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Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials

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Summary

Background Since the prevalence of obesity continues to increase, there is a demand for effective and safe anti-obesity agents that can produce and maintain weight loss and improve comorbidity. We did a meta-analysis of all published randomised controlled trials to assess the efficacy and safety of the newly approved anti-obesity agent rimonabant.

Methods We searched The Cochrane database and Controlled Trials Register, Medline via Pubmed, Embase via WebSpirs, Web of Science, Scopus, and reference lists up to July, 2007. We collected data from four double-blind, randomised controlled trials (including 4105 participants) that compared 20 mg per day rimonabant with placebo.

Findings Patients given rimonabant had a 4·7 kg (95% CI 4·1–5·3 kg; p<0·0001) greater weight reduction after 1 year than did those given placebo. Rimonabant caused significantly more adverse events than did placebo (OR=1·4; p=0·0007; number needed to harm=25 individuals [95% CI 17–58]), and 1·4 times more serious adverse events (OR=1·4; p=0·03; number needed to harm=59 [27–830]). Patients given rimonabant were 2·5 times more likely to discontinue the treatment because of depressive mood disorders than were those given placebo (OR=2·5; p=0·01; number needed to harm=49 [19–316]). Furthermore, anxiety caused more patients to discontinue treatment in rimonabant groups than in placebo groups (OR=3·0; p=0·03; number needed to harm=166 [47–3716]).

Interpretation Our findings suggest that 20 mg per day rimonabant increases the risk of psychiatric adverse events—ie, depressed mood disorders and anxiety—despite depressed mood being an exclusion criterion in these trials. Taken together with the recent US Food and Drug Administration finding of increased risk of suicide during treatment with rimonabant, we recommend increased alertness by physicians to these potentially severe psychiatric adverse reactions.

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Introduction

The prevalence of obesity continues to increase worldwide,[1] and there is a demand for effective and safe anti-obesity agents that can produce and maintain weight loss and improve comorbidities. Obesity is producing several health-related consequences.[2,3] Weight loss of 5–10% of bodyweight, irrespective of how it is achieved, is associated with improvements in cardiovascular risk profiles and reduced incidence of type 2 diabetes.[2,4,5] Non-pharmacological treatment can be effective, but success rate in the long term is low.[6,7] Obesity guidelines recommend that anti-obesity pharmacotherapy is to be regarded as a potentially important adjunctive treatment to non-pharmacological therapy for patients with a body-mass index (BMI) greater than or equal to 30 kg/m², or a BMI of 27·0–29·9 kg/m² with one or more major obesity-related comorbidities.[2] The anti-obesity agent rimonabant (acomplia, Sanofi-Aventis, Paris, France), has been approved by the European Agency for the Evaluation of Medicinal Products (EMEA) in June, 2006, and is available in Argentina, Austria, Denmark, Finland, Germany, Ireland, Norway, Sweden, Greece, and the UK.

Rimonabant is a selective antagonist of the cannabinoid type 1 receptor, and it is the first member of a new class of compounds that targets the endocannabinoid system, which has been shown to be involved in the central and peripheral regulation of food intake and the CNS rewarding system.[8,9] So far, four clinical trials on rimonabant have been published,[10–13] and all show an increased weight loss compared with placebo of 4–6 kg over 6–12 months, with few tolerability or safety concerns. In the Rimonabant in Obesity (RIO)-Europe study,[10] the investigators concluded that rimonabant was generally well tolerated with mild and transient side-effects. However, the individual trials showed trends to increases in depressed mood, depression, and severe adverse events. Furthermore, because patients with serious mental illness were excluded from the RIO programme, the estimates of the potential psychiatric side-effects of the drug are conservative.[14] Rimonabant was recently assessed by the US Food and Drug Administration (FDA), and coinciding with the submission of this paper, the FDA's Advisory Committee unanimously concluded that more detailed safety information about rimonabant in larger patient numbers over the long term was needed before the drug could be approved.[15]

We aimed to do a meta-analysis of rimonabant studies to assess efficacy and safety of the drug, emphasising psychiatric adverse events such as depressive disorders that could potentially lead to suicide.

Methods

Search strategy and selection criteria
Five bibliographic databases (Medline from mid-1950s, Embase from 1980, Web of Science from 1945–54, Scopus from 1966, and the Cochrane Library) were searched up

to November, 2006, for randomised controlled trials investigating rimonabant and weight loss. Search terms were ("rimonabant" OR "Acomplia" OR ["antagonist" AND "cannabinoid" AND "receptor"]) AND ("obesity" OR "weight loss" OR "overweight" OR "weight reduction" OR "slimming") AND "controlled". All clinical trials relating rimonabant to weight loss were identified. The reference lists of review articles and of included studies were searched to identify other potentially eligible studies. There was no limitation on language.

Only double-blind, randomised controlled trials using rimonabant for weight loss in overweight or obese participants were eligible for inclusion. Included studies had to first, enrol patients with BMI levels of 30 kg/m² or greater or 27 kg/m² or greater plus one or more obesity-related comorbidity, and second, include a placebo control group. Studies assessing any of the following terms were included: "rimonabant", "acomplia", "(endo) cannabinoid antagonist", "SR141716", and "SR141716A" (phase I and II codes for rimonabant).

Data extraction and quality assessment

Two investigators (PKK, EMB) did the literature search and reviewed the results. Full articles were retrieved for further assessment if the information in the abstract suggested that the study: (1) compared rimonabant with placebo or any other intervention; (2) included participants who where overweight or obese; and (3) assessed weight loss (in kg) as outcome. Two investigators (RC, PKK) were responsible for the assessment and extraction of data. The efficacy outcomes were the difference in mean weight change and the number of individuals achieving at least 10% weight reduction handled as a dichotomous responder criterion. The Jadad assessment method (Instrument to Measure the Likelihood of Bias)[16] for quality assessment of randomised controlled trials was used as a guide to assess study quality. Quality of the included studies was assessed independently by two reviewers (RC, PKK) and any differences were resolved at the subsequent consensus meeting (AA).

Statistical analysis

We calculated the weighted mean difference for the difference in mean weight change, standardised mean difference for the hospital anxiety and depression scale (HADS) score, and odds ratios (OR) for dichotomous outcomes. Since asymptotic results can be unreliable when the distribution of the dichotomous data is sparse (as would be expected for serious adverse events, depression, and anxiety), we used exact methods for the calculation of the confidence intervals around the ORs. However, since the confidence coefficient for these exact confidence limits is not necessarily exact on a nominal level, these confidence limits are conservative, which is the recommended approach when handling sparse data.[17] The SAS procedure PROC FREQ computes exact

confidence limits for the OR.[18] We applied the Fisher's exact test to calculate the exact probabilities of the possible (2×2) tables, enabling us to estimate the Wald test associated variance, corresponding to the ratio of its estimate ($\log_e$-OR) to its standard error. Accordingly, these variances are applicable for subsequent mixed-effects meta-analysis. All analyses were based on data reported as intention to treat, for which all RIO studies applied the last observation carried forward (LOCF) techniques for missing outcome data.

To combine the individual study results we did meta-analyses using SAS software (version 9.1.3), applying a restricted maximum likelihood (REML) method to estimate the between study variance and the combined efficacy and safety data.[19,20] We examined heterogeneity between trials with a standard Q-test statistic (testing the hypothesis of homogeneity),[21] and present the I^2 value, which can be interpreted as the percentage of total variation across several studies due to heterogeneity.[22] On the basis of combined OR values, we estimated the number needed to treat and the number needed to harm, with 95% CIs, since this method enables direct translation into clinical practice; these data were calculated on the basis of the combined OR measure, applying the overall event rate in the placebo group as a proxy for baseline risk.[23] To investigate potential sources of clinical heterogeneity, we assessed the extent to which study-level variables were associated with safety by fitting REML-based metaregression models.[24]

227 citations from Medline, Embase, and other databases

170 studies excluded because they did not include rimonabant and weight loss

57 potentially relevant studies identified and screened for retrieval

51 studies excluded
 22 lifestyle modification trials (not a drug study)
 14 animal models
 2 same clinical design of already included studies
 5 non-research reports
 1 results of 2 year treatment of already included studies
 7 duplicate, preliminary, or subgroup analyses of already included studies

6 potentially appropriate randomised controlled trials to be included

2 studies excluded
 1 study in progress
 1 meta-analysis of trials already included

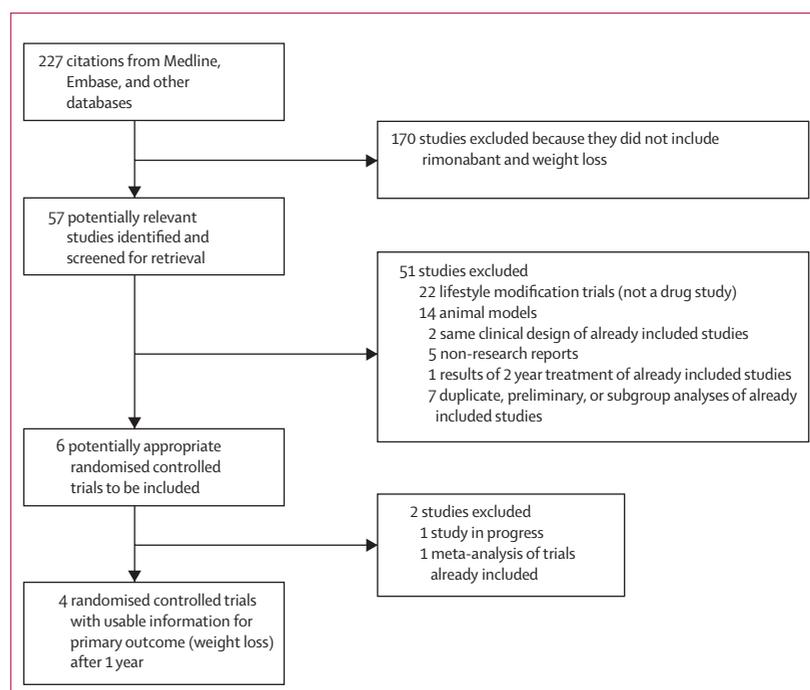4 randomised controlled trials with usable information for primary outcome (weight loss) after 1 year

Figure 1: **Flow chart of the search strategy and selection of trials**
Webfigure shows the full list of excluded studies.

	Year	ITT* individuals	Women	Age (years)	BMI (kg/m²)	Weight (kg)	Glucose (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	Metabolic syndrome	Smokers	Definite sample size (ITT)	
												n_E	n_c
RIO-Europe[10]	2005	904	722 (80%)	44·7 (11·8)	36·0 (5·8)	101·1 (19·8)	5·27 (0·70)	1·45 (0·86)	1·27 (0·33)	372 (41%)	162 (18%)	599	305
RIO-Lipids[11]	2005	688	411 (60%)	47·7 (10·0)	33·9 (3·4)	96·1 (15·2)	5·29 (0·62)	2·08 (1·18)	1·11 (0·25)	361 (52%)	114 (17%)	346	342
RIO-North America[12]	2006	1826	1483 (81%)	45·3 (11·7)	37·3 (6·3)	103·7 (20·8)	5·11 (0·61)	1·53 (0·88)	1·27 (0·33)	611 (33%)	182 (10%)	1219	607
RIO-Diabetes[13]	2006	687	360 (52%)	55·4 (8·6)	34·2 (3·6)	97·3 (14·8)	8·35 (2·20)	2·02 (1·17)	1·16 (0·26)	538 (78%)	81 (12%)	339	348

Data are number (%) or mean (SD). ITT=intention to treat. BMI=body-mass index. TG=triglycerides. HDL-C=high-density lipoprotein cholesterol. *The number of ITT individuals is based on patients allocated to the rimonabant 20 mg and placebo groups, respectively; patients receiving rimonabant 5 mg were excluded. n_E and n_c are the number of individuals in the exposed and control group (ie, rimonabant and placebo), respectively.

Table 1: Summary of baseline characteristics of all participants in the eligible trials
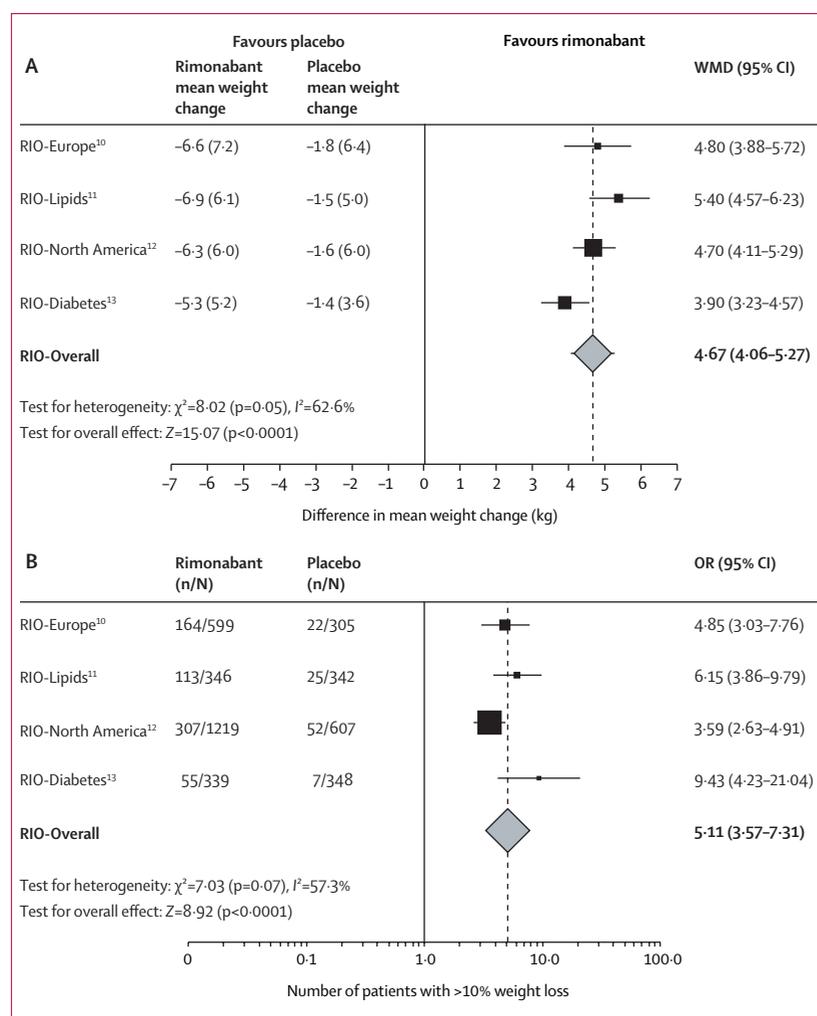
Figure 2: Efficacy of rimonabant compared with placebo in overweight individuals
(A) Mean weight change. (B) Number of participants achieving a weight loss of 10% or more during 1 year. Every square represents the individual study's weight loss estimate with 95% CI indicated by horizontal lines. Square sizes are directly proportional to the precision of the estimate. WMD=weighted mean difference.

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results
We identified 227 studies in the database searches (figure 1). If a study contained phases for both weight loss and weight maintenance, we included only data from the weight loss phase. After review of the identified studies, 57 were identified and retrieved for further scrutiny. We included only four randomised placebo-controlled, double-blind trials,[10–13] which were of high quality (Jadad assessment score of about 5) and met the inclusion criteria. All included trials were in the RIO programme (RIO-Europe,[10] RIO-Lipids,[11] RIO-North America,[12] and RIO-Diabetes[13]), which investigated the efficacy and safety of rimonabant for treatment of obesity, diabetes, and metabolic disorders in overweight and obese individuals.

Table 1 shows the average baseline characteristics of the included studies. The trials were undertaken between 2001 and 2005 (published in 2005–06), and varied in participant size (table 1). All trials were multicentre studies and 4105 participants were assessed in total (focusing solely on the intention-to-treat individuals receiving either 20 mg per day or placebo). The length of the trials varied from 12 months to 24 months. However, all the studies published detailed statistics after 1 year of treatment. The manufacturer Sanofi-Aventis sponsored all the included studies. The studies had the same primary endpoint and similar secondary endpoints (adapted to the specific population recruited in the study and the tests undertaken). The scheduled visits were planned at the same time-points. After a weight maintenance diet for 4 weeks, patients who were compliant to dietary instruction and coping with therapy were randomly assigned to placebo, rimonabant 5 mg per day, or rimonabant 20 mg per day, in addition to a hypocaloric diet (600 kcal per day deficits).

The objectives of all the available studies were to establish the long-term (1 year) efficacy and safety of rimonabant in the treatment of obesity and metabolic disorders related to obesity.

Since all analyses were based on published intention-to-treat (LOCF) data, we extracted the exact number of patients randomly assigned and who completed the first year of treatment from the studies' trial profiles (CONSORT recommended).[25] The OR values associated with the individual study's 2×2 cross-table of reported adherent individuals (who completed 1 year of treatment) were consistent when rimonabant was compared with placebo ($I^2 \leq 0\%$). There was no reason to suggest a rejection of the hypothesis of homogeneity based on the Cochran Q test ($Q=0.65$; $p=0.89$), with the likelihood of completing the 1 year therapy with rimonabant or placebo being equal (OR=1.12; 95% CI 0.99–1.28). These data correspond to 1486 (59%) of the individuals randomly assigned to rimonabant for 1 year, and 932 (58%) taking placebo.

Compared with placebo, rimonabant therapy resulted in a greater reduction in bodyweight of 4.7 kg (95% CI 4.1–5.3) than did placebo (p<0.0001). All studies reported greater reductions in bodyweight in the rimonabant group than in the placebo group (figure 2). Some heterogeneity between the individual efficacy estimates was evident when we compared the magnitude of weight reduction ($Q=8.02$; $p=0.05$), corresponding to a high effect on the combined estimate ($I^2=62.6\%$). Individuals receiving rimonabant therapy were five times more likely to achieve at least 10% weight loss (OR=5.1 [95% CI 3.6–7.3]; p<0.0001) than were those taking placebo (figure 2). On the basis of the average number of responders within the rimonabant and placebo groups (639 [26%] and 106 [7%], respectively), this OR corresponded to a number needed to treat of six individuals (95% CI four to eight).

Mood was assessed with HADS at baseline and every 3 months. HADS contains seven items to assess depressive symptoms and seven items to assess anxiety symptoms, with scores ranging from 0 to 3 for each item. Depressive and anxiety symptoms are separately summarised. Scores of 0–7 are regarded as normal, 8–10 represent borderline symptoms, and 11 is regarded as high enough to warrant further assessment of the patient.[26] Questions about suicidal thoughts are not part of the questionnaire.

All four individual studies reported HADS subscores for depression and anxiety. Since the RIO-Europe study did not report changes from baseline, we estimated the group mean differences as the standardised mean difference. There was no significant difference between rimonabant and placebo in regard to the depression subscore, whereas the increase in the anxiety score was greater in the rimonabant group than in the placebo group (table 2).

Adverse events were more likely to arise with rimonabant treatment than with placebo (figure 3). The Cochran Q test for homogeneity suggested that the effect of rimonabant on adverse events was much the same in all the studies ($I^2=0\%$; $Q=0.58$; $p=0.90$). Patients

|	Rimonabant		Placebo		SMD (95% CI)
	n	Mean (SD)	n	Mean (SD)	
Depression* (p=0·21)					
RIO-Europe†[10]	363	3·4 (3·4)	178	2·7 (2·9)	0·22 (0·04 to 0·40)
RIO-Lipids[11]	221	0·1 (3·1)	214	0·2 (2·7)	–0·03 (–0·22 to 0·15)
RIO-North America[12]	1026	0·1 (3·0)	490	0·1 (2·8)	0·00 (–0·11 to 0·11)
RIO-Diabetes[13]	262	0·3 (2·9)	279	–0·2 (2·6)	0·18 (0·01 to 0·35)
Total	1872		1161		0·08 (–0·05 to 0·21)
Anxiety‡ (p=0·0009)					
RIO-Europe†[10]	363	5·6 (4·1)	178	4·4 (4·0)	0·29 (0·11 to 0·47)
RIO-Lipids[11]	221	0·3 (3·0)	214	0·1 (2·7)	0·07 (–0·12 to 0·26)
RIO-North America[12]	1026	0·9 (3·3)	490	0·2 (3·0)	0·22 (0·11 to 0·33)
RIO-Diabetes[13]	262	0·4 (3·4)	279	–0·3 (3·2)	0·21 (0·04 to 0·38)
Total	1872		1161		0·18 (0·07 to 0·28)

SMD=standardised mean difference. *Test for homogeneity for depression: $\chi^2=6.99$, $I^2=57.1\%$, (p=0·07). †Value after 1-year intervention—ie, change within group is not explicitly reported. ‡Test for homogeneity for anxiety: $\chi^2=3.00$, $I^2=0\%$, (p=0·39).

Table 2: Hospital anxiety and depression (HAD) scale subscores for all eligible studies
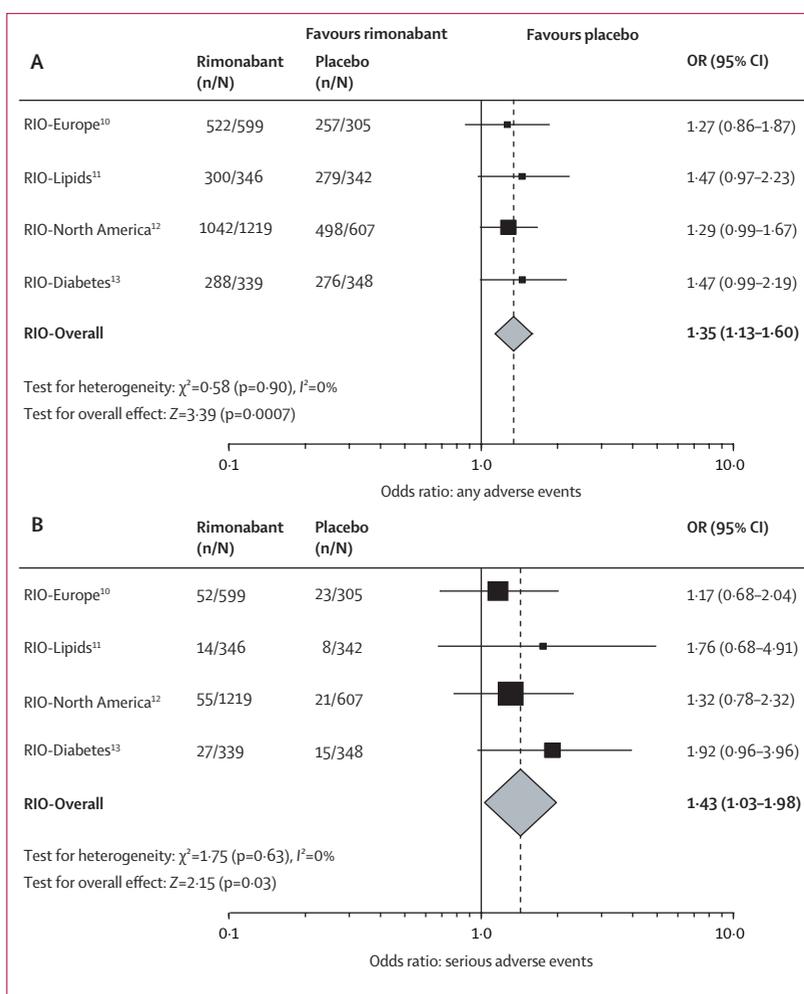
Figure 3: Safety of 20 mg per day rimonabant treatment compared with placebo
(A) The number of individuals who had an adverse event. (B) The number of individuals who had a serious adverse event. Data based on an exact computation algorithm.
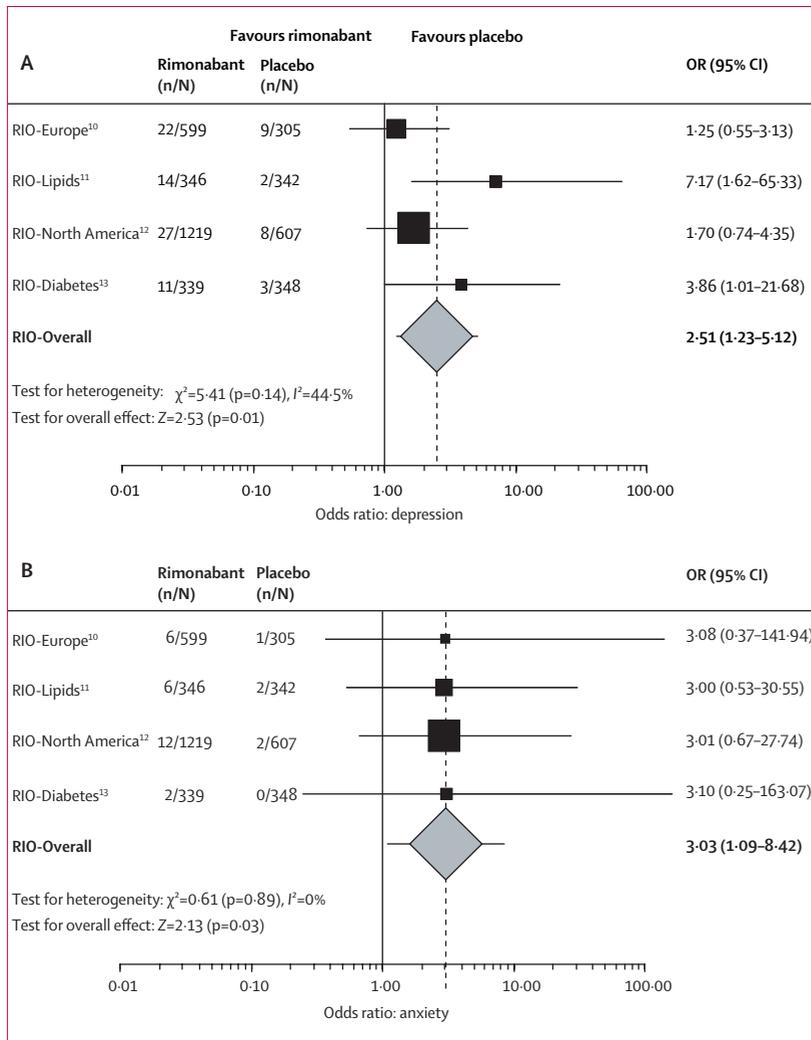
Figure 4: Number of individuals who discontinued treatment because of adverse psychiatric events
(A) Discontinuation because of depressed mood disorders, which is a composite endpoint that consists of depression, major depression, depressive mood, and depressive symptoms. (B) Discontinuation because of anxiety. Data based on exact computation algorithms.

receiving 20 mg per day rimonabant were 1·4 times more likely to report adverse events than were those receiving placebo (OR=1·4 [95% CI 1·1–1·6]; p=0·0007). The average numbers of events within the rimonabant and placebo groups were 2152 (86·0%) and 1310 (81·8%), respectively, corresponding to a number needed to harm of 25 individuals (95% CI 17–58). Serious adverse events also occurred more frequently in the rimonabant than in the placebo groups (148 [5·9%] vs 67 [4·2%]; OR=1·4 [1·0–2·0]; p=0·03), corresponding to a number needed to harm of 59 individuals (27–830; figure 3).

In the RIO-Lipids study,[11] the depressive mood disorders defined as a cause of discontinuation were subcategorised into depression, major depression, and depressed mood, whereas the RIO-Diabetes,[13] RIO-Europe,[10] and RIO-North America[12] only reported the composite group depressed mood disorders.

Depressed mood disorders consisted of depression, major depression, depressive mood, and depressive symptoms. To analyse this endpoint we used the composite endpoint depressed mood disorder also for RIO-Lipids (estimated as the sum of subcategories). More psychiatric disorders were evident in the rimonabant groups than in the placebo groups leading to discontinuation (figure 4). Patients assigned to rimonabant were 2·5 times more likely to discontinue in the trial because of depressive mood disorders than were those receiving placebo (74 [3·0%] vs 22 [1·4%]; OR=2·5 [1·2–5·1]; p=0·01; number needed to harm=49 individuals [19–316]; figure 4). Furthermore, anxiety caused more frequent discontinuation in rimonabant groups than in placebo groups (26 [1·0%] vs 5 [0·3%]; OR=3·0 [1·1–8·4]; p=0·03; number needed to harm=166 individuals [47–3716]; figure 4).

To explore the reasons for heterogeneity we undertook multiple metaregression models to reduce the between-study variance, based on the study-level covariates shown in table 1. We only focused on covariates that were able to reduce the effect of heterogeneity for two of the outcome measures: the log-OR values considering the number of patients with depressed mood and serious adverse events. We noted an association between the OR of depressed mood and the average triglyceride concentration at baseline, which could suggest that high concentrations of triglyceride at baseline might be a predictor for individuals who are likely to have depression during their use of rimonabant. Mean age at baseline seemed to be a predictor of the log OR for serious adverse events, suggesting that elderly people are more likely to have serious adverse events during treatment with rimonabant than are younger patients.

Discussion

Four trials in the RIO programme assessed the efficacy and safety of the anti-obesity agent rimonabant compared with placebo, and our meta-analysis has shown that rimonabant therapy produced a greater weight loss than did placebo. Patients who were allocated to rimonabant were much more likely to achieve a 10% weight reduction after 1 year compared with those allocated to placebo. These figures are in agreement with the outcome of a Cochrane meta-analysis,[27] and suggest that rimonabant is similar to or slightly better than existing weight-loss drugs.

A meta-analysis[28] of 11 orlistat trials and five sibutramine trials lasting 1 year or longer showed that patients given orlistat lost 2·7 kg (95% CI 2·3–3·1) more weight, and patients taking sibutramine lost 4·3 kg (3·6–4·9) more weight than did those taking placebo. The intensity and the enforcement of the restriction in calories in the RIO programme was fairly weak, and produced only modest weight loss of less than 2 kg in the placebo groups. However, the more strictly the

energy restriction is enforced and adhered to, the greater weight loss that is seen in both treatment groups, thus leaving little room for an appetite suppressant such as rimonabant to further reduce energy intake and produce weight loss. With a more effective dietary treatment programme, the additional weight loss produced by rimonabant would probably be less than that we reported.

In the RIO trials, no follow-ups were reported after discontinuation of active treatment, thus any weight regain could not be assessed. As with other weight-loss drugs, relapse is expected to occur after treatment has ended, and to achieve weight maintenance and maintain the improvement of the cardiovascular and diabetes risk factors the drug needs to be taken for life.

In our meta-analysis, patients with type 2 diabetes achieved a lower placebo-subtracted weight reduction with rimonabant than did non-diabetic patients, which is consistent with the general observation that weight loss is more difficult to achieve in patients with type 2 diabetes.[29]

Obesity has been shown to be associated with depression in the general population and in clinical samples,[30] especially in women and severely obese men.[31] Obese individuals who are seeking treatment are especially prone to depression. Depression has been reported to range up to 48% in these individuals, and this proportion increases as the severity of obesity increases.[32,33] Obese women are 20% more likely to report suicidal ideation and 23% more likely to have made a suicide attempt in the past year compared with non-obese women.[34] By contrast with the Cochrane review,[27] we found it pertinent to assess the effect of rimonabant on psychiatric events with a focus on mood and depression. Because of the limitations of the trials, the risk of a severe psychiatric adverse event could not be examined, and the assessment could be achieved by only two different analyses: changes in the HADS score[35] and discontinuation of treatment because of depressive mood disorder and anxiety.

We noted a greater increase in anxiety reported by the HADS score in participants taking rimonabant than in those taking placebo, but we failed to find any effect on depression. However, HADS is generally not used as a primary outcome measure in clinical trials of depression, but it is regarded as an acceptable method to screen for depression and anxiety primarily in non-psychiatric patients.[35] According to the RIO protocols, an increase in the HADS score above 11 would imply that the patient should be seen by a psychiatrist for further assessment, but none of the RIO trials reported the number of participants who were discontinued from trials after psychiatric consultations. Another limitation of HADS is the absence of questions investigating suicidal thoughts.

Our meta-analysis has shown that more obese people in the 20 mg per day rimonabant groups than in placebo groups were taken off treatment because of depressed

mood disorders. Participants given rimonabant were also at greater risk to discontinue treatment because of an increased risk of developing anxiety.

Our study had several limitations mainly because of the absence of access to all available sources reporting safety data, including unpublished phase 2 trials and several studies in progress, but also because of an absence of consistent reporting of psychiatric severe adverse effects. Additionally, the endpoint reported in the studies was depressed mood disorders, which consisted of depression, major depression, depressive mood, and depressive symptoms, and these disorders have substantially different severity and clinical implications.

Our analysis did not allow examination for psychiatric disorders other than depression and anxiety. However, according to the FDA analysis, rimonabant treatment led to more adverse events than did placebo: irritability, insomnia, stress, and nervousness were present in more than 1% of the treated patients. Panic attacks, agitation, nightmare, and abnormal dreams were more frequently reported by patients treated with rimonabant than with placebo.[15] Although the number of patients discontinuing therapy because of adverse events seemed to be small, high study attrition rates raise the possibility that some events were not documented.

Moreover, in all the RIO studies the enrolled patient populations were highly selected, since patients with a past history of severe depression or those with present severe psychiatric illness were excluded. Antidepressant treatment was not permitted and warranted mandatory treatment discontinuation, as prespecified by the original RIO protocols. Information about depression, depressed mood, anxiety, etc, was self-reported, which means that under-reporting bias could have been present. For these reasons, our estimates of depressive mood disorders are probably conservative.

Our findings strongly accord with the FDA report about the safety of rimonabant that was released after the initial submission of the present paper,[15] although the investigators did report endpoints other than those reported in our analysis. The FDA reported in their meta-analysis of RIO studies that 26% of people given rimonabant 20 mg versus 14% of those given placebo had a psychiatric symptom reported as an adverse event. They noted that 9% of participants given rimonabant 20 mg versus 5% given placebo reported symptoms of depression (depressed mood, depression, depressive symptom, or major depression), and consistent with our findings these incidents often led to withdrawal of the drug. The FDA further reported that the overall relative risk for psychiatric adverse events in the rimonabant 20 mg group versus placebo group was 1·9 (95% CI 1·5–2·3). The number of participants needing an anxiolytic or hypnotic agent for a psychiatric adverse event was 185 (9%) taking rimonabant 20 mg, 102 (5%) taking rimonabant 5 mg, and 66 (4%) taking placebo. Another 104 (5%) taking rimonabant 20 mg, 88 (4%) taking rimonabant 5 mg, and 46 (3%)

taking placebo needed an antidepressant agent for a psychiatric adverse event.

The OR for the incidence of suicide was examined by the FDA from all available studies, including smoking cessation trials, and was found to be 1·9 (1·1–3·1) for 20 mg rimonabant versus placebo. When limited to seven obesity studies, including the unpublished and contiuning trials, the OR for incidence of suicide for 20 mg rimonabant versus placebo was 1·8 (0·8–3·8). In the entire database for rimonabant clinical trials, there have been only two deaths from suicide—one in RIO North America in a patient taking rimonabant 5 mg and one in a study in progress in a patient taking rimonabant 20 mg.[15]

The use of pretreatment markers to identify obese patients at high risk for developing depressed mood disorders would be of great clinical importance. We therefore looked for possible predictive baseline markers, and found that high triglyceride concentrations were associated with an increased probability of having depression during treatment with rimonabant. In published work there is suggestive evidence from cross-sectional studies that lends support to a link between high triglyceride concentrations and depression,[36,37] but any causal relation remains to be established. Furthermore, increasing age seemed to be a predictor of serious adverse events arising from rimonabant, which could be because of altered pharmacokinetics. These findings deserve to be further addressed, and we suggest that the available raw data is provided from every patient in all existing trials, enabling an individual patient data meta-analysis to be undertaken.[38] Such a meta-analysis is seen as a gold standard compared with the study-level meta-analysis.[39] This would be the simplest way to investigate the safety concerns proposed by the present study, and by the FDA analyses, and also to address whether the psychiatric adverse events are associated with the magnitude of the weight loss.

Although all the included trials excluded patients with existing depression, or those with a history of depressed mood a priori, this selected population of obese individuals had an increased risk of developing depressive mood disorders during 20 mg per day rimonabant therapy. That obese patients who are prescribed rimonabant in clinical practice are less likely to be screened for depression disorders than the participants in the trials is a matter of concern. Consequently, the number needed to harm could be much lower than this finding in clinical practice. Patients who seek treatment in clinical practice are often obese women with less comorbidity, and for this group the risk of severe adverse events is less acceptable.

Other potential anti-obesity drugs that increase the risk of depression have been withdrawn because of cases of suicide ideation, suicide attempts, and death from suicide.[40] The findings of our meta-analysis suggest that the potential of rimonabant to induce depressive symptoms and depression in overweight patients needs greater attention.

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Depression and anxiety with rimonabant

The first endogenous cannabinoid was isolated in the early 1990s, followed soon after by identification of the endocannabinoid receptors CB_1 and CB_2. Clinical observations that cannabis stimulates appetite (the "munchies") suggested that the endocannabinoid system is involved in the control of energy balance.[1] Rimonabant, the first of the CB_1-receptor antagonists to be marketed, was developed as an anti-obesity agent on the premise that blocking central cannabinoid activity might reduce food intake.[2] Its efficacy for weight reduction was shown by a series of major reports.[3,4]

In a meta-analysis of the four pivotal RIO (Rimonabant In Obesity) studies in today's *Lancet*, Robin Christensen and colleagues provide compelling evidence that rimonabant is associated with development of severe adverse psychiatric events.[5] Participants who received rimonabant 20 mg were 2·5 times (95% CI 1·2–5·1; p=0·01) more likely than those who took placebo to discontinue treatment because of depression or depressive symptoms (3·0% *vs* 1·4%) and 3·0 times (95% CI 1·1–8·4; p=0·03) more likely to discontinue treatment because of anxiety (1·0% *vs* 0·3%). Furthermore, rimonabant was associated with significantly increased anxiety (odds ratio 3·03, 95% CI 1·09–8·42), as measured on the Hospital Anxiety and Depression Scale. These findings are especially striking since people who had a history of serious depression or other psychiatric illnesses had been excluded before study entry and people with severe obesity have been shown to be at high risk of depression.[6]

Submission of Christensen and colleagues' report to *The Lancet* coincided with release of a report by an Advisory Committee of the US Food and Drug Administration (FDA),[7] which also raised major concerns that rimonabant might be linked to adverse psychiatric events. In fact, the FDA report suggested that Christensen could have underestimated the magnitude of psychiatric complications of this drug, because the published trials did not provide detailed data on rates of psychiatric adverse effects. Examining the same four studies, the FDA Committee found that 26% of participants who took rimonabant 20 mg had an adverse psychiatric event (mainly anxiety or depression) compared with 14% of those who took placebo. This increase in psychiatric complications with rimonabant (relative risk 1·9) was significant compared with placebo (95% CI 1·5–2·3). Survival analysis

showed that these adverse events developed early in treatment. Moreover, in a broader suite of rimonabant studies, the FDA identified substantial evidence for an increased risk of suicide attempts or suicidal ideation in participants who took rimonabant 20 mg compared with placebo (odds ratio 1·9, 95% CI 1·1–3·1).

These clinical findings coincide with reports of animal studies that implicate the CB_1 receptor in mediation of antidepressant-like or anxiolytic-like effects of the endocannabinoid system. Inhibition of the breakdown of the endogenous cannabinoid anandamide has an antidepressant-like effect in rodents; this effect was blocked by rimonabant.[8] In rodents exposed to stress induced by swimming, another CB_1 antagonist (AM251) impaired the reduction in corticosterone secretion that results from exposure to tricyclic antidepressants.[9] Mice that were either genetically deficient for an enzyme (fatty acid amide hydrolase) that degrades anandamide or received a specific inhibitor of this enzyme displayed reduced anxiety-like behaviour; moreover, this effect was blocked by rimonabant.[10] These studies consistently showed that pharmacological blockade of the CB_1 receptor impaired the antidepressant-reducing or anxiety-reducing actions of endocannabinoids. However, some discrepancies in
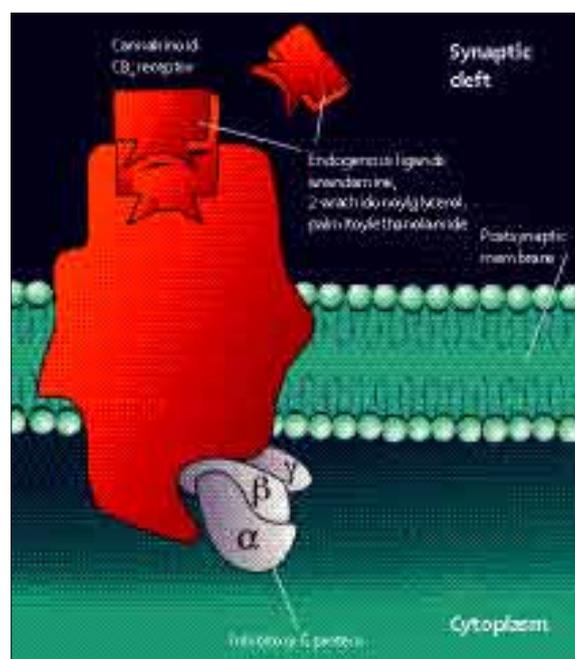
CB_1-cannabinoid receptor system, by which cannabinoids can inhibit neurotransmission

animal studies should be acknowledged, since some reports[11] have suggested that rimonabant might have antidepressant or anxiolytic actions. Another observation that might provide an alternative physiological basis for increased mood disorders seen with greatest weight-loss comes from evidence that leptin, the adipose-derived hormone, had an antidepressant action after intrahippocampal but not hypothalamic injection.[12] However, direct clinical correlates are difficult to draw.

What is the significance of the findings reported by Christensen and colleagues? First, their meta-analysis has raised major questions about the safety of rimonabant in obese people, who are already at an increased risk of depression, especially since the FDA review suggests that the risk of suicide is increased by use of this agent. Moreover, at least four other companies have CB_1 antagonists in phase II or III development. The findings of Christensen and colleagues' meta-analysis suggest that phase III studies of such CB_1 antagonists should monitor psychiatric complications very carefully. Second, the link between depression and this CB_1-receptor blocker raises theoretical questions about a potential central role for the endocannabinoid system in both normal and clinical mood states.[13]

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Benefits and risks of homoeopathy

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Five large meta-analyses of homoeopathy trials have been done. All have had the same result: after excluding methodologically inadequate trials and accounting for publication bias, homoeopathy produced no statistically significant benefit over placebo.[1–5] And yet homoeopathy can still be clinically useful.

During the cholera epidemic in the 19th century, death rates at the London Homoeopathic Hospital were three times lower than those at the Middlesex Hospital.[6] The reason for homoeopathy's success in this epidemic is even more interesting than the placebo effect. At the time, nobody could treat cholera, and while medical treatments such as blood-letting were actively harmful, the homoeopaths' treatments were at least inert.

Similarly, modern medicine can offer little for conditions such as many types of back pain, stress at work, medically unexplained fatigue, and most common colds. Going through a theatre of medical treatment, and trying every drug in the book, will only elicit side-effects. An inert pill in these circumstances seems a sensible option.

However, just as homoeopathy has unexpected benefits, so it can have unexpected side-effects. The very act of prescribing a pill carries its own risks: medicalisation, reinforcement of counterproductive illness behaviours, and promotion of the idea that a pill is an appropriate response to a social problem, or a modest viral illness.

Similarly, when a health-care practitioner of any description prescribes a pill which they know is no more effective than placebo—without disclosing that fact to