Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials

CRD summary
This review aimed to assess the efficacy of approved pharmacotherapies for smoking cessation. The authors concluded that all seven of the pharmacotherapies assessed were more efficacious than placebo at promoting smoking abstinence at 6 and 12 months. Whilst the authors' conclusion follows from the results presented, poor reporting and small effect sizes suggest that some caution is advisable when interpreting the results.

Authors' objectives
To determine the efficacy of seven pharmacotherapies approved for smoking cessation; to directly compare varenicline and bupropion; and to indirectly compare all seven pharmacotherapies.

Searching
The U.S. Centers for Disease Control and Prevention's Tobacco Information and Prevention databases, MEDLINE, EMBASE and the Cochrane Library were searched up to January 2008 for papers published in English. The references of relevant papers were also checked.

Study selection
Double-blind, randomised controlled trials (RCTs) of pharmacotherapies approved for smoking cessation (varenicline, bupropion and nicotine replacement therapies such as gum, inhaler, nasal spray, tablet and transdermal patch), which reported biologically validated outcomes of abstinence at 6 and 12 months, were eligible for inclusion. Studies assessing cigarette use or spontaneous cessation of smokers unwilling to quit were excluded, as were studies of smokers with chronic disease. Studies in which both trial arms received equivalent levels of adjunctive support (e.g. counselling, group therapy) were included, irrespective of intensity. Studies were included irrespective of setting, such as hospital or smoking cessation clinic. Where reported, the mean number of cigarettes smoked per day at study entry ranged from 16 to 38.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not formally assess the quality of the included studies.

Data extraction
Abstinence was defined as either continuous abstinence (no smoking from initial target quit date until follow-up) or point prevalence of abstinence (no smoking over a given period, e.g. 7 days, directly before follow-up appointment). Smoking abstinence was considered in terms of the most conservative outcome reported in any given trial; in descending order these were continuous abstinence at 12 months, continuous abstinence at 6 months, point prevalence of abstinence at 12 months, point prevalence of abstinence at 6 months. Odds ratios (ORs) and their 95% credible interval (CrI) were calculated for the outcomes of interest. The authors stated that the outcomes were assessed on an intention-to-treat basis. The authors of the primary studies were contacted where additional data were required.

Two reviewers independently extracted the data from the primary studies, and any disagreements were resolved through consensus or by a third reviewer.

Methods of synthesis
Bayesian hierarchical meta-analysis models were used to combine the studies. The authors appear to have performed a meta-analysis for each of the pharmacotherapies, a large meta-analysis across all pharmacotherapies (with dummy variables), and a meta-analysis for trials directly comparing varenicline and bupropion. Meta-regression was used to adjust for variation in trial-level characteristics. The authors stated that separate models were performed for outcomes
at 6 and 12 months for both continuous and point prevalence abstinence (i.e. 4 models for each of the seven pharmacotherapies).

**Results of the review**
Sixty-nine RCTs (n=32,908) were included in the review. There were 16 trials of bupropion (n=6,653), 22 trials of nicotine gum (n=5,200), 4 trials of nicotine inhaler (n=976), 4 trials of nicotine nasal spray (n=887), 30 trials of transdermal nicotine (n=14,459), 6 trials of nicotine tablet (n=2,306) and 13 trials of varenicline (n=3,395).

The results from the large hierarchical meta-analysis showed a statistically significant difference in favour of bupropion (OR 2.12, 95% CrI: 1.76, 2.56), nicotine gum (OR 1.65, 95% CrI: 1.37, 2.01), transdermal nicotine (OR 1.88, 95% CrI: 1.60, 2.22), varenicline (OR 2.42, 95% CrI: 1.91, 3.12), nicotine inhaler (OR 2.18, 95% CrI: 1.38, 3.45) and nasal spray (OR 2.37, 95% CrI: 1.57, 3.60), compared with placebo, for smoking cessation (based on the results from the most conservative outcome of smoking cessation). These results were adjusted by mean age, gender and the mean number of cigarettes per day.

When varenicline was directly compared with bupropion, a statistically significant difference was found in favour of varenicline for smoking cessation (OR 2.18, 95%CI: 1.09, 4.08).

**Authors' conclusions**
All seven pharmacotherapies assessed were more efficacious than placebo at promoting smoking abstinence at 6 and 12 months.

**CRD commentary**
The review question was supported by clear inclusion criteria. Several relevant databases were searched, although the literature search was restricted by language. The authors used methods likely to minimise reviewer error and bias for the data extraction, but did not report whether similar methods were used at the study selection stage, and also restricted inclusion to double-blinded RCTs with biologically validated outcomes of abstinence, but did not assess the internal validity of the included studies. Few patient or study details were provided, which limits the ability to assess the validity of combining the studies or to generalise the results. Participants who died during the trial were excluded from the analysis. The methodology used to combine the studies is not clear and there appears to be some confusion: while the authors stated that they examined smoking abstinence with respect to the most rigorous criterion of abstinence reported, they then claimed that separate models were performed for both continuous and point prevalence abstinence. Although the authors’ conclusion, that all the pharmacotherapies considered are more efficacious than placebo, follows from the results presented, unclear reporting and small effect sizes suggest that some caution is advisable when interpreting the results.

**Implications of the review for practice and research**
The authors stated that there remains a need to develop improved smoking cessation agents and to develop optimal cessation strategies, including alternative ways to use existing agents.

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