Does combination pharmacological intervention for smoking cessation prevent post-cessation weight gain? A systematic review  
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CRD summary
The authors concluded that more than half of the studies indicated that combination smoking cessation medications (with at least one Food and Drug Administration approved drug) resulted in less post cessation weight gain compared to controls in the short term. Limitations of the evidence and uncertainty regarding the significance of benefit suggest that the authors’ conclusions may not be reliable.

Authors’ objectives
To assess the effectiveness in combination pharmacological therapy for smoking cessation in reducing post-cessation weight gain.

Searching
Four databases including MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched through to January 2012 for peer reviewed articles in English. Search terms were reported. Reference lists of included studies were searched manually.

Study selection
Eligible studies were randomised controlled trials (RCTs) and observational studies that assessed the effectiveness of combination pharmacotherapy for smoking cessation in limiting weight gain during and after smoking cessation. At least one pharmacological smoking cessation medication had to be Food and Drug Administration approved. Eligible studies had to include at least 30 adult smokers (aged at least 18 years) who were willing to quit smoking. The outcome of interest was weight change from baseline to the end of follow-up (minimum two weeks). Interventions that included behavioural components and studies that switched pharmacological medications were excluded.

Included studies were conducted between 1999 and 2010 and most were undertaken in USA. Interventions included a combination of nicotine replacement therapy and one of nine drugs (such as naltrexone, bupropion plus varenicline). Intervention durations and regimens varied across studies. It appeared that some studies compared treatment groups to abstinent and non-abstinent participants (quitters and continued smokers) receiving individual drugs or placebo pills.

Two reviewers independently screened studies for inclusion.

Assessment of study quality
Two reviewers independently assessed the risk of bias for clinical trials using Cochrane methods and the quality of observational studies according to the STROBE (strengthening the reporting of observational studies epidemiology) checklist.

Data extraction
Two reviewers independently extracted weight change data for treatment groups and abstinent and non-abstinent participants at baseline and follow-up.

Methods of synthesis
Data were presented in tables and as a narrative synthesis.

Results of the review
Twelve studies (4,776, range 32 to 893) were included in the review: nine RCTs, one retrospective cohort study, one open-label clinical trial and one open-label matched control study. The quality of one clinical trial was not reported and the other trials and retrospective study were at some risk of bias. Follow-up ranged from the end of treatment at two weeks up to 52 weeks.
Seven studies (six RCTs and one open label matched control study) showed that participants who received combination therapy gained less weight post smoking cessation in the short-term compared to participants who received individual drugs or placebo. Results from three studies did not appear to be statistically significant.

One RCT reported greater weight gain with combination therapy but this was not statistically significant. The other four studies (two of which were RCTs) reported no statistically significant differences in weight change between treatment and control groups.

**Authors' conclusions**

More than half of the selected studies indicated that combination of smoking cessation medications (with at least one Food and Drug Administration approved drug) resulted in less post smoking cessation weight gain compared to individual drugs or placebo in the short term.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. Several electronic databases were searched. The search was restricted by language and did not include grey literature or unpublished sources, so potentially relevant data may have been missed. Study quality was assessed for 11 studies and suggested some quality issues with the included studies. Each stage of the review process was conducted in duplicate, thereby minimising the potential for reviewer error and bias.

Given the variability between studies, a narrative synthesis was appropriate but this was somewhat limited. The limitations of the evidence – including study variability, small sample sizes, only short-term benefit and the suggestion that benefit shown in some studies was not statistically significant – suggest that the authors' conclusions may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that one drug (rimonabant) used in one of the included studies has been withdrawn from the market by the European Medicines Agency (EMEA).

**Research:** The authors stated that further long-term RCTs were needed and should use standardised follow-up periods and assess post cessation weight change as the primary outcome. Further large cohort studies were needed to evaluate long-term effects of combination regimens on post cessation weight gain and weight gain related metabolic events such as diabetes. Future studies could assess long-term effects of combination pharmacological intervention plus behavioural intervention on smoking cessation and prevention of weight gain.

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