	228 (114/114)	–	36/42 (8/6)
Hauptman *et al.*, 2000 (18) *Funding? Corr. Author from Roche*	12	42	36.0	Prescribed energy programme 1200–1500 kcal d^{-1}, exercise; educational video	4 weeks placebo	422 (210/212)	–	28/42 (–/–)
Lindgarde, 2000 (32) *F.Hoffman-La Roche*	12	53	33.2	600–900 kcal d^{-1} deficit diet; exercise counselling; educational video	2 weeks placebo	376 (190/186)	Risk factor/s of CVD¶	16/12 (5/3)
Rossner *et al.*, 2000 (40) *F.Hoffman-La Roche*	12	44	35.1	600 kcal d^{-1} deficit diet	4 weeks placebo	487 (244/243)	–	26/35 (6/2)
Davidson *et al.*, 1999 (37) *F.Hoffman-La Roche*	12	46	37.1	600–800 kcal d^{-1} deficit diet and exercise counselling	4 weeks placebo	892 (668/224)	–	31/38 (9/4)
Hollander *et al.*, 1998(26) *F.Hoffman-La Roche*	12	55	34.3	500 kcal d^{-1} deficit diet	5 weeks placebo	322†† (159/163)	T2DM	15/28 (7/14)
Sjostrom *et al.*, 1998 (41) *F.Hoffman-La Roche*	12	45	36.1	600–900 kcal d^{-1} deficit diet	4 weeks placebo	688 (345/343)	–	17/23 (7/3)§§

*Calculated as weight (kg) height (m)$^{-2}$.

¶T2DM, hypercholesterolemia and/or hypertension.

**Impaired glucose tolerance, dyslipidemia and/or hypertension.

††Unclear how many patients that were randomized. Table 1 shows that 162 were randomized, but in the text and flow-chart for dropout, the number randomized for orlistat is 163.

AE, adverse event; CAD, coronary artery disease.

The $AE_{dropout}$ in the placebo groups differed between compounds, with the median proportions being the lowest for orlistat studies (4.0%; range 0–14.5%), intermediate for rimonabant (7.2%; 5.5–9.2%) and highest for sibutramine (8.9%; 0–14.7%).

Risk ratios, risk differences and number needed to harm

Compared with placebo, the pooled RRs (Fig. 2) and RDs (Fig. 3) for $AE_{dropout}$ were significantly elevated for both rimonabant and orlistat, but not sibutramine, with little heterogeneity for rimonabant and sibutramine. Heterogeneity of moderate magnitude (10) was seen for orlistat for the RR ($I^2 = 36.3\%$; $P = 0.08$; Fig. 2) and the RD ($I^2 = 39.7\%$; $P = 0.06$; Fig. 3), but the associations did not reach statistical significance. After stratification for non-diabetic ($n = 11$) and diabetic ($n = 4$) study groups, no further heterogeneity could be detected among studies of non-diabetics ($I^2 = 0.0\%$; $P = 0.52$). For diabetics, significant heterogeneity was detected ($I^2 = 71.3\%$; $P = 0.02$), with the study by Hollander *et al.* (26) showing a significantly lower risk of orlistat regarding $AE_{dropout}$ (RR 0.51; 0.26–0.99; RD –0.07; –0.14–0), greatly contrasting with the other orlistat studies.

The NNH was the lowest for rimonabant (14; 11–19), followed by orlistat (39; 25–83) and sibutramine (500; non-significant).

For dropout from any cause, there was little difference between drug and placebo groups. The point estimates compared with placebo were lower for orlistat (0.78; 0.71–0.86) and sibutramine (RR 0.90; 95% CI 0.79–1.04), and higher for rimonabant (1.05; 0.87–1.26), but reached statistical significance only for orlistat.

Reasons for discontinuations

The causes of dropout due to any cause and AEs are presented in Table 2. These numbers ought to be interpreted with some caution because of lack of reporting in several studies. In the rimonabant studies, STRADIVARIUS did not report reasons of discontinuation other than AEs. Four

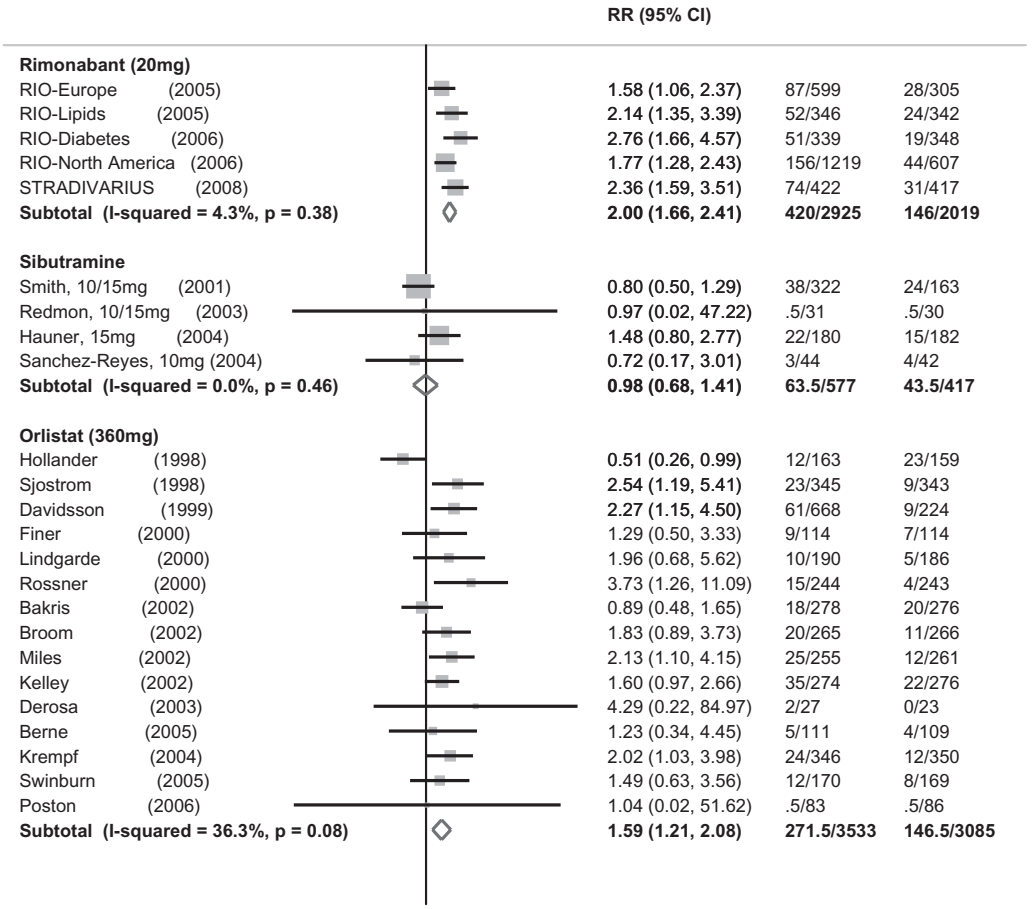

Figure 2 Forest plot of the risk ratio (RR) of dropout from adverse events in the drug vs. the placebo groups in rimonabant, sibutramine and orlistat trials. *0.5 was added to each cell of the 2 × 2 table when a zero was encountered in the analysis of both the treatment and control groups.

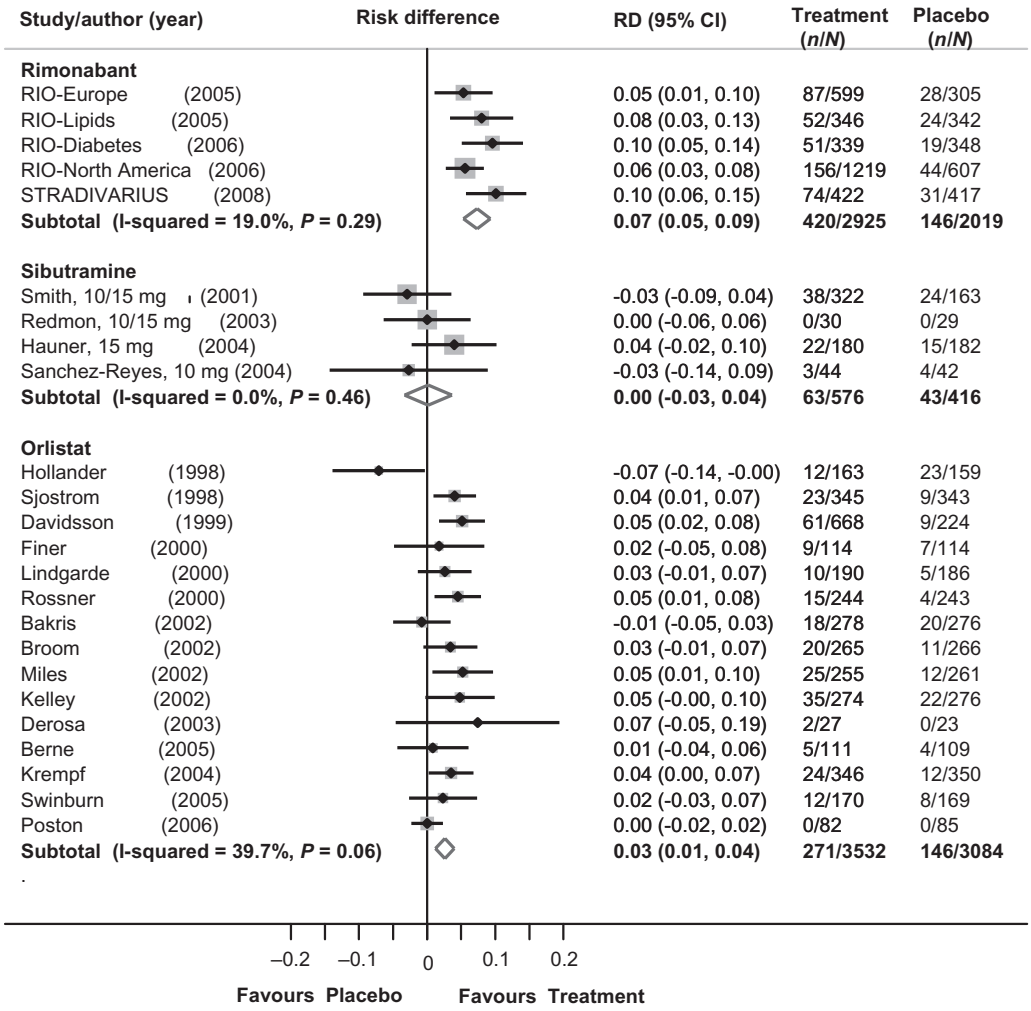

Figure 3 Forest plot of the risk difference (RD) of dropout from adverse events in the drug vs. the placebo groups in rimonabant, sibutramine and orlistat trials.

(23,24,35,36) of the seven sibutramine studies and 13 (25,27–33,37–41) of the 16 orlistat studies reported the reasons for discontinuation. In addition, some of the orlistat trials only reported the most common reasons of dropout, leading to a large number of reasons being categorized as 'other'.

In the drug groups, the most common reasons for withdrawal were AEs and patient request in rimonabant studies, and poor compliance and AEs were most common in sibutramine studies. In orlistat studies, similar percentages (≈25%) discontinued as a result of AEs, patient request and loss to follow-up. In the placebo groups, withdrawal due to patient request was most common in the rimonabant and orlistat trials, while poor compliance was most common in the sibutramine trials.

Dropout due to lack of effectiveness was specified in four rimonabant (20,21,42,43), one sibutramine (36) and five orlistat studies (27,28,37,39,40). Patients tended to drop out less frequently as a result of lack of effectiveness compared with placebo when treated with orlistat (RR 0.49, 0.24–1.02), sibutramine (0.35, 0.14–0.91) and rimonabant (0.52, 0.35–0.78).

Of the three drugs, only rimonabant described the reasons for $AE_{dropout}$ in all trials. The main reason for $AE_{dropout}$ was psychiatric disorders in both the drug and placebo groups, but with a greater proportion in the drug group. Depression/depressed mood was the most common psychiatric cause for $AE_{dropout}$ in both arms, followed by anxiety and sleep disorder. Of the four sibutramine trials reporting $AE_{dropout}$, only one (24) reported the underlying causes. In the drug group, three withdrew because of AEs (one blood pressure increase, one hypertriglyceridaemia, one intermittent abdominal pain) and, in the placebo group, four withdrew because of AEs (three blood pressure increases, one insomnia). In the orlistat trials, only the number of AEs due to gastrointestinal problems was

Table 2 Reason for dropout and type of adverse events (AEs) underlying discontinuation due to AE in randomized controlled trials of rimonabant, sibutramine and orlistat

All causes of dropout	Rimonabant		Sibutramine		Orlistat	
	Drug *n* (%)	Placebo *n* (%)	Drug *n* (%)	Placebo *n* (%)	Drug *n* (%)	Placebo *n* (%)
N (studies reporting withdrawal)	2925	2019	818	657	3742	3296
N withdrawals (% of total *N*)	1134 (38.8)	735 (36.4)	277 (33.9)	223 (33.9)	1116 (30)	1247 (38)
Studies reporting underlying withdrawal causes*	1017	670	235	183	1005	1056
AE	346 (34)	115 (17.2)	63 (26.8)	43 (23.5)	259 (26)	122 (12)
Lack of effectiveness	46 (4.5)	48 (7.2)	7 (3.0)	10 (5.5)	34 (3)	57 (5)
Poor compliance	86 (8.5)	66 (9.9)	120 (51.1)	80 (43.7)	72 (7)	72 (7)
Patient request	389 (38.2)	327 (48.8)	14 (6.0)	16 (8.7)	251 (25)	382 (36)
Lost to follow-up	111 (10.9)	94 (14.0)	11 (4.7)	9 (4.9)	227 (23)	202 (19)
Other	39 (3.8)	20 (3.0)	20 (8.5)	25 (13.7)	162 (16)	221 (21)
Dropout due to Aes†						
N (studies reporting withdrawal due to AE)	2925	2019	576	416	3532	3084
N AEs (% of total *N*)	420 (14.4)	146 (7.2)	63 (10.9)	43 (10.3)	271 (7.7)	146 (4.7)
Studies reporting underlying AE causes‡	420	146	–	–	155	87
Psychiatric disorders	197 (47)	54 (37)	–	–	–	–
Nervous system disorders	71 (17)	16 (11)	–	–	–	–
Gastrointestinal disorders	71 (17)	9 (6)	–	–	62 (40)	21 (24)

*$n_{rimonbant}$ = 4 out of 5, $n_{sibutramine}$ = 4 out of 7, $n_{orlistat}$ = 13 out of 16.
†The trials only report the AEs of the main organ system and some AEs will therefore be 'missing'. These have not been assigned as 'other reasons' as one patient may report several reasons for discontinuation.
‡Only one sibutramine study described the reason of withdrawal due to AE and is described in the text. Nine orlistat trials described withdrawal due to gastrointestinal problems.

specified in eight of the trials (26,29,31,33, 37,38,41,44). They constituted 40% and 24% of the $AE_{dropout}$ in the drug and placebo arms, respectively.

Publication bias

No evidence of publication bias could be found for any of the three drugs based on the Egger's test ($p_{orlistat} = 0.53$, $p_{sibutramine} = 0.99$, $p_{rimonbant} = 0.23$) nor by visual inspection of funnel plots (Appendix Fig. A1). A limitation for sibutramine and rimonabant was, however, the small number of trials.

Sensitivity analyses

There was no change in the result of the pooled RRs or RDs when excluding the sibutramine or orlistat trials that did not specify whether they were double-blinded or not (Appendix Table A3) (17,23,34).

Exclusion of the 18-month STRADIVARIUS study of rimonabant, the only study with a study duration greater than 12 months, did not change the RD and NNH estimates, but a marginal reduction of the RR from 2.00 (1.66–2.41) to 1.92 (1.55–2.38) resulted.

Discussion

We searched the literature for placebo-controlled randomized trials of weight loss drugs reporting discontinuation due to AEs. A total of 24 trials reported $AE_{dropout}$, although an additional four reported dropout due to any cause. Significant risk increases of $AE_{dropout}$ were seen for both rimonabant and orlistat, but not sibutramine. Given the large number of patients eligible for treatment by these compounds, the NNH of 14 for rimonabant is a concern.

Previous meta-analyses have reported discontinuation due to gastrointestinal AEs and psychiatric AEs to be significantly elevated for orlistat and rimonabant, respectively (2,3). None of the previously published meta-analyses have investigated discontinuation due to AEs in patients treated with sibutramine. Although these specific AE outcomes are of great interest, so is the overall AE discontinuation rate, which previously only has been described for rimonabant in a Cochrane review (not including the STRADIVARIUS study) (1). For specific cause of dropout in rimonabant studies, Christensen *et al.* (3) reported an NNH for discontinuation due to depressive mood disorders and anxiety to be 49 (19–316) and 166 (47–3716), respectively. They also reported that the NNH for occurrence of (not discontinua-

tion due to) any AE and any severe AE to be 25 (17–58) and 59 (27–830), respectively. In a Cochrane review of orlistat, Padwal *et al.* (2) reported the RD of discontinuation due to gastrointestinal AEs to be 0.02 (0.01–0.04), corresponding to an NNH of 50. For discontinuation due to any AE, we found an NNH of 14 and 50 for rimonabant and orlistat, respectively. Only four sibutramine trials matching our search criteria reported $AE_{dropout}$, and the pooled risk did not differ from that observed in the placebo arms. The placebo rate was, however, high in both sibutramine and rimonabant compared with orlistat trials. The reason for this is unclear, but may reflect differences in the ascertainment of AEs.

It is important to distinguish AEs leading to discontinuation caused by orlistat from those caused by rimonabant, and also to emphasize that there may be important AEs not resulting in discontinuation associated with sibutramine treatment. The most common AE caused by orlistat is diarrhoea and other gastrointestinal problems directly associated with non-compliance to the dietary recommendations given along with the orlistat prescription. The mechanism of action of orlistat is blocking of pancreatic lipase, which leads to fat malabsorption. If fat intake is high, oily stools result with high certainty. If fat intake is reduced, the risk of such problems is low. For rimonabant, on the other hand, 47% of $AE_{dropout}$ were from psychiatric causes, including suicidal ideation. It should further be kept in mind that the patients enrolled in the trials from which the data originate were highly selected, with history of severe depression and present severe psychiatric illness being exclusion criteria. Hence, the NNH in clinical practice may be even lower. For sibutramine, the AE that has received most attention is the noradrenergic effect on blood pressure and heart rate. However, it does not seem as if this has led to a greater discontinuation rate, as no difference was found between $AE_{dropout}$ in the sibutramine and placebo arms. A word of caution may be warranted, as only four of the seven identified studies reported $AE_{dropout}$ separated from overall dropouts. Furthermore, slight blood pressure elevations may not lead to treatment discontinuation but still remain a concern.

Rimonabant has not been licensed for use in the USA and was recently withdrawn in the EU after European Medicines Agency concluded that the benefits of the drug no longer outweigh its risks. The very low NNH found in this study for discontinuation due to any AE and previous findings regarding psychiatric AEs specifically highlight these risks. It is possible that the risk/benefit ratio is different in certain subgroups of patients who may benefit from treatment, but these groups remain to be characterized. In the large trials, significant risk elevations for discontinuation due to AEs were seen in general obesity patients, diabetics and patients with dyslipidemia.

The main limitation of this study is the indirect nature of the comparisons. Head-to-head studies including the three compounds are the only way of achieving full comparability. Head-to-head studies including rimonabant have not yet emerged, but several randomized controlled trials have compared sibutramine vs. orlistat directly (45). Although four such studies have presented data on dropout from any cause, only one provided $AE_{dropout}$ data, leaving little to compare the current results with. A second limitation was the lack of reporting of $AE_{dropout}$ in three sibutramine trials and one orlistat trial. Third, as mentioned in previous Cochrane reviews and other meta-analyses (1–3), the total discontinuation rates were high, leaving a possibility for many AEs to go undetected; if patients discontinue because of other reasons, their time at risk for $AE_{dropout}$ decreases. Fourth, reporting of AEs in different studies, both within and between drugs, could possibly vary. However, as all studies were randomized, this is unlikely to have any larger impact on the results. Fifth, the potential for publication bias cannot be overlooked, with studies with even higher attrition possibly unpublished, as higher attrition may have influenced the primary outcome, i.e. weight loss, negatively as well. Almost all trials were funded by the manufacturers, which may increase the risk of publication bias and reporting of positive results (12,13). However, no such indications could be found in funnel plots or by use of Egger's test, although the number of studies was small. Finally, extrapolation to adolescents, the elderly and non-white subjects should be made with caution, as most of the included studies focused on middle-aged white, predominantly female, patients.

In summary, we found high overall attrition rates in both drug and placebo groups, and significantly higher $AE_{dropout}$ in patients treated with rimonabant and orlistat than placebo. Despite patients in the included trials being highly selected compared with what may be encountered in primary care, the NNH was as low as 14 for rimonabant. Head-to-head trials comparing all three compounds would be of interest to improve the validity of comparisons, as the available evidence today is almost exclusively indirect.

Conflict of Interest Statement

No conflict of interest was declared.

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Appendix

Table A1 The Verhagen Delphi list (8)

1. Treatment allocation	
(a) Was a method of randomization performed?	Yes/No/Don't know
(b) Was the treatment allocation concealed?	Yes/No/Don't know
2. Were the groups similar at baseline regarding the most important prognostic indicators?	Yes/No/Don't know
3. Were the eligibility criteria specified?	Yes/No/Don't know
4. Was the outcome assessor blinded?	Yes/No/Don't know
5. Was the care provider blinded?	Yes/No/Don't know
6. Was the patient blinded?	Yes/No/Don't know
7. Were point estimates and measures of variability presented for the primary outcome measures?	Yes/No/Don't know
8. Did the analysis include an intention-to treat analysis?	Yes/No/Don't know

Table A2 Excluded studies of 1-year duration or more

Study	Behavioural intervention	*N*	Reason not included
SIBUTRAMINE (15–20 mg d^{-1})			
Porter *et al.*, 2004 (46)	Weight management programme	588 (296, 296 per arm)	Not reporting dropout
McMahon *et al.*, 2002 (47)	Dietary advice	220 (146,74 per arm)	20-mg sibutramine
McMahon *et al.*, 2000 (48)	Minimal behavioural intervention	224 (150,74 per arm)	20-mg sibutramine
ORLISTAT (360 mg d^{-1})			
Torgerson *et al.*, 2004 (19)	Lifestyle change	3305 (1650,1655 per arm)	Only dropout after 4 years
Lucas *et al.*, 2003 (49)	Reduced diet	444 (256, 188 per arm)	Not reporting dropout

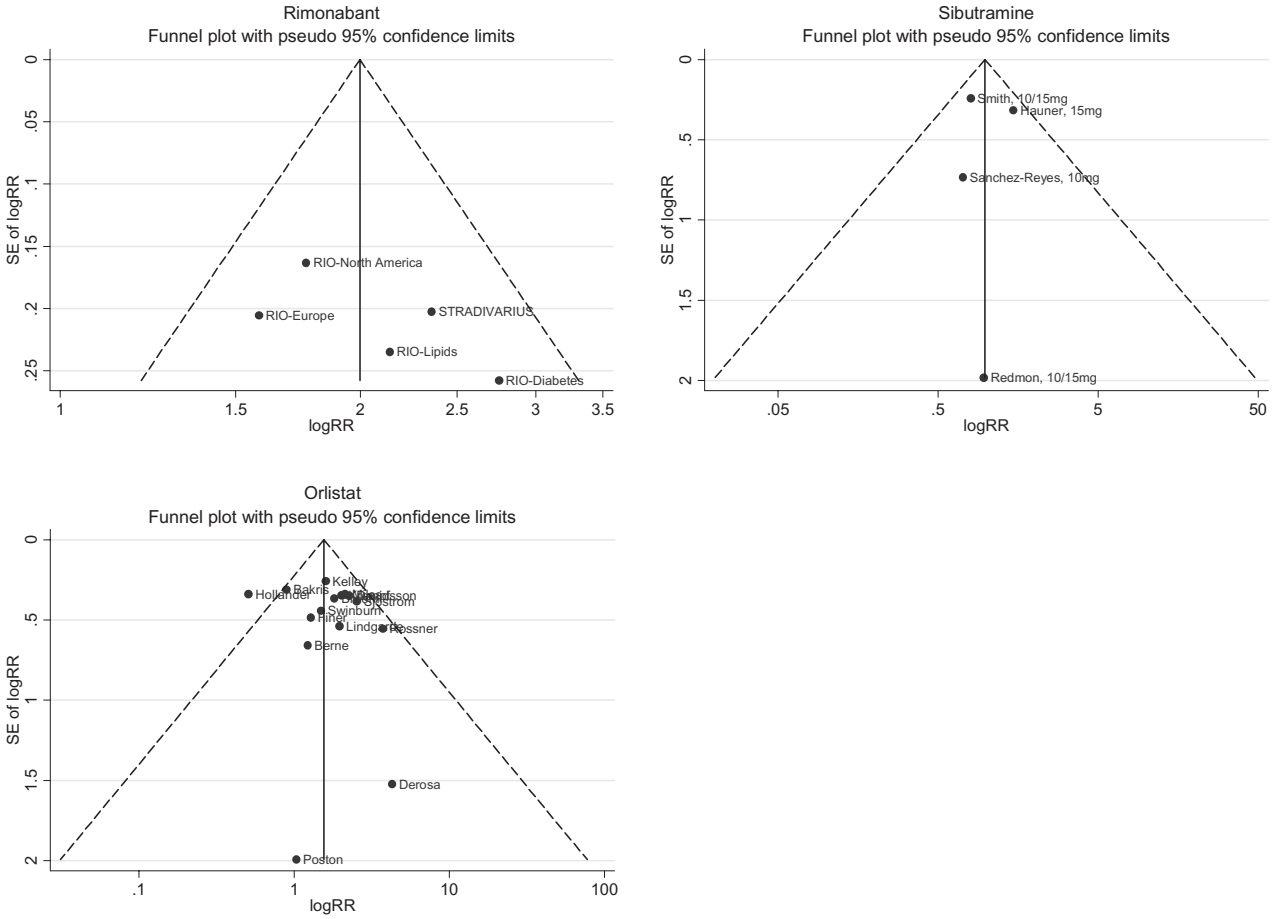

Figure A1 Funnel plot, with pseudo 95% confidence limits, investigating publication bias.

Table A3 Meta-analysis results for risk ratios and risk differences of dropout from all causes and adverse events in the drug group vs. the placebo group in the sensitivity analysis **excluding orlistat and sibutramine trials** that did not specify whether they were double-blinded*

	Exclusion of three trials not stating whether they were double-blinded Drug vs. placebo							
	All-cause dropout				Adverse event dropout			
	Studies (*n*)	Unweighted proportion	Risk difference (95% CI)	Risk ratio (95% CI)	Studies (*n*)	Unweighted proportion	Risk difference (95% CI)	Risk ratio (95% CI)
Orlistat	15	30% vs. 40%	–0.06 (–0.10,–0.03)	0.80 (0.73,0.88)	14	8% vs. 5%	0.03 (0.02,0.04)	1.59 (1.21,2.10)
Sibutramine	5	36% vs. 37%	–0.03 (–0.08,0.01)	0.89 (0.78,1.03)	3	12% vs. 11%	0.00 (–0.05,0.05)	1.00 (0.64,1.56)
	All trials in meta-analysis Drug vs. placebo							
Orlistat	16	30% vs. 38%	–0.07 (–0.11,–0.03)	0.78 (0.71,0.86)	15	8% vs. 5%	0.03 (0.01,0.04)	1.59 (1.21,2.08)
Sibutramine	7	34% vs. 34%	–0.02 (–0.06,0.02)	0.90 (0.79,1.04)	4	11% vs. 10%	0.00 (–0.03,0.04)	0.98 (0.68,1.41)

*Pooled risk ratios and risk differences calculated by use of a random effects meta-analytic model. Crude (%) = total number of dropouts divided by total number of subjects in all studies.

