



**Cochrane**  
**Library**

**Cochrane** Database of Systematic Reviews

## **Cannabinoid type 1 receptor antagonists for smoking cessation (Review)**

Cahill K, Ussher MH

Cahill K, Ussher MH.

Cannabinoid type 1 receptor antagonists for smoking cessation.

*Cochrane Database of Systematic Reviews* 2011, Issue 3. Art. No.: CD005353.

DOI: 10.1002/14651858.CD005353.pub4.

**[www.cochranelibrary.com](http://www.cochranelibrary.com)**

## TABLE OF CONTENTS

HEADER . . . . .	1
ABSTRACT . . . . .	1
PLAIN LANGUAGE SUMMARY . . . . .	2
BACKGROUND . . . . .	3
OBJECTIVES . . . . .	4
METHODS . . . . .	4
RESULTS . . . . .	5
DISCUSSION . . . . .	8
AUTHORS' CONCLUSIONS . . . . .	9
ACKNOWLEDGEMENTS . . . . .	10
REFERENCES . . . . .	10
CHARACTERISTICS OF STUDIES . . . . .	12
DATA AND ANALYSES . . . . .	17
Analysis 1.1. Comparison 1 Rimonabant 20mg vs placebo, Outcome 1 Prolonged abstinence at wk 50. . . . .	18
Analysis 1.2. Comparison 1 Rimonabant 20mg vs placebo, Outcome 2 Continuous 4-wk abstinence at EOT (wks 7-10). . . . .	18
Analysis 2.1. Comparison 2 Relapse prevention, Outcome 1 rimonabant 20mg vs placebo at 52 weeks. . . . .	19
Analysis 2.2. Comparison 2 Relapse prevention, Outcome 2 rimonabant 5mg vs placebo at 52 weeks. . . . .	20
Analysis 3.1. Comparison 3 Rimonabant 5mg vs placebo, Outcome 1 Prolonged abstinence at wk 50. . . . .	20
Analysis 3.2. Comparison 3 Rimonabant 5mg vs placebo, Outcome 2 Continuous 4-wk abstinence at EOT (wks 7-10). . . . .	21
Analysis 4.1. Comparison 4 Rimonabant 20mg vs rimonabant 5mg, Outcome 1 Prolonged abstinence at wk 50. . . . .	21
Analysis 4.2. Comparison 4 Rimonabant 20mg vs rimonabant 5mg, Outcome 2 Continuous 4-wk abstinence at EOT (wks 7-10). . . . .	22
APPENDICES . . . . .	22
WHAT'S NEW . . . . .	25
HISTORY . . . . .	25
CONTRIBUTIONS OF AUTHORS . . . . .	25
DECLARATIONS OF INTEREST . . . . .	26
SOURCES OF SUPPORT . . . . .	26
INDEX TERMS . . . . .	26

[Intervention Review]

# Cannabinoid type 1 receptor antagonists for smoking cessation

Kate Cahill<sup>1</sup>, Michael H Ussher<sup>2</sup>

<sup>1</sup>Department of Primary Care Health Sciences, University of Oxford, Oxford, UK. <sup>2</sup>Division of Population Health Sciences and Education, St George's, University of London, London, UK

Contact address: Kate Cahill, Department of Primary Care Health Sciences, University of Oxford, 23-38 Hythe Bridge Street, Oxford, OX1 2ET, UK. [kate.cahill@phc.ox.ac.uk](mailto:kate.cahill@phc.ox.ac.uk).

**Editorial group:** Cochrane Tobacco Addiction Group.

**Publication status and date:** Edited (no change to conclusions), published in Issue 7, 2012.

**Citation:** Cahill K, Ussher MH. Cannabinoid type 1 receptor antagonists for smoking cessation. *Cochrane Database of Systematic Reviews* 2011, Issue 3. Art. No.: CD005353. DOI: 10.1002/14651858.CD005353.pub4.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## ABSTRACT

### Background

Selective type 1 cannabinoid (CB1) receptor antagonists may assist with smoking cessation by restoring the balance of the endocannabinoid system, which can be disrupted by prolonged use of nicotine. They also seek to address many smokers' reluctance to persist with a quit attempt because of concerns about weight gain.

### Objectives

To determine whether selective CB1 receptor antagonists (currently rimonabant and taranabant) increase the numbers of people stopping smoking

To assess their effects on weight change in successful quitters and in those who try to quit but fail.

### Search methods

We searched the Cochrane Tobacco Addiction Review Group specialized register for trials, using the terms ('rimonabant' or 'taranabant') and 'smoking' in the title or abstract, or as keywords. We also searched MEDLINE, EMBASE, CINAHL and PsycINFO, using major MESH terms. We acquired electronic or paper copies of posters of preliminary trial results presented at the American Thoracic Society Meeting in 2005, and at the Society for Research on Nicotine and Tobacco European Meeting 2006. We also attempted to contact the authors of ongoing studies of rimonabant, and Sanofi Aventis (manufacturers of rimonabant). The most recent search was in January 2011.

### Selection criteria

#### *Types of studies*

Randomized controlled trials

#### *Types of participants*

Adult smokers

#### *Types of interventions*

Selective CB1 receptor antagonists, such as rimonabant and taranabant.

---

**Cannabinoid type 1 receptor antagonists for smoking cessation (Review)**

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

### *Types of outcome measures*

The primary outcome is smoking status at a minimum of six months after the start of treatment. We preferred sustained cessation rates to point prevalence, and biochemically verified cessation to self-reported quitting. We regarded smokers who drop out or are lost to follow up as continuing smokers. We have noted any adverse effects of treatment.

A secondary outcome is weight change associated with the cessation attempt.

### **Data collection and analysis**

Two authors checked the abstracts for relevance, and attempted to acquire full trial reports. One author extracted the data, and a second author checked them.

### **Main results**

We found three trials which met our inclusion criteria, covering 1567 smokers (cessation: STRATUS-EU and STRATUS-US), and 1661 quitters (relapse prevention: STRATUS-WW). At one year, the pooled risk ratio (RR) for quitting with rimonabant 20 mg was 1.50 (95% confidence interval (CI) 1.10 to 2.05). No significant benefit was demonstrated for rimonabant at 5 mg dosage. Adverse events included nausea and upper respiratory tract infections.

In the relapse prevention trial, smokers who had quit on the 20 mg regimen were more likely to remain abstinent on either active regimen than on placebo; the RR for the 20 mg maintenance group was 1.29 (95% CI 1.06 to 1.57), and for the 5 mg maintenance group 1.30 (95% CI 1.06 to 1.59). There appeared to be no significant benefit of maintenance treatment for the 5 mg quitters.

One trial of taranabant was not included in our meta-analyses, as it followed participants only until end of treatment; at eight weeks it found no benefit for treatment over placebo, with an OR of 1.2 (90% CI 0.6 to 2.5).

For rimonabant, weight gain was reported to be significantly lower among the 20 mg quitters than in the 5 mg or placebo quitters. During treatment, overweight or obese smokers tended to lose weight, while normal weight smokers did not. For taranabant, weight gain was significantly lower for 2-8 mg versus placebo at the end of eight weeks of treatment.

In 2008, post-marketing surveillance led the European Medicines Agency (EMA) to require Sanofi Aventis to withdraw rimonabant, because of links to mental disorders. The development of taranabant was also suspended by Merck & Co because of unacceptable adverse events.

### **Authors' conclusions**

From the trial reports available, rimonabant 20 mg may increase the chances of quitting approximately 1½-fold. The evidence for rimonabant in maintaining abstinence is inconclusive.

Rimonabant 20 mg may moderate weight gain in the long term. Taranabant 2-8 mg may moderate weight gain, at least in the short term.

In 2008, development of both rimonabant and taranabant was discontinued by the manufacturers.

## **PLAIN LANGUAGE SUMMARY**

### **Can cannabinoid type 1 receptor antagonists help smokers to quit, and could they also reduce the amount of weight gained during the quitting process?**

Long-term use of nicotine can upset the endocannabinoid system in the brain, which controls food intake and energy balance. Rimonabant and similar drugs may help smokers to quit by rebalancing the system, which then reduces nicotine and food cravings. We searched our own specialised register of controlled trials. We also contacted Sanofi Aventis, the manufacturers of rimonabant, and researchers who presented early findings at conferences. We found two randomized controlled trials (RCTs) of rimonabant for smoking cessation, covering 1567 smokers, and one RCT of rimonabant for relapse prevention covering 1661 quitters. The available information shows that rimonabant at the 20 mg dose increased by 1½-fold the chances of not smoking at one year, compared with placebo. Rimonabant 5 mg did no better than placebo at any time point. In the relapse prevention trial, smokers who quit successfully with rimonabant 20 mg were 1½ times more likely to remain abstinent on active treatment (5 mg or 20 mg for 42 weeks) than on

placebo. For those who quit successfully on 5 mg, neither active nor placebo treatment appeared to benefit them in avoiding relapse. This inconsistent picture makes it difficult to find a clear benefit for rimonabant in preventing relapse. One trial of taranabant (317 smokers) did not find a benefit for treatment over placebo, and the taranabant group suffered more side effects than the placebo group. Main side effects for rimonabant included nausea and upper respiratory tract infections, and serious harms were reported to be low. For taranabant, the main side effects included problems with digestive, nervous, psychiatric, skin and blood vessel organ systems. For both drugs, the number and severity of the side effects increased in those taking higher doses. Although the evidence on weight change is sparse in these trials, weight gain was reported to be significantly lower among the rimonabant 20 mg quitters than in the 5 mg or placebo quitters. During treatment, overweight or obese smokers tended to lose weight on 20 mg, while normal weight smokers did not. Taranabant also limited weight gain during cessation attempts. In 2008 both rimonabant and taranabant were withdrawn by the manufacturers, because of links to mental disorders and unacceptable side effects.

## BACKGROUND

About 70% of smokers want to quit, with the majority citing concerns about their health as a primary reason for giving up smoking (ONS 2002). There is widespread concern among smokers, however, about the risks of gaining weight after quitting. In the USA it is estimated that 75% of smokers gain weight when they stop smoking (USPHS 1990), with the majority of the weight gain in the first year of smoking abstinence (O'Hara 1998). Men who sustain abstinence have been shown to gain an average of 4.9 kilograms in the first year of abstinence, and women 5.2 kilograms, with further gains of 2.7 kilograms and 3.5 kilograms respectively across the following four years of abstinence (O'Hara 1998). Other evidence suggests that in the longer term ex-smokers' weight may return to the comparable weight of someone who has never smoked (Mizoue 1998). While some studies have suggested that nicotine replacement therapy or bupropion may moderate post-cessation weight gain (Filozof 2004), no pharmacotherapies are yet available that target both smoking cessation and weight control simultaneously.

The central cannabinoid (CB1) receptors have recently been implicated in brain reward function, and are thought to have a role in controlling food consumption and in dependence and habituation. Excessive eating and fat accumulation are associated with over-activation of the endocannabinoid system, which is involved in the regulation of food intake and energy expenditure. Repeated nicotine use may also overstimulate the endocannabinoid system. It is thought that rimonabant may work by selectively blocking the CB1 receptors, thereby restoring the balance and inhibiting nicotine and food cravings.

Rimonabant (SR 141716; trade name Acomplia) was the first selective cannabinoid type 1 receptor antagonist to be produced and clinically tested. It was developed initially as a possible treatment for obesity, but it was subsequently proposed as an aid to smoking cessation, with the potential to protect successful quitters from

significant post-cessation weight gain (ACC 2004; Sanofi-Synth 2004). The development and testing of rimonabant was of particular interest to clinicians, as it appeared to offer an effective and simultaneous treatment for the two major cardiac risk factors of obesity and smoking (Fagerström 2006; Gelfand 2006; Le Foll 2008). Moreover, smoking cessation is itself associated with weight gain. Rimonabant therefore also addressed many smokers' reluctance to persist with a quit attempt because of concerns over weight gain (Pomerleau 2000). The beneficial effects of rimonabant on weight loss have been demonstrated in a recent Cochrane review (Curioni 2006).

Rimonabant 20 mg dose was licensed as an aid for weight control in the European Union in June 2006, but was not licensed for smoking cessation. It has not been approved by the FDA for sale in the USA. The Summary of Product Characteristics (Acomplia SPC 2006) advises against its use by those with severe hepatic or renal impairment, severe psychiatric illness or lactose intolerance, and advises caution in its use by the elderly, by patients with epilepsy or by those on antidepressant treatment. It is also contraindicated during pregnancy or while breast-feeding. Reports of raised levels of depression and suicidal thoughts led in October 2008 to the withdrawal of rimonabant as a prescription drug in European countries (see Results section).

Phase III trials were conducted to test the use of rimonabant for long-term smoking cessation with the avoidance of significant weight gain. The STRATUS program (STudies with Rimonabant And Tobacco Use), produced conference reports of two cessation trials (STRATUS-EU 2006 and STRATUS-US 2006), and reported intermediate outcomes for a two-year relapse prevention trial (STRATUS-WW 2005).

Another CB1 receptor antagonist, taranabant, has been developed by the US drug major Merck & Co (Fremming 2008). Although primarily targeting obesity, it was also tested as an aid to smoking

cessation. Because the trial lasted only eight weeks, we have not included it in our review findings, but we report the findings for weight gain, and the adverse events profile is considered in the Discussion section. Because of the neuropsychiatric side effects, the development of taranabant for any condition was discontinued in October 2008.

## OBJECTIVES

1. To determine whether selective CB1 receptor antagonists increase the numbers of people stopping smoking.
2. To assess their effects on weight change in successful quitters and in those who try to quit but fail.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized controlled trials

#### Types of participants

Adult smokers

#### Types of interventions

Selective CB1 receptor antagonists, such as rimonabant and taranabant, and any other drugs of this class as they reach Phase II or Phase III trial stage. The drugs may be used alone or in combination with behavioural therapies or other pharmacotherapies.

#### Types of outcome measures

The primary outcome is smoking status at a minimum of six months after the start of treatment. Trials with shorter follow up have not been included in the meta-analysis. We have used sustained cessation rates in preference to point prevalence; sustained cessation refers either to complete abstinence (continuous) or to prolonged abstinence (complete abstinence following a post-quit two-week period of grace in which minor relapse may occur) (Hughes 2003). We prefer biochemically verified cessation to self-reported quitting. The strictest definition of smoking cessation reported was used in the meta-analysis. Types of abstinence (continuous, prolonged, point prevalence) and levels of verification (biochemical, self-report) have been considered as potential moderators of outcome. We regard smokers who drop out or are lost

to follow up as continuing smokers. We have noted any adverse effects of treatment.

A secondary outcome is change in weight associated with the cessation attempt. We have assessed change in baseline weight at longest follow up (currently one year), and at the end of pharmacotherapy. We have considered weight change in the subgroup of successful quitters, in all those who were randomized, in the subgroup of those who have failed to quit, according to weight classification at baseline, and in the total sample, testing the sensitivity of the results to different ways of handling missing data.

The possible findings include:

- (i) Selective CB1 receptor antagonists may increase smoking abstinence rates relative to a control or non-intervention group, and there may be a significantly larger average weight gain in the intervention than in the control group. Interpretation: The weight gain in the intervention group would most probably be due to the higher number of quitters in this group and there would be no evidence to suggest that the intervention has reduced weight gain.
- (ii) Selective CB1 receptor antagonists may increase quit rates relative to a control or non-intervention group, but without a significant difference in average weight gain between the groups. Interpretation: This result would be difficult to interpret. It is possible that the intervention may have counteracted some of the anticipated weight gain among the quitters. However, it is also possible that there was a similar weight gain in quitters and continuing smokers independently of the effects of the intervention.
- (iii) Selective CB1 receptor antagonists may increase quit rates relative to a control or non-intervention group, and there may be a significantly smaller average weight gain in the intervention group than in the control group. Interpretation: This would be good evidence to suggest that the intervention has reduced weight gain.
- (iv) There may be no difference in quit rates between the selective CB1 receptor antagonists group and the control group, but a significantly smaller average weight gain in the intervention group than in the control group. Interpretation: This would be evidence for selective CB1 receptor antagonists counteracting weight gain. Since selective CB1 receptor antagonists may have beneficial effects on other risk factors for the development of cardiovascular disease (Cleland 2004) these outcomes have also been considered.

### Search methods for identification of studies

We searched the Cochrane Tobacco Addiction Review Group specialized register for trials, using the terms ('rimonabant' or 'taranabant') and 'smoking' in the title or abstract, or as keywords. This register has been developed from electronic searching of MEDLINE, EMBASE, Science Citation Index and PsycINFO, together with handsearching of specialist journals, conference proceedings and reference lists of previous trials and overviews. We have also searched MEDLINE, EMBASE, and PsycINFO, using the major MESH terms (Endocannabinoids-physiology, Re-

ceptors,-cannabinoid-agonists or Receptors,-cannabinoid-antagonists-and-inhibitors) or equivalent for other databases, combined with MeSH or free text smoking-related terms (smok\* or tobacco or cigar\* or nicotine). We have acquired electronic and/or paper copies of posters of preliminary trial results presented at the American Thoracic Society Meeting in 2005, and at the Society for Research on Nicotine and Tobacco European Meeting 2006. We have also attempted to contact the authors of studies of rimonabant, and Sanofi Aventis (manufacturers of rimonabant). The most recent search was in January 2011.

## Data collection and analysis

Two authors checked the abstracts of studies generated by the search strategy for relevance, and attempted to acquire full reports of any trials that might be included in the review, but with only limited success. One author extracted the data, and a second author checked them. Any discrepancies were resolved by mutual consent, or by recourse to the editorial base. We have noted reasons for the non-inclusion of studies.

### DATA EXTRACTION

The following information, where it was available for each trial, is reported in the Table 'Characteristics of Included Studies':

- Country and setting (e.g. primary care, community, hospital outpatient/inpatient). no change
- Method of selection of participants (e.g. willingness to make a quit attempt).
- Definition of smoker used.
- Method of randomization, and blinding of trialists, participants and assessors.
- Demographic characteristics of participants (e.g. average age, sex, average cigs/day).
- Intervention and control description (provider, length of treatment, number of visits, etc.).
- Outcomes including definition of abstinence used, and biochemical validation of cessation.
- Proportion of participants with follow-up data.
- Any adverse events.
- Secondary outcomes, including weight changes during and after cessation, and other outcomes relevant to cardiovascular risk, including lipid levels.

### EVALUATION OF QUALITY

We evaluated the studies on the basis of the quality of the randomization and allocation concealment procedure used, as described in the [Cochrane Handbook](#). Studies are scored A if a method of randomization and allocation concealment are reported that minimize the chance of selection bias. If insufficient information is available they are scored B, and studies where allocation was not concealed at the point of enrolment are scored C.

We calculated quit rates based on the numbers of patients randomized to an intervention, and excluding any deaths. We have used

an intention-to-treat (ITT) analysis, i.e. including all randomized participants in the groups to which they were originally assigned. We have regarded those who drop out or are lost to follow up as continuing smokers. We have noted any deaths and adverse events in the Results section.

### WEIGHT CHANGE

For assessing the impact on weight change we have considered the following outcomes where reported:

- Mean change in weight from baseline (pre-cessation) for confirmed quitters. Since quitting is likely to be associated with weight gain, an examination of the subgroup of successful quitters will provide the most sensitive test of the impact of selective CB1 receptor antagonists on weight gain.
- Mean weight change from baseline in point prevalence quitters compared with quitters with continuous or prolonged abstinence.
- Mean change in weight from baseline for those failing to quit smoking. This outcome allows an assessment of whether selective CB1 receptor antagonists affect changes in weight among those who relapse or who continue to smoke.
- Mean change in weight from baseline for those completing the study.
- Mean change in weight for those sub-groups who are classed as obese, overweight or normal weight at baseline.
- Mean change in weight from baseline, using an intention-to-treat (ITT) analysis, with last weight measure carried forward for study dropouts and losses to follow up. Some of the findings by ITT may be difficult to interpret as quitting is of itself associated with weight gain.

We have considered weight change at the end of pharmacotherapy and at the longest follow up. We have reported weight change for a study of taranabant which was excluded from the studies reporting outcomes for smoking cessation. The other excluded studies did not report the effects of rimonabant on weight gain.

Other outcomes relevant to cardiovascular risk, for example lipid levels, have been extracted if reported at long-term follow up.

Where appropriate, we have conducted a meta-analysis of the included studies, using the Mantel-Haenszel risk ratio and a fixed-effect model, provided that there was no significant heterogeneity. Previous versions of this review reported the results as odds ratios, but we have now revised our standard metric in an attempt to clarify the findings.

We include in this review the Tobacco Addiction Group glossary of tobacco-specific terms ([Appendix 1](#)).

## RESULTS

### Description of studies

We identified three trials which met our inclusion criteria. All were Phase III trials, funded and managed by the makers of rimonabant, Sanofi Aventis. Two trials of identical design ([STRATUS-EU 2006](#); [STRATUS-US 2006](#)) evaluated rimonabant for smoking cessation, and one trial evaluated rimonabant as an aid to relapse prevention ([STRATUS-WW 2005](#)).

The two cessation trials covered 1567 smokers, 1046 of whom were on active treatment (20 mg or 5 mg). The relapse prevention trial began with 5055 smokers, all of whom were on active treatment. During the second phase the 1661 quitters were re-randomized to a maintenance dose of active or placebo treatment for a further 42 weeks. Full details of each trial are given in the Table of Included Studies.

[STRATUS-EU 2006](#) was a multi-centre study, set in seven European countries ([Sanofi 2003](#)), while [STRATUS-US 2006](#) was conducted at a clinic in Pennsylvania. The relapse prevention trial ([STRATUS-WW 2005](#)) was set in Canada, Australia and the USA. All three trials tested rimonabant at dosage levels of 5 mg and 20 mg, and compared it with a placebo. For the cessation trials, the treatment period was 10 weeks, with a target quit date set for day 15, and follow up for an additional 40 weeks. In the relapse prevention trial ([STRATUS-WW 2005](#)) participants who achieved abstinence after 10 weeks of treatment on either a 5 mg or a 20 mg regimen were then re-randomized to either 5 mg or placebo (the 5 mg quitters) or to 5 mg, 20 mg or placebo (the 20 mg quitters) for a further 42 weeks of relapse prevention treatment. Successful abstainers at one year in this trial were then followed for a further 52 weeks without treatment.

The cessation trials included brief behavioural counselling at weekly visits throughout the treatment phase, covering cessation-related topics such as craving and relapse prevention, and also diet and exercise but without dietary restrictions. Brief counselling continued at regular clinic visits throughout the follow-up phase. The relapse prevention trial did not report on behavioural support.

The primary outcome for the cessation trials was continuous abstinence through weeks 7 to 10 (end of treatment). Both trials also reported the secondary outcome of continuous abstinence through weeks 2 to 50, and also 7-day point prevalence abstinence at weeks 8, 10 and 50. Although cessation and/or relapse prevention were the focus of the three trials, all of them also reported weight change as a secondary outcome of interest. The relapse prevention trial also reported on changes in HDL-cholesterol and in triglycerides.

## Risk of bias in included studies

None of the rimonabant trials has reported their methods of randomization or allocation concealment, and are therefore rated as 'unclear' for their attempts to control selection bias.

In our dependence upon unpublished reports, we have sometimes found the data to be inconsistent across different sources. The

denominators for the STRATUS-EU groups shift between sources and within the same source.

All three trials defined their abstinence outcome as 'prolonged' i.e. continuous after a post-quit date grace period of two weeks ([Hughes 2003](#)), and biochemically verified at each visit by expired carbon monoxide (CO) levels of 10 or fewer parts per million. In the cessation trials, cotinine was also used to verify abstinence at baseline, at weeks 8 and 10, and during the follow-up phase at weeks 14, 32 and 50. The relapse prevention trial used exhaled CO to verify abstinence during the 10-week cessation phase, and has not reported its validation procedure for the relapse prevention or the no-treatment phases.

Rates of non-completion of the treatment phase were around 30% for [STRATUS-US 2006](#), and around 40% for [STRATUS-EU 2006](#), without significantly different losses between groups. Non-completion rates for phases 1 and 2 have not been reported for the relapse prevention trial, and none of the trials has reported long-term losses to follow up.

## Effects of interventions

### Cessation

Both trials ([STRATUS-EU 2006](#); [STRATUS-US 2006](#)) detected a benefit of rimonabant 20 mg over placebo for prolonged abstinence at 50 weeks, although the odds ratio (OR) for the [STRATUS-EU 2006](#) trial failed to reach statistical significance (1.31, 95% confidence interval [CI] 0.83 to 2.09). The pooled risk ratio (RR) for the two trials was 1.50 (95% CI 1.10 to 2.05; *comparison 01.01*). The pooled RR for continuous abstinence at end of treatment (7 to 10 weeks) was similar, at 1.46 (95% CI 1.16 to 1.85; *comparison 01.02*). No significant benefit of rimonabant 5 mg over placebo was demonstrated at either 50 weeks (RR 1.12, 95% CI 0.80 to 1.56; *comparison 03.01*) or at end of treatment (RR 1.12, 95% CI 0.87 to 1.44; *comparison 03.02*).

We compared the effect of the two doses of rimonabant for prolonged abstinence at 50 weeks and at end of treatment across both trials, and found a modest benefit of the 20 mg regimen over the 5 mg regimen: RR 1.35, 95% CI 1.00 to 1.82 at 50 weeks (*comparison 04.01*), and RR 1.31, 95% CI 1.05 to 1.64 at end of treatment (*comparison 04.02*).

### Relapse prevention

At the end of the phase 1 10-week treatment regimen in [STRATUS-WW 2005](#), both the 5 mg and the 20 mg groups had similar cessation rates of 31.8% and 33.6% respectively. Those 5 mg quitters who were then randomized to the same treatment for phase 2 did not differ significantly from the 5 mg/placebo quitters in relapse rates at 52 weeks. The phase 1 20 mg quitters who were then randomized to the two active treatment groups in phase 2 maintained significantly higher cessation rates than the placebo group, with an RR for the phase 2 20 mg group of 1.29 (95% CI 1.06 to 1.57; *comparison 02.01*) and an RR for the phase 2 5 mg group of 1.30 (95% CI 1.06 to 1.59; *comparison 02.02*),



compared with placebo. Phase 2 participants were scheduled to be followed up for a period of 104 weeks, but we have no results beyond the 52-week outcomes described here.

### Weight change

#### *Findings for those maintaining abstinence from smoking:*

Among participants maintaining smoking abstinence from 2 to 48 weeks after their quit date, a pooled analysis for [STRATUS-EU 2006](#) and [STRATUS-US 2006](#) shows that those on rimonabant 20 mg gained significantly less weight than those on 5 mg or placebo ( $P < 0.05$ ; [STRATUS-EU 2006](#)). There was no significant difference for 5 mg versus placebo. Separate data for the American and European trials were not presented. At the 52-week follow up in [STRATUS-WW 2005](#), among those avoiding relapse to smoking post-cessation weight gain was significantly lower in the rimonabant 20 mg group versus placebo ( $P < 0.001$ ). Weight gain was similar in the placebo and rimonabant 5 mg groups. The extent of the weight gain in [STRATUS-WW 2005](#) was shown graphically, but not reported as absolute changes in kilos.

In a pooled analysis of [STRATUS-US 2006](#) and [STRATUS-EU 2006](#), among those remaining abstinent from smoking throughout the final four weeks of treatment, those taking rimonabant 20 mg gained significantly less weight than those on placebo ( $P < 0.001$ ), although it is unclear whether this was measured at ten or at 48 weeks. There were no significant differences when comparing 5 mg rimonabant with placebo. In [STRATUS-EU 2006](#), among non-obese participants, the rimonabant 20 mg users ( $N = 54$ ) had a mean weight gain of 0.5 kg; for rimonabant 5 mg (users  $N = 53$ ) the gain was 1.6 kg; those on placebo ( $N = 44$ ) gained 2.3 kg. Details of weight changes were not given for [STRATUS-US 2006](#).

#### *Findings using intention-to-treat (ITT) analysis:*

When considering all those smokers who were randomized (ITT analysis), in the [STRATUS-US 2006](#) trial, on average across the 10-week treatment period, those on rimonabant 20 mg lost 0.3 kg, while those on placebo gained 1.1 kg ( $P < 0.001$ ). Participants who were overweight (body mass index [BMI: weight in kg/height in m<sup>2</sup>] = 25 to 29.9) or obese (BMI = 30+) tended to lose weight using rimonabant 20 mg, while normal-weight participants (BMI = 18.5 to 24.9) did not. Overweight smokers on rimonabant 20 mg lost 0.5 kg on average, versus a gain of 0.9 kg for those on placebo. Obese smokers on rimonabant 20 mg lost 0.6 kg compared with a gain of 1.3 kg for those on placebo. For those of normal weight there was no weight change when using rimonabant 20 mg, but those on placebo gained 1.0 kg. Only the finding for obese smokers reached statistical significance ( $P < 0.001$ ). Weight change for the rimonabant 5 mg group was not reported.

Again using an ITT analysis, in [STRATUS-EU 2006](#) those on rimonabant 20 mg ( $N = 267$ ) lost 0.5 kg, while those on placebo ( $N = 260$ ) and 5 mg ( $N = 256$ ) gained 1.0 kg and 0.2 kg respectively, across the treatment period. In [STRATUS-WW 2005](#), among all re-randomized participants at the 52 week follow-up, those on rimonabant 20 mg ( $N=340$ ), 5 mg ( $N=335$ ) and placebo

( $N=342$ ) gained an average of 0.6 kg, 1.9 kg and 2.0 kg respectively. As with [STRATUS-US 2006](#), for [STRATUS-EU 2006](#) and [STRATUS-WW 2005](#) the difference in weight gain for 20 mg versus placebo reached statistical significance ( $P = 0.001$ ,  $P < 0.001$  respectively). Where there were missing data, the ITT analysis for [STRATUS-EU 2006](#) and [STRATUS-WW 2005](#) was based on 'last observation carried forward'. It is not clear whether this approach was also used for the ITT analysis for [STRATUS-US 2006](#). A study of taranabant ([Morrison 2010](#)), excluded from the report of findings for smoking cessation outcomes, reported weight change using ITT analysis for a comparison of taranabant (2-8 mg) versus placebo. After eight weeks of treatment, participants on taranabant lost an average of 1.5 kg, while those on placebo gained 0.6 kg. This difference reached statistical significance ( $P < 0.001$ ).

### Adverse events:

The three rimonabant trials demonstrated disparate patterns of adverse events. [STRATUS-US 2006](#) reported nausea as the most frequent side effect, occurring in 15.7% of the 20 mg group compared with 9.2% in the 5 mg group and 8.8% in the control group (differences not statistically significant). This paralleled the predominance and rates of nausea as the main side effect reported in the RIO trials, which tested rimonabant as a treatment for weight control ([Curioni 2006](#)). Nausea was not mentioned as a significant side effect in [STRATUS-EU 2006](#), which listed fatigue, depressed mood, anxiety and nasopharyngitis as the most commonly reported events. Upper respiratory tract infection was the most frequent adverse event for the [STRATUS-WW 2005](#) participants, at around 18% across all groups, with nasopharyngitis as the next most commonly reported event (mean 10.5% across all groups). Again, nausea was not mentioned as a significant side effect for any group in this trial. It should be noted, however, that the Summary of Product Characteristics ([Acomplia SPC 2006](#)) reports the incidence of nausea and upper respiratory tract infections as 'very common' (i.e.  $> 10\%$ ) when rimonabant is used for weight control.

Drop-out rates attributable to adverse events were consistently highest in the 20 mg groups and lowest in the control groups, with only [STRATUS-EU 2006](#) reporting a statistically significantly higher drop-out rate in the 20 mg group (14.6%) compared with the placebo group (6.9%;  $P = 0.004$ ). [STRATUS-EU 2006](#) reported significantly higher rates of drop-out attributable to adverse events across all groups (placebo 6.9%, 5 mg 9.8%, 20 mg 14.6%) compared with [STRATUS-US 2006](#) (3.8%, 5.7%, 6.9% respectively) and with [STRATUS-WW 2005](#) (6.1%, 6.3%, 9.7% respectively). However, the [STRATUS-EU 2006](#) attributable drop-out rates were similar to those reported in the four RIO trials ([Curioni 2006](#)).

Information on serious adverse events (SAEs) is sparse. At one year follow up, [STRATUS-WW 2005](#) reports SAE rates of 5%, 3.6% and 5.3% in placebo, 5 mg and 20 mg groups respectively. The corresponding figures for [STRATUS-EU 2006](#) are 2.7%, 0.8% and

2.2%, i.e. the placebo group reporting the highest rate, but with a statistically non-significant difference. [STRATUS-US 2006](#) has not reported separate group rates, but has confirmed that no cardiovascular safety concerns were raised by their findings. A pooled analysis of STRATUS-EU, STRATUS-META and STRATUS-US reports SAEs running at 2% in the rimonabant 20 mg group compared with 2.2% in the placebo group ([STRATUS META 2006](#)). This may be compared with SAE rates in the RIO (rimonabant in obesity) trials, which ranged from 4% to 8%, with a pooled relative risk increase of 1.37 (95% CI 1.04 to 1.80,  $P = 0.03$ ) in the 20 mg groups compared with placebo groups ([Curioni 2006](#)). Since the initial publication of our review in *The Cochrane Library* 2007 Issue 3, there have been trial reports of episodes of depression (in up to 10% of participants) and suicidal thoughts (in up to 1%), with possibly an increased risk in patients with a past history of psychiatric illness. In the USA, the FDA advisory board ([FDA 2007](#)) voted unanimously not to approve the drug for any use at present, until further data on its risk-benefit profile are available. In October 2008, the European Medicines Agency (EMA) instructed Sanofi Aventis to withdraw rimonabant, because of links with mental disorders ([Sanofi Aventis 2008](#)). There now seems no prospect of it ever being approved in any part of the world as an aid for smoking cessation.

[Morrison 2010](#) demonstrated no clear benefit of taranabant over placebo for smoking cessation, returning an OR for continuous abstinence at eight weeks of 1.2 (90% CI 0.6 to 2.5). Because the trial did not report abstinence rates beyond week eight (end of treatment), we have not included it in our meta-analyses. However, it provides data for consideration of adverse events. During the treatment phase, 83.6% of participants in the taranabant group suffered clinical adverse events, compared with 69.6% of the placebo group. SAE rates were 2.5% for the taranabant group versus 0.6% for the placebo group. Discontinuations ran at 12.6% for taranabant users versus 3.2% of those on placebo. The four SAEs in the taranabant group were agitation, palpitations, melanoma, and basal cell carcinoma, none of which was attributed directly to the active treatment. There was no suicidal behaviour by any participant during the treatment period, although suicidal ideation was reported in 3.2% of the taranabant group, compared with none in the placebo group. There were no significant differences in adverse events or SAEs between the groups during the post-treatment six-week follow-up period.

Taranabant as a treatment for obesity was found in another trial to be effective at relatively low doses (2 mg and 4 mg) over a two-year test period ([Aronne 2010](#)). However, the incidence of adverse events (gastrointestinal, nervous, psychiatric, cutaneous and vascular organ systems) was found to be dose-related, and was deemed unacceptable. The manufacturers (Merck & Co) decided in 2008 to discontinue further development of the drug for any indication.

## DISCUSSION

Our review has suffered from a lack of peer-reviewed and published study reports. Despite our best efforts to obtain information, we have had to rely on conference presentations, press releases and pharmaceutical company reports, and we are aware that the findings of this review are tentative and incomplete. We currently lack much methodological detail, including randomization and allocation procedures, exclusion criteria, verification methods, and levels of behavioural support. We would also welcome full details of attrition rates, losses to follow up, individual trial results and comprehensive long-term outcome data. Furthermore, all the trials reviewed were sponsored by the pharmaceutical company manufacturing rimonabant. Since conflicts of interest could influence the results, their findings should be treated with caution.

### Smoking cessation

Two cessation trials have detected a benefit of rimonabant 20 mg over placebo at longest reported follow up, with a statistically significant pooled risk ratio (RR) of 1.50. There was also a modest but significant benefit of the 20 mg dose over the 5 mg dose (pooled RR 1.35). These data are compatible with rimonabant's failure at the 5 mg dose to out-perform placebo treatment in these trials.

The pooled results mask the differential between the findings of the two trials. [STRATUS-EU 2006](#) consistently failed to demonstrate the superiority of rimonabant 20 mg over either placebo or rimonabant 5 mg for prolonged abstinence at either 50 weeks or at end of treatment (7 to 10 weeks). [STRATUS-US 2006](#) found statistically significant benefits for the 20 mg regimen for both comparisons and at both time points. The failure of rimonabant 20 mg to establish a significant benefit in the [STRATUS-EU 2006](#) trial can be largely attributed to an exceptionally high placebo quit rate (19.6% at end of treatment, 14.6% at 50 weeks). This sustained discrepancy between the two trials weakens the validity of the findings.

### Relapse prevention

It is worth noting that for the phase 1 (cessation) 20 mg quitters in [STRATUS-WW 2005](#), those randomized to a 5 mg maintenance dose (RR of 1.30 compared with placebo at 52 weeks) did at least as well as those randomized to a 20 mg maintenance dose (RR 1.29). This finding is difficult to interpret; considering only the phase 1 group who quit on 20 mg, it would suggest that the lower dose of maintenance therapy is as effective as the higher dose, and that both regimens yield better success rates than placebo treatment. However, for the phase 1 group who quit on 5 mg, randomized either to 5 mg or to placebo during the maintenance phase, the active treatment group did no better than the placebo group, suggesting that the presence or absence of treatment made no difference during the maintenance phase. Since the quit rates in both phase 1 groups were similar (31.8% in the 5 mg group

versus 33.6% in the 20 mg group), we have no consistent evidence from this trial for the relative efficacy of the two doses, either for cessation or for maintenance. We also lack information on the phase 3 findings, which covered a further 52 weeks without treatment.

### Weight change

Among abstinent smokers, we found a statistically significant effect of rimonabant 20 mg on body weight. Compared with placebo, rimonabant 20 mg produced significantly less weight gain at end of treatment in two trials. Only one of these trials reported the magnitude of the weight reduction and only for non-obese participants. In this study those on rimonabant gained 1.8 kg less than those on placebo. At 48-week follow-up a pooled analysis of the two trials showed that there was significantly less weight gain for rimonabant 20 mg versus placebo, among those maintaining abstinence. However, a separate analysis for each trial was not presented. In the trial of relapse prevention, those avoiding relapse up to 52 weeks gained significantly less weight on rimonabant 20 mg versus placebo, but the magnitude of the weight gain was not given. Using an intention to treat (ITT) approach, one trial showed significantly less weight gain for rimonabant 20 mg versus placebo at end of treatment, and another study showed the same benefit at 52 weeks follow-up. However, both these analyses were based on 'last observation carried forward', which makes interpretation difficult (see comments below). In addition, only one of these trials presented the weight changes and in this study those on rimonabant 20 mg gained just 1.4 kg less than those on placebo at 52 weeks. The third trial reported a significant benefit of rimonabant 20 mg, compared with placebo, on weight gain only for obese individuals. Overall, the findings suggest that rimonabant 20 mg may have a modest benefit for moderating weight gain following smoking cessation both in the short-term and the long-term, but the magnitude of this benefit is not clear and methodological limitations make interpretation problematic. Without further data it is not possible to judge the clinical significance of any benefits for rimonabant on weight gain.

In nearly all cases the magnitude of the weight change was not reported or was reported only for a sub-sample, and in no cases were 95% confidence intervals given. For two trials the key outcome of weight change among confirmed quitters at the final follow up was reported using only a pooled analysis combining data from both studies. None of the studies presented an analysis exclusively for those who relapsed or continued to smoke. Only one report examined weight changes according to whether participants were obese, overweight or of normal weight at baseline. The outcomes for prolonged smoking cessation were based on the recommended two-week grace period (Hughes 2003), whereas weight change was assessed among those who had abstained following a four-week grace period. It is not clear why this unconventional criterion for prolonged abstinence was used for weight change.

For the ITT analysis, where there were missing weight data the last observation was carried forward. This approach makes the unrealistic assumption that weight remains constant since the last measurement. Consequently, the results may have been biased in either direction. For example, if those on placebo dropped out of the study because they were gaining weight, then carrying the last observation forward is likely to underestimate their weight gain. This may then lead to underestimation of the benefit of rimonabant compared with placebo. Conversely, if some of those on rimonabant withdrew because of weight gain, then carrying their last observation forward may underestimate the mean weight gain in this group. The benefit of rimonabant versus placebo would in that case be overestimated. As the attrition rates were not reported it is not possible to estimate the extent of this problem. High attrition rates would compromise the validity of an ITT analysis. The obvious solution would be to measure all participants, even if they did not adhere to the treatment. Another issue related to drop-outs is that it is possible that some individuals did not take rimonabant as prescribed but still managed to stop smoking with little weight gain and attended the follow-up visits. The number of these individuals is not given, and this may distort the results in a way that overestimates the benefit of rimonabant for weight loss.

The taranabant trial, excluded from the analysis for smoking cessation outcomes, reported a benefit for taranabant over placebo in reducing or eliminating weight gain by end of treatment (eight weeks). An ITT analysis was used, with the last observation carried forward in the case of missing data. As discussed in the previous paragraph, this approach may compromise the results.

## AUTHORS' CONCLUSIONS

### Implications for practice

- From the limited evidence available, rimonabant 20 mg increased by about 1½-fold the chances of long-term cessation. The 5 mg dose appeared to confer no significant benefit. However, in the absence of detailed peer-reviewed reports, the trial findings remain inconsistent and provisional.
- Taranabant as an aid to smoking cessation (assessed after eight weeks of treatment) was not found to confer significant benefit over placebo treatment.
- Adverse events for rimonabant may be dose-related, and may include upper respiratory tract infection and nausea. The severity and type of adverse event were inconsistent across the three trials included in this review.

- Rates of serious adverse events were reported in the trials to be low. However, the use of rimonabant as an aid to weight loss was suspended in European countries in October 2008, because of links to mental disorders including depression and suicidal thoughts. Adverse events for taranabant were dose-related, and contributed to the manufacturer's decision in 2008 to suspend development of the drug for any indication.

- Partial study reports, without long-term outcomes at the end of the no-treatment phase, preclude any clear findings on the use of rimonabant for maintenance of abstinence.

- Based on the findings of one study, rimonabant 20 mg may moderate weight gain among those who abstain from smoking for approximately one year. There is insufficient information from the other two trials to substantiate this finding.

- Based on the findings of one study, taranabant 2-8 mg may moderate weight gain by the end of eight weeks of treatment.

### Implications for research

- Rimonabant's withdrawal as a prescription drug in Europe and the FDA's decision not to license it for any indication make

it unlikely that rimonabant will ever be approved anywhere as an aid to smoking cessation.

- Taranabant's lack of efficacy for smoking cessation, combined with an unacceptable adverse events profile, means that it will no longer be developed or promoted either for obesity or for smoking cessation.

- Although neither drug will be licensed or promoted for smoking cessation, the principle of modulating the endocannabinoid system to reduce urges to smoke remains a plausible approach, provided that adverse events can be reduced to acceptable levels.

## ACKNOWLEDGEMENTS

We thank David Balfour and Bess Marcus for reading and commenting on the protocol, and David Balfour and John Stapleton for commenting on the full review. We also thank Professor RM Anthenelli for clarifying some data issues on the STRATUS-US trial report from the 2004 ACC Meeting.

## REFERENCES

### References to studies included in this review

#### STRATUS-EU 2006 {published and unpublished data}

\* Cinciripini PM, Aubin H-J, Dale LC, Niaura R, Anthenelli RM, Robinson J. Pooled analysis of three short-term, randomised, double-blind, placebo-controlled trials with rimonabant 20 mg/d in smoking cessation [PI-TS-01]. Society for Research on Nicotine and Tobacco 8th European Conference, September 2006, Kusadasi Turkey. 2006. [clinicaltrials.gov ID NCT00464165]  
Sanofi Aventis. Information Meeting. [http://en.sanofi-aventis.com/Images/en\\_050301\\_up\\_2004\\_Full\\_Year\\_Results\\_Analysts\\_Investors\\_meeting\\_in\\_Paris\\_presentation\\_2006.pdf](http://en.sanofi-aventis.com/Images/en_050301_up_2004_Full_Year_Results_Analysts_Investors_meeting_in_Paris_presentation_2006.pdf) (accessed 23rd November 2006) 2005.

#### STRATUS-US 2006 {published and unpublished data}

Anthenelli RM, Depres J-P. Effects of rimonabant in the reduction of major cardiovascular risk factors. Results from the STRATUS-US Trial (smoking cessation in smokers motivated to quit) and the RIO-LIPIDS Trial (weight reducing and metabolic effects in overweight/obese patients with dyslipidemia. American College of Cardiology Annual Scientific Session. March 2004.

Boyd ST, Fremming BA. Rimonabant - a selective CB1 antagonist. *Annals of Pharmacotherapy* 2005;39:684-90.

\* Cinciripini PM, Aubin H-J, Dale LC, Niaura R, Anthenelli RM, Robinson J. Pooled analysis of three short-

term, randomised, double-blind, placebo-controlled trials with rimonabant 20 mg/d in smoking cessation [PI-TS-01]. Society for Research on Nicotine and Tobacco 8th European Conference, September 2006, Kusadasi Turkey. 2006. [clinicaltrials.gov ID NCT00358228]

#### STRATUS-WW 2005 {published and unpublished data}

\* Niaura R. Long-term maintenance of abstinence from smoking with rimonabant: results from the STRATUS Worldwide trial. 1-year efficacy/safety results. *American Thoracic Society Conference* 2005. [clinical trials.gov ID NCT00459173]

Niaura R. Long-term maintenance of abstinence from smoking with rimonabant: results from the STRATUS Worldwide trial. 6-month efficacy/safety results [POS1-054]. *American Thoracic Society Conference*. 2004.

Sanofi Aventis. Information Meeting. [http://en.sanofi-aventis.com/Images/en\\_050301\\_up\\_2004\\_Full\\_Year\\_Results\\_Analysts\\_Investors\\_meeting\\_in\\_Paris\\_presentation\\_2006.pdf](http://en.sanofi-aventis.com/Images/en_050301_up_2004_Full_Year_Results_Analysts_Investors_meeting_in_Paris_presentation_2006.pdf) (accessed 23rd November 2006) 2005.

### References to studies excluded from this review

#### Morrison 2010 {published data only}

Morrison MF, Ceesay P, Gantz I, Kaufman KD, Lines CR. Randomized, controlled, double-blind trial of taranabant

- for smoking cessation. *Psychopharmacology* 2010;**209**: 245–53. [clinicaltrials.gov ID NCT00109135]
- Rigotti 2009** {published data only}  
 \* Rigotti NA, Gonzales D, Dale LC, Lawrence D, Chang Y. A randomized controlled trial of adding the nicotine patch to rimonabant for smoking cessation: efficacy, safety and weight gain. *Addiction* 2009;**104**(2):266–76.  
 Stapleton J. Trial comes too late as psychiatric side effects end hope for rimonabant. *Addiction* 2009;**104**(2):277–8.
- STRATUS META 2006** {unpublished data only}  
 Cinciripini PM, Aubin H-J, Dale LC, Niaura R, Anthenelli RM, Robinson J. Pooled analysis of three short-term, randomised, double-blind, placebo-controlled trials with rimonabant 20 mg/d in smoking cessation [PI-TS-01]. Society for Research on Nicotine and Tobacco 8th European Conference, September 2006, Kusadasi Turkey. 2006.  
 \* Sanofi Aventis. Comparison of efficacy and safety of rimonabant 20mg/day versus placebo in smoking cessation. <http://clinicaltrials.gov/show/NCT00464256> (accessed 17th October 2007) 2007. [clinicaltrials.gov ID NCT00464256]
- Topol 2010** {published data only}  
 Topol EJ, Boussier MG, Fox KA, Creager MA, Despres JP, Easton JD, et al. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. *Lancet* 2010;**376** (9740):517–23. [clinicaltrials.gov ID NCT00263042]
- Additional references**
- ACC 2004**  
 American College of Cardiology. Data shows new drug, rimonabant, helps smokers quit while limiting post cessation weight gain. [www.eurekalert.org/pub\\_releases/2004-03/k-dsn030904.php](http://www.eurekalert.org/pub_releases/2004-03/k-dsn030904.php) (accessed September 15 2004).
- Acomplia SPC 2006**  
 Sanofi-Aventis. Acomplia 20mg Summary of Product Characteristics. <http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=18283> (accessed 18th April 2007) 2006.
- Aronne 2010**  
 Aronne LJ, Tonstad S, Moreno M, Gantz I, Erondun N, Suryawanshi S, et al. A clinical trial assessing the safety and efficacy of taranabant, a CB1R inverse agonist, in obese and overweight patients: a high-dose study. *International Journal of Obesity* 2010;**34**(5):919–35.
- Cleland 2004**  
 Cleland JGF, Ghosh J, Freemantle N, Kaye GC, Nasir M, Clark AL, et al. Clinical trials update and cumulative meta-analyses from the American College of Cardiology: WATCH, SCD-HeFT, DINAMIT, CASINO, INSPIRE, STRATUS-US, RIO-LIPIDS and cardiac resynchronisation therapy in heart failure. *European Journal of Heart Failure* 2004;**6**:501–8.
- Cochrane Handbook**  
 Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. <http://www.cochrane.org/resources/handbook/hbook.htm> (accessed 18th April 2007) 2006.
- Curioni 2006**  
 Curioni C, Andre C. Rimonabant for overweight or obesity. *Cochrane Database of Systematic Reviews* 2006, Issue 4.
- Fagerström 2006**  
 Fagerström K, Balfour DJK. Neuropharmacology and potential efficacy of new treatments for tobacco dependence. *Expert Opinion on Investigational Drugs* 2006;**15**(2):107–16.
- FDA 2007**  
 Food, Drug Administration. Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee meeting on June 13, 2007. [www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4306m1-final.pdf](http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4306m1-final.pdf) (accessed 6th August 2007) 2007.
- Filozof 2004**  
 Filozof C, Pinilla MC, Fernandez-Cruz A. Smoking cessation and weight gain. *Obesity Review* 2004;**5**:95–103.
- Fremming 2008**  
 Fremming BA, Boyd ST. Taranabant, a novel cannabinoid type 1 receptor inverse agonist. *Current Opinion in Investigational Drugs* 2008;**9**(10):1116–29.
- Gelfand 2006**  
 Gelfand EV, Cannon CP. Rimonabant: a selective blocker of the cannabinoid CB1 receptors for the management of obesity, smoking cessation and cardiometabolic risk factors. *Expert Opinion on Investigational Drugs* 2006;**15**(3):307–15.
- Hughes 2003**  
 Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: issues and recommendations. *Nicotine & Tobacco Research* 2003;**5**(1):13–25.
- Le Foll 2008**  
 Le Foll B, Forget B, Aubin H-J, Goldberg SR. Blocking cannabinoid CB1 receptors for the treatment of nicotine dependence: insights from preclinical and clinical studies. *Addiction Biology* 2008;**13**(2):239–52.
- Mizoue 1998**  
 Mizoue T, Ueda R, Tokui N, Hino Y, Yoshimura T. Body mass decrease after initial gain following smoking cessation. *International Journal of Epidemiology* 1998;**27**:984–8.
- O'Hara 1998**  
 O'Hara P, Connett JE, Lee WW, Nides M, Murray R, Wise R. Early and late weight gain following smoking cessation in the Lung Health Study. *American Journal of Epidemiology* 1998;**148**(9):821–30.
- ONS 2002**  
 Office for National Statistics. Smoking-related behaviour and attitudes. <http://www.dh.gov.uk/assetRoot/04/06/81/56/04068156.pdf> (accessed 11th April 2005).
- Pomerleau 2000**  
 Pomerleau CS, Pomerleau OF, Namenek RJ, Mehlinger AM. Short-term weight gain in abstaining women smokers.

*Journal of Substance Abuse and Treatment* 2000;**18**(4): 339–42.

**Sanofi 2003**

Sanofi--Synthelabo. *RIO and STRATUS Clinical Studies Guide*. Sanofi-Synthelabo, 2003.

**Sanofi Aventis 2008**

Sanofi Aventis. Acomplia update post EMEA recommendation. [http://en.sanofi-aventis.com/binaries/20081023\\_Acomplia\\_Update\\_presentation\\_tcm28-22428.pdf](http://en.sanofi-aventis.com/binaries/20081023_Acomplia_Update_presentation_tcm28-22428.pdf) 2008.

**Sanofi-Synth 2004**

Sanofi-Synthelabo. Two pivotal studies indicate ACOMPLIA (rimonabant) offers a novel approach to cardiovascular risk management in overweight/obese

people and smokers. [http://es.sanofi-synthelabo.com/press/ppc\\_23804.asp](http://es.sanofi-synthelabo.com/press/ppc_23804.asp) (accessed September 15 2004).

**USPHS 1990**

US Public Health Service. The health benefits of smoking cessation: A report of the Surgeon General. DHHS Publication No CDC 90-8416 1990; Vol. Washington DC.

**References to other published versions of this review**

**Cahill 2007**

Cahill K, Ussher M. Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation. *Cochrane Database of Systematic Reviews* 2007, Issue 4. DOI: 10.1002/14651858.CD005353.pub3

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### STRATUS-EU 2006

Methods	SMOKING CESSATION Country: Belgium, Denmark, France, Spain, Sweden, Switzerland, UK Setting: Study Design: Double-blind placebo-controlled parallel-assignment RCT. Analysis: Logistic regression on ITT basis.
Participants	783 adults ( $\geq 18$ ) smoking at least 10 CPD. Randomized to rimonabant 5mg (N=256), rimonabant 20mg (N=267), or placebo (N=260). 46% M, 98% W, mean age 42.4, av CPD 22.5, mean yrs smoking 24.9, mean quit attempts 2.9, mean FTND score 5.6, 35% with a FTND score $>7$ . Mean BMI 25.0
Interventions	(i) Rimonabant 5 mg (ii) Rimonabant 20 mg (iii) Placebo tablets 2-wk pre-treatment screening period, then 10 wks treatment, with TQD at day 15. Behavioural support: Treatment phase: Participants were seen weekly for 12 wks (-2 to +10 wks). Brief behavioural counselling at every visit on tobacco-related topics (e.g. craving, relapse prevention) including diet and exercise, but no dietary restrictions. Follow-up phase: clinic visits at wks 11, 14, 22, 30, 39, 48
Outcomes	Primary outcome: Continuous validated abstinence at 7-10 wks. Maximum follow up: 48 wks. Strictest measure of abstinence: Prolonged validated abstinence from tobacco or nicotine products from wk 2 to wk 48. Validation method: Expired CO $<10$ ppm at all visits, + cotinine at baseline, wks 8 and 10, and at wks 14, 32 and 50. Other outcomes: weight change; adverse events.
Notes	Identical design to STRATUS-US trial. Trial was funded by the manufacturers, Sanofi Aventis.

#### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Reported as double-blind, but no details given
Other bias	Unclear risk	Not stated

## STRATUS-US 2006

Methods	<p>SMOKING CESSATION</p> <p>Country: USA</p> <p>Setting: Sanofi Clinic, Pennsylvania</p> <p>Study Design: Double-blind placebo-controlled parallel-assignment RCT.</p> <p>Analysis: Logistic regression on ITT basis.</p>
Participants	<p>784 adults (<math>\geq 18</math>) smoking at least 10 CPD. Randomized to rimonabant 5mg (N=262), rimonabant 20mg (N=261), or placebo (N=261).</p> <p>51% M, 87% W, mean age 42.3, av CPD 23.6, mean yrs smoking 24.1, mean quit attempts 4.1, mean FTND score 5.4, 31.7% with a FTND score <math>&gt;7</math>. Mean BMI 27.8</p>
Interventions	<p>(i) Rimonabant 5 mg (ii) Rimonabant 20 mg (iii) Placebo tablets</p> <p>2-wk pre-treatment screening period, then 10 wks treatment, with TQD at day 15.</p> <p>Behavioural support:</p> <p>Treatment phase: Participants were seen weekly for 12 wks (-2 to +10 wks). Brief behavioural counselling at every visit on tobacco-related topics (e.g. craving, relapse prevention) including diet and exercise, but no dietary restrictions.</p> <p>Follow-up phase: clinic visits at wks 11, 14, 22, 30, 39, 48</p>
Outcomes	<p>Primary outcome: Continuous validated abstinence at 7-10 wks. Maximum follow up: 48 wks. Strictest measure of abstinence: Prolonged validated abstinence from tobacco or nicotine products from wk 2 to wk 48.</p> <p>Validation method: Expired CO <math>&lt;10</math>ppm at all visits, + cotinine at baseline, wks 8 and 10, and at wks 14, 32 and 50.</p> <p>Other outcomes: weight change; adverse events.</p>
Notes	<p>Identical design to STRATUS-EU trial.</p> <p>Trial was funded by the manufacturers, Sanofi Aventis.</p>

### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Reported as double-blind, but no details supplied
Other bias	Unclear risk	Not stated



## STRATUS-WW 2005

Methods	RELAPSE PREVENTION TRIAL Country: Australia, Canada, USA Study Design: Double-blind placebo-controlled parallel-assignment RCT. Analysis: Logistic regression on ITT basis.
Participants	5055 adult smokers (>+18) motivated to quit. randomized to rimonabant 5mg (N=2026) or rimonabant 20mg (N=3029). 50% M, 88.8% W, mean age 44.1, av CPD 23.6, mean yrs smoking 24.1, mean quit attempts 4.1, mean FTND score 5.4, 31.7% with a FTND score >7. Mean BMI 27.8
Interventions	Phase 1: Cessation: Participants randomized to rimonabant 5mg [R5] (N=2026) or rimonabant 20mg [R20] (N=3029) for 10 wks, with TQD at day 15. Cessation rates at EoT: R5: 644/2026 (31.8%); R20 1017/3029 (33.6%), difference non-significant; Quitters eligible for Phase 2 if: (a) self-reported abstinence for 7+ days, (b) CO <= 10ppm, and (c) compliance level of 80%+ in last 4 wks of Phase 1. Phase 2: Relapse prevention: Re-randomized 644 quitters in R5 group to (i) R5 (N=322) or (ii) placebo (N=322), and 1017 quitters in R20 group to (i) R5 (N=335) or (ii) R20 (N=340) or (iii) placebo (N=342). All groups received treatment for a further 42 wks. Behavioural support: Not reported.
Outcomes	Primary outcome: Time to relapse for quitters from wks 10 to 32. Relapse defined as >= 7 consecutive days of smoking (even a puff), or >= 2 consecutive days with >= 5 cigs (even a puff) smoked per day. Long-term follow up: 52 wks, 104 wks. Secondary outcome: time to relapse for quitters from wks 10 to 52. Other outcomes: weight change; fasting HDL-cholesterol, triglycerides; safety, adverse events. Validation: Phase 1: expired CO <10ppm; Phase 2: not reported
Notes	Two-year follow-up data were not reported. Trial was funded by the manufacturers, Sanofi Aventis.

### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Reported as double-blind, but no details given.
Other bias	Unclear risk	Not stated

BMI: body mass index (metric measure of weight/height squared)

CPD: cigarettes per day  
 EoT: end of treatment  
 FTND: Fagerstrom Test for Nicotine Dependence  
 ITT: Intention to treat (includes all randomized in original groups)  
 M: male  
 TQD: target quit date  
 W: white

### Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
<a href="#">Morrison 2010</a>	RCT of 317 smokers randomized to taranabant 2-8 mg daily vs placebo. Trial lasted 8 wks, with primary outcome PPA for wks 5-8. Adverse events covered in Discussion section
<a href="#">Rigotti 2009</a>	The CIRRUUS trial. RCT of 755 smokers; all received open-label rimonabant. Intervention being tested was the addition of an active nicotine patch or placebo patch
<a href="#">STRATUS META 2006</a>	RCT in USA of 530 smokers randomized to rimonabant 20mg or placebo; cessation reported at 10 wks, EoT, with no long-term follow up
<a href="#">Topol 2010</a>	CRESCENDO trial: Multicentre in 42 countries, with 18,695 pts. Trial was prematurely discontinued in November 2008, because of concerns at raised levels of gastrointestinal, neuropsychiatric and serious psychiatric side effects in rimonabant pts compared with placebo pts. Four rimonabant pts had committed suicide, compared with 1 placebo pt

## DATA AND ANALYSES

### Comparison 1. Rimonabant 20mg vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Prolonged abstinence at wk 50	2	1049	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.10, 2.05]
2 Continuous 4-wk abstinence at EOT (wks 7-10)	2	1049	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.16, 1.85]

### Comparison 2. Relapse prevention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 rimonabant 20mg vs placebo at 52 weeks	1	682	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.06, 1.57]
2 rimonabant 5mg vs placebo at 52 weeks	1	677	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.06, 1.59]

### Comparison 3. Rimonabant 5mg vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Prolonged abstinence at wk 50	2	1039	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.80, 1.56]
2 Continuous 4-wk abstinence at EOT (wks 7-10)	2	1039	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.87, 1.44]

### Comparison 4. Rimonabant 20mg vs rimonabant 5mg

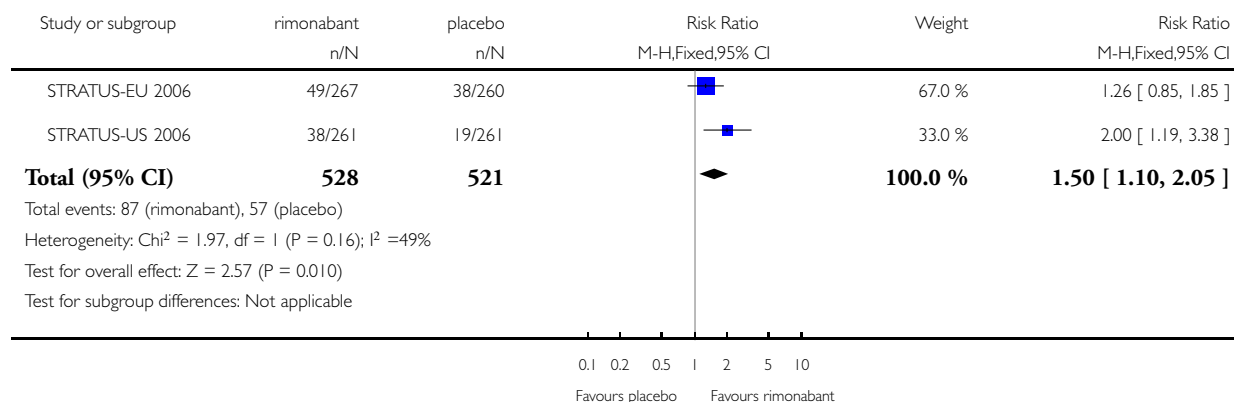
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Prolonged abstinence at wk 50	2	1046	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.00, 1.82]
2 Continuous 4-wk abstinence at EOT (wks 7-10)	2	1046	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.05, 1.64]

### Analysis 1.1. Comparison 1 Rimonabant 20mg vs placebo, Outcome 1 Prolonged abstinence at wk 50.

Review: Cannabinoid type 1 receptor antagonists for smoking cessation

Comparison: 1 Rimonabant 20mg vs placebo

Outcome: 1 Prolonged abstinence at wk 50

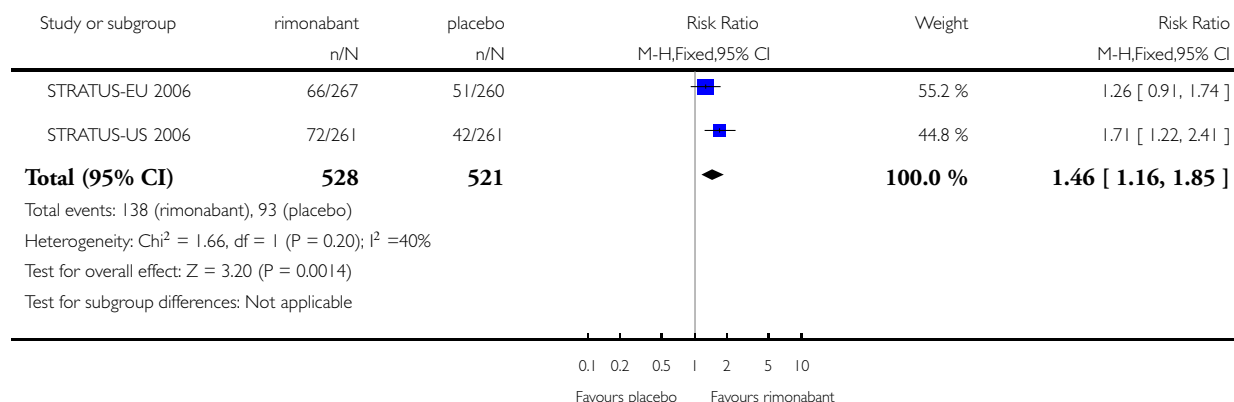


### Analysis 1.2. Comparison 1 Rimonabant 20mg vs placebo, Outcome 2 Continuous 4-wk abstinence at EOT (wks 7-10).

Review: Cannabinoid type 1 receptor antagonists for smoking cessation

Comparison: 1 Rimonabant 20mg vs placebo

Outcome: 2 Continuous 4-wk abstinence at EOT (wks 7-10)

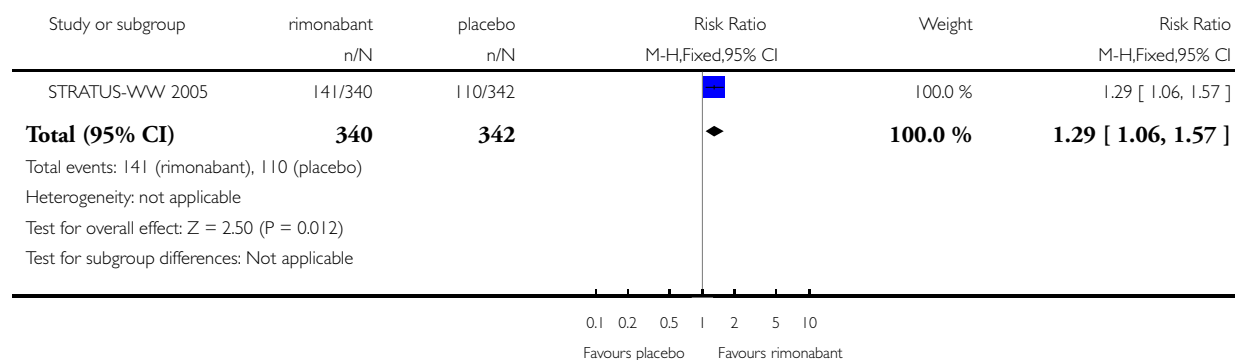


## Analysis 2.1. Comparison 2 Relapse prevention, Outcome 1 rimonabant 20mg vs placebo at 52 weeks.

Review: Cannabinoid type 1 receptor antagonists for smoking cessation

Comparison: 2 Relapse prevention

Outcome: 1 rimonabant 20mg vs placebo at 52 weeks

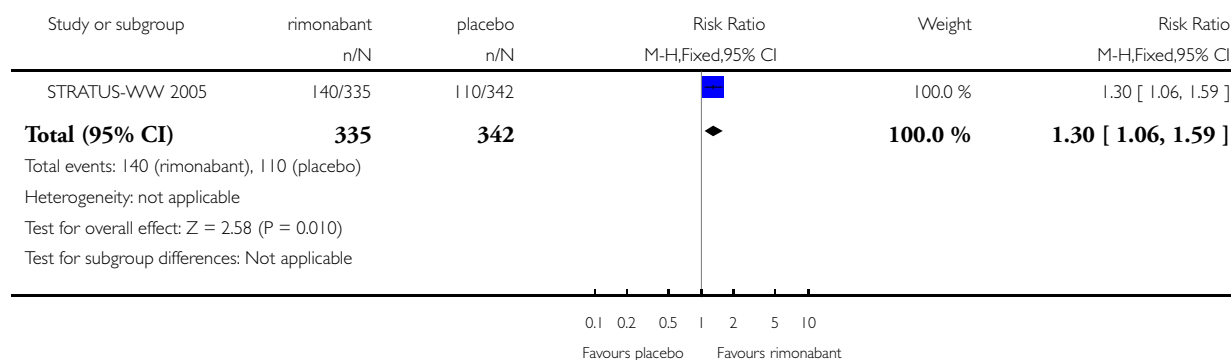


## Analysis 2.2. Comparison 2 Relapse prevention, Outcome 2 rimonabant 5mg vs placebo at 52 weeks.

Review: Cannabinoid type 1 receptor antagonists for smoking cessation

Comparison: 2 Relapse prevention

Outcome: 2 rimonabant 5mg vs placebo at 52 weeks

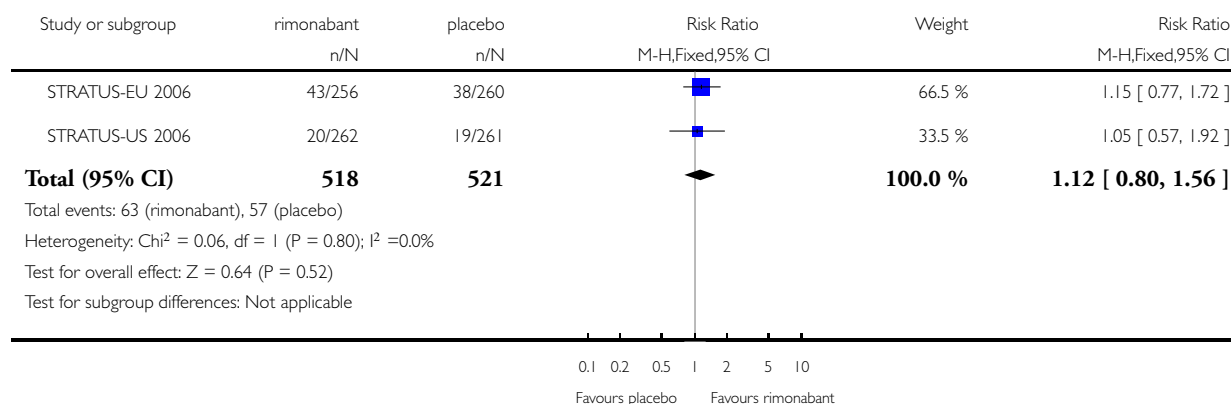


## Analysis 3.1. Comparison 3 Rimonabant 5mg vs placebo, Outcome 1 Prolonged abstinence at wk 50.

Review: Cannabinoid type 1 receptor antagonists for smoking cessation

Comparison: 3 Rimonabant 5mg vs placebo

Outcome: 1 Prolonged abstinence at wk 50

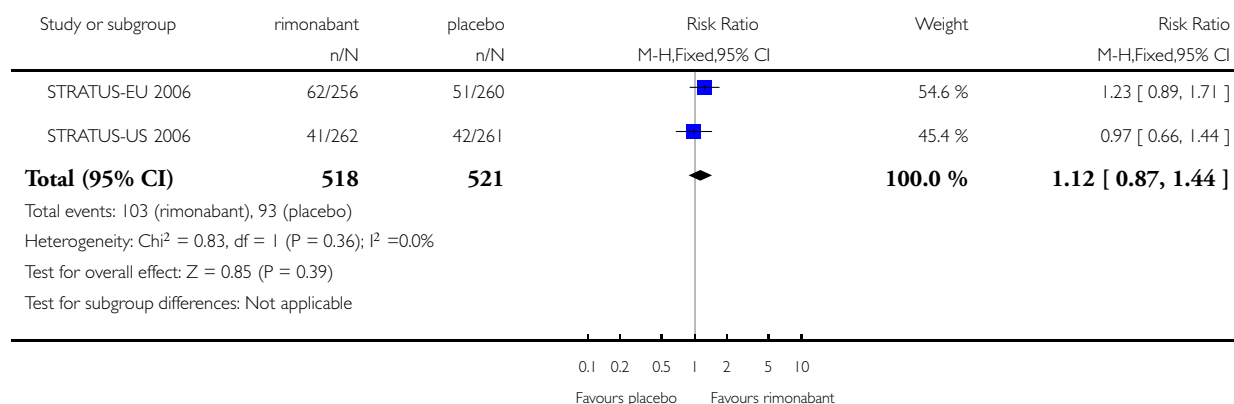


### Analysis 3.2. Comparison 3 Rimonabant 5mg vs placebo, Outcome 2 Continuous 4-wk abstinence at EOT (wks 7-10).

Review: Cannabinoid type 1 receptor antagonists for smoking cessation

Comparison: 3 Rimonabant 5mg vs placebo

Outcome: 2 Continuous 4-wk abstinence at EOT (wks 7-10)

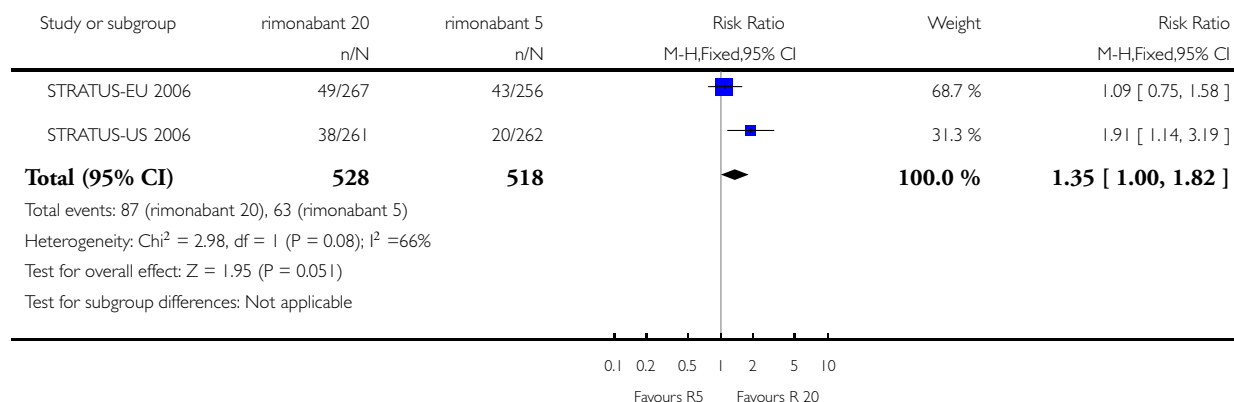


### Analysis 4.1. Comparison 4 Rimonabant 20mg vs rimonabant 5mg, Outcome 1 Prolonged abstinence at wk 50.

Review: Cannabinoid type 1 receptor antagonists for smoking cessation

Comparison: 4 Rimonabant 20mg vs rimonabant 5mg

Outcome: 1 Prolonged abstinence at wk 50

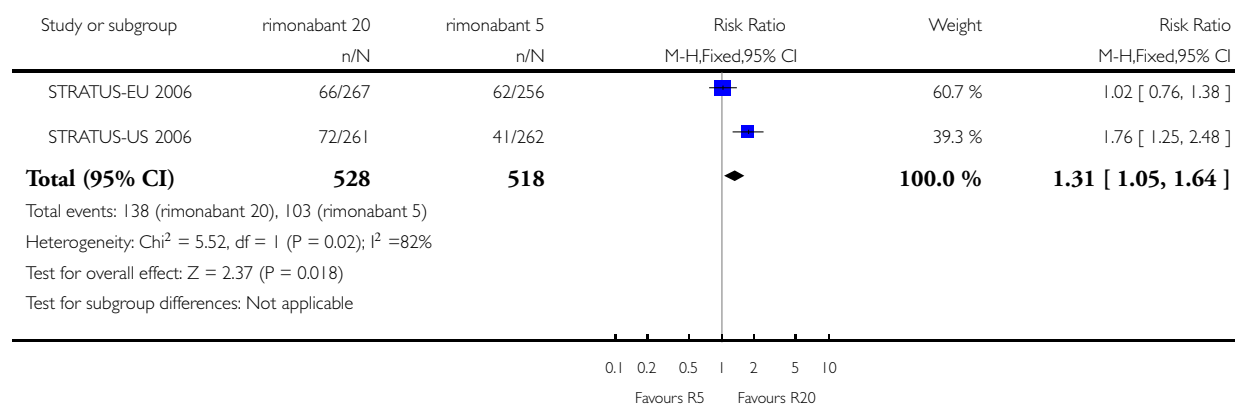


## Analysis 4.2. Comparison 4 Rimonabant 20mg vs rimonabant 5mg, Outcome 2 Continuous 4-wk abstinence at EOT (wks 7-10).

Review: Cannabinoid type 1 receptor antagonists for smoking cessation

Comparison: 4 Rimonabant 20mg vs rimonabant 5mg

Outcome: 2 Continuous 4-wk abstinence at EOT (wks 7-10)



## APPENDICES

### Appendix I. Glossary of tobacco-specific terms

Term	Definition
Abstinence	A period of being quit, i.e. stopping the use of cigarettes or other tobacco products, May be defined in various ways; see also: point prevalence abstinence; prolonged abstinence; continuous/sustained abstinence



(Continued)

Biochemical verification	Also called 'biochemical validation' or 'biochemical confirmation': A procedure for checking a tobacco user's report that he or she has not smoked or used tobacco. It can be measured by testing levels of nicotine or cotinine or other chemicals in blood, urine, or saliva, or by measuring levels of carbon monoxide in exhaled breath or in blood
Bupropion	A pharmaceutical drug originally developed as an antidepressant, but now also licensed for smoking cessation; trade names Zyban, Wellbutrin (when prescribed as an antidepressant)
Carbon monoxide (CO)	A colourless, odourless highly poisonous gas found in tobacco smoke and in the lungs of people who have recently smoked, or (in smaller amounts) in people who have been exposed to tobacco smoke. May be used for biochemical verification of abstinence
Cessation	Also called 'quitting' The goal of treatment to help people achieve abstinence from smoking or other tobacco use, also used to describe the process of changing the behaviour
Continuous abstinence	Also called 'sustained abstinence' A measure of cessation often used in clinical trials involving avoidance of all tobacco use since the quit day until the time the assessment is made. The definition occasionally allows for lapses. This is the most rigorous measure of abstinence
'Cold Turkey'	Quitting abruptly, and/or quitting without behavioural or pharmaceutical support
Craving	A very intense urge or desire [to smoke]. See: Shiffman et al 'Recommendations for the assessment of tobacco craving and withdrawal in smoking cessation trials' Nicotine & Tobacco Research 2004: 6(4): 599-614
Dopamine	A neurotransmitter in the brain which regulates mood, attention, pleasure, reward, motivation and movement
Efficacy	Also called 'treatment effect' or 'effect size': The difference in outcome between the experimental and control groups
Harm reduction	Strategies to reduce harm caused by continued tobacco/nicotine use, such as reducing the number of cigarettes smoked, or switching to different brands or products, e.g. potentially reduced exposure products (PREPs), smokeless tobacco
Lapse/slip	Terms sometimes used for a return to tobacco use after a period of abstinence. A lapse or slip might be defined as a puff or two on a cigarette. This may proceed to relapse, or abstinence may be regained. Some definitions of continuous, sustained or prolonged abstinence require complete abstinence, but some allow for a limited number or duration of slips. People who lapse are very likely to relapse, but some treatments may have their effect by helping people recover from a lapse

(Continued)

nAChR	[neural nicotinic acetylcholine receptors]: Areas in the brain which are thought to respond to nicotine, forming the basis of nicotine addiction by stimulating the overflow of dopamine
Nicotine	An alkaloid derived from tobacco, responsible for the psychoactive and addictive effects of smoking
Nicotine Replacement Therapy (NRT)	A smoking cessation treatment in which nicotine from tobacco is replaced for a limited period by pharmaceutical nicotine. This reduces the craving and withdrawal experienced during the initial period of abstinence while users are learning to be tobacco-free. The nicotine dose can be taken through the skin, using patches, by inhaling a spray, or by mouth using gum or lozenges
Outcome	Often used to describe the result being measured in trials that is of relevance to the review. For example smoking cessation is the outcome used in reviews of ways to help smokers quit. The exact outcome in terms of the definition of abstinence and the length of time that has elapsed since the quit attempt was made may vary from trial to trial
Pharmacotherapy	A treatment using pharmaceutical drugs, e.g. NRT, bupropion
Point prevalence abstinence (PPA)	A measure of cessation based on behaviour at a particular point in time, or during a relatively brief specified period, e.g. 24 hours, 7 days. It may include a mixture of recent and long-term quitters. cf. prolonged abstinence, continuous abstinence
Prolonged abstinence	A measure of cessation which typically allows a 'grace period' following the quit date (usually of about two weeks), to allow for slips/lapses during the first few days when the effect of treatment may still be emerging. See: Hughes et al 'Measures of abstinence in clinical trials: issues and recommendations'; Nicotine & Tobacco Research, 2003; 5 (1); 13-25
Relapse	A return to regular smoking after a period of abstinence
Secondhand smoke	Also called passive smoking or environmental tobacco smoke [ETS] A mixture of smoke exhaled by smokers and smoke released from smouldering cigarettes, cigars, pipes, bidis, etc. The smoke mixture contains gases and particulates, including nicotine, carcinogens and toxins
Self-efficacy	The belief that one will be able to change one's behaviour, e.g. to quit smoking
SPC [Summary of Product Characteristics]	Advice from the manufacturers of a drug, agreed with the relevant licensing authority, to enable health professionals to prescribe and use the treatment safely and effectively
Tapering	A gradual decrease in dose at the end of treatment, as an alternative to abruptly stopping treatment
Titration	A technique of dosing at low levels at the beginning of treatment, and gradually increasing to full dose over a few days, to allow the body to get used to the drug. It is designed to limit side effects

(Continued)

Withdrawal	A variety of behavioural, affective, cognitive and physiological symptoms, usually transient, which occur after use of an addictive drug is reduced or stopped. See: Shiffman et al 'Recommendations for the assessment of tobacco craving and withdrawal in smoking cessation trials' Nicotine & Tobacco Research 2004; 6(4): 599-614
------------	--

## WHAT'S NEW

Last assessed as up-to-date: 25 January 2011.

Date	Event	Description
7 June 2012	Amended	Minor correction made (no effect on content)

## HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 3, 2007

Date	Event	Description
25 January 2011	New citation required and conclusions have changed	Taranabant trial information on efficacy and adverse events, leading to suspension of the drug
25 January 2011	New search has been performed	Three trials added to excluded studies; risk of bias tables completed
7 November 2008	Amended	From October 2008, rimonabant has been withdrawn by the manufacturers, because of links with mental disorders
31 July 2008	Amended	Odds ratios converted to risk ratios throughout
31 July 2008	Amended	Converted to new review format.
6 August 2007	New citation required and conclusions have changed	Substantive amendment

## CONTRIBUTIONS OF AUTHORS

Both authors were involved in the conceptual and practical development of the review. KC primarily contributed to the smoking cessation sections, and MU to the weight gain sections, but both authors take responsibility for the content of the entire review.

## DECLARATIONS OF INTEREST

None known

## SOURCES OF SUPPORT

### Internal sources

- Department of Primary Health Care, Oxford University, UK.
- National School for Health Research School for Primary Care Research, UK.
- Division of Population Health Sciences and Education, St George's, University of London, UK.

### External sources

- NHS Research and Development Fund, UK.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Smoking Cessation; Amides [adverse effects; \*therapeutic use]; Body Weight [drug effects]; Piperidines [adverse effects; \*therapeutic use]; Pyrazoles [adverse effects; \*therapeutic use]; Pyridines [adverse effects; \*therapeutic use]; Randomized Controlled Trials as Topic; Receptor, Cannabinoid, CB1 [\*antagonists & inhibitors]; Secondary Prevention; Smoking [\*drug therapy]; Smoking Prevention

### MeSH check words

Humans