Pharmacological interventions for smoking cessation: an overview and network meta-analysis (Review)

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[Overview of Reviews]

Pharmacological interventions for smoking cessation: an overview and network meta-analysis

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ABSTRACT

Background

Smoking is the leading preventable cause of illness and premature death worldwide. Some medications have been proven to help people to quit, with three licensed for this purpose in Europe and the USA: nicotine replacement therapy (NRT), bupropion, and varenicline. Cytisine (a treatment pharmacologically similar to varenicline) is also licensed for use in Russia and some of the former socialist economy countries. Other therapies, including nortriptyline, have also been tested for effectiveness.

Objectives

How do NRT, bupropion and varenicline compare with placebo and with each other in achieving long-term abstinence (six months or longer)?

How do the remaining treatments compare with placebo in achieving long-term abstinence?

How do the risks of adverse and serious adverse events (SAEs) compare between the treatments, and are there instances where the harms may outweigh the benefits?

Methods

The overview is restricted to Cochrane reviews, all of which include randomised trials. Participants are usually adult smokers, but we exclude reviews of smoking cessation for pregnant women and in particular disease groups or specific settings. We cover nicotine replacement therapy (NRT), antidepressants (bupropion and nortriptyline), nicotine receptor partial agonists (varenicline and cytisine), anxiolytics, selective type 1 cannabinoid receptor antagonists (rimonabant), clonidine, lobeline, dianicline, mecamylamine, Nicobrevin, opioid antagonists, nicotine vaccines, and silver acetate. Our outcome for benefit is continuous or prolonged abstinence at least six months from the start of treatment. Our outcome for harms is the incidence of serious adverse events associated with each of the treatments.

We searched the Cochrane Database of Systematic Reviews (CDSR) in *The Cochrane Library*, for any reviews with 'smoking' in the title, abstract or keyword fields. The last search was conducted in November 2012. We assessed methodological quality using a revised version of the AMSTAR scale. For NRT, bupropion and varenicline we conducted network meta-analyses, comparing each with the others and with placebo for benefit, and varenicline and bupropion for risks of serious adverse events.

Main results

We identified 12 treatment-specific reviews. The analyses covered 267 studies, involving 101,804 participants. Both NRT and bupropion were superior to placebo (odds ratios (OR) 1.84; 95% credible interval (CredI) 1.71 to 1.99, and 1.82; 95% CredI 1.60 to 2.06 respectively). Varenicline increased the odds of quitting compared with placebo (OR 2.88; 95% CredI 2.40 to 3.47). Head-to-head comparisons between bupropion and NRT showed equal efficacy (OR 0.99; 95% CredI 0.86 to 1.13). Varenicline was superior to single forms of NRT (OR 1.57; 95% CredI 1.29 to 1.91), and to bupropion (OR 1.59; 95% CredI 1.29 to 1.96).

Varenicline was more effective than nicotine patch (OR 1.51; 95% CredI 1.22 to 1.87), than nicotine gum (OR 1.72; 95% CredI 1.38 to 2.13), and than 'other' NRT (inhaler, spray, tablets, lozenges; OR 1.42; 95% CredI 1.12 to 1.79), but was not more effective than combination NRT (OR 1.06; 95% CredI 0.75 to 1.48). Combination NRT also outperformed single formulations. The four categories of NRT performed similarly against each other, apart from 'other' NRT, which was marginally more effective than NRT gum (OR 1.21; 95% CredI 1.01 to 1.46).

Cytisine (a nicotine receptor partial agonist) returned positive findings (risk ratio (RR) 3.98; 95% CI 2.01 to 7.87), without significant adverse events or SAEs.

Across the 82 included and excluded bupropion trials, our estimate of six seizures in the bupropion arms versus none in the placebo arms was lower than the expected rate (1:1000), at about 1:1500. SAE meta-analysis of the bupropion studies demonstrated no excess of neuropsychiatric (RR 0.88; 95% CI 0.31 to 2.50) or cardiovascular events (RR 0.77; 95% CI 0.37 to 1.59). SAE meta-analysis of 14 varenicline trials found no difference between the varenicline and placebo arms (RR 1.06; 95% CI 0.72 to 1.55), and subgroup analyses detected no significant excess of neuropsychiatric events (RR 0.53; 95% CI 0.17 to 1.67), or of cardiac events (RR 1.26; 95% CI 0.62 to 2.56).

Nortriptyline increased the chances of quitting (RR 2.03; 95% CI 1.48 to 2.78). Neither nortriptyline nor bupropion were shown to enhance the effect of NRT compared with NRT alone. Clonidine increased the chances of quitting (RR 1.63; 95% CI 1.22 to 2.18), but this was offset by a dose-dependent rise in adverse events. Mecamylamine in combination with NRT may increase the chances of quitting, but the current evidence is inconclusive. Other treatments failed to demonstrate a benefit compared with placebo. Nicotine vaccines are not yet licensed for use as an aid to smoking cessation or relapse prevention. Nicobrevin's UK license is now revoked, and the manufacturers of rimonabant, taranabant and dianicline are no longer supporting the development or testing of these treatments.

Authors' conclusions

NRT, bupropion, varenicline and cytisine have been shown to improve the chances of quitting. Combination NRT and varenicline are equally effective as quitting aids. Nortriptyline also improves the chances of quitting. On current evidence, none of the treatments appear to have an incidence of adverse events that would mitigate their use.

Further research is warranted into the safety of varenicline and into cytisine's potential as an effective and affordable treatment, but not into the efficacy and safety of NRT.

PLAIN LANGUAGE SUMMARY

Medications to help people to stop smoking: an overview of reviews

Background

Smoking is a main cause of early death throughout the world. There are a number of medications which can help people to quit smoking. Three of these, nicotine replacement therapy (NRT), bupropion and varenicline, are licensed for this purpose in the USA and Europe. Cytisine (similar to varenicline) is licensed for use in Russia and Eastern Europe. We reviewed studies of these and other treatments, including nortriptyline, to compare their benefits and risks.

Methods

We found 12 Cochrane reviews of different treatments. The treatments include nicotine replacement therapy (NRT); antidepressants (bupropion and nortriptyline); nicotine receptor partial agonists (varenicline and cytisine); anxiolytics; selective type 1 cannabinoid receptor antagonists (rimonabant); clonidine; lobeline; dianicline; mecamylamine; Nicobrevin; opioid antagonists; nicotine vaccines; and silver acetate. The reviews were conducted between 2008 and 2012, and analysed 267 trials, covering more than 101,000 smokers. All the reviews used randomised controlled trials, and compared the active treatment with a placebo, and sometimes with other

treatments. The outcomes were measured at least six months from the start of treatment, and the results were usually checked by testing breath, blood or urine. We also assessed the risk of harms from each treatment. We then compared NRT, bupropion and varenicline with each other, using a network meta-analysis.

Results

NRT and bupropion helped about 80% more people to quit than placebo; this means that for every 10 people who quit with placebo about 18 could be expected to quit with NRT or with bupropion. Varenicline more than doubled the chances of quitting compared with placebo, so that for every 10 who quit with placebo about 28 could be expected to quit with varenicline.

Varenicline helped about 50% more people to quit than nicotine patch and 'other' NRT (tablets, sprays, lozenges and inhalers), and about 70% more people than nicotine gum. So for every 10 people who quit with NRT patch or with 'other' NRT, about 15 could be expected to quit with varenicline, and for every 10 who quit with NRT gum about 17 could be expected to quit with varenicline. Combining two type of NRT was as effective as using varenicline, and helped more people to quit than single types of NRT. There was little to choose between different types of NRT, apart from 'other' NRT, which helped slightly more people than nicotine gum; for every 10 people who quit with NRT gum, about 12 could be expected to quit with 'other' NRT.

NRT combined with nortriptyline or with bupropion was not more effective than NRT alone.

Both cytisine and nortriptyline compared with placebo improved the chances of quitting, with minimal risk of harms.

Bupropion carries a known risk of seizures (about 1 per 1000 users), but we found fewer than expected in the included and excluded trials, at about 1 in 1500. Although there may be a marginal increase in the likelihood of any serious adverse event while taking bupropion, we did not find increased risks of neuropsychiatric or heart and circulatory problems in the bupropion studies. The evidence for the safety of varenicline is still under investigation; we found no evidence from the trials that it is linked to an increase in neuropsychiatric problems, or with increased heart and circulatory problems.

Clonidine helped people to quit, but caused side effects. It is not clear whether or not mecamylamine used with NRT helps people to quit. Other treatments did not seem to help. So far, nicotine vaccines are not licensed for use anywhere in the world. Nicobrevin is no longer available in the UK, and rimonabant, taranabant and dianicline have all been withdrawn from the market.

Conclusions

NRT, bupropion and varenicline all improve the chances of quitting, with a low risk of harms.

Combination use of NRT is as effective as varenicline, and more effective than single types of NRT.

Cytisine has potential as a safe, effective and affordable treatment.

Nortriptyline improves the chances of quitting, with little evidence of harmful events.

We need continued monitoring of the safety of varenicline.

More research into NRT versus placebo is unlikely to change our understanding of the treatment.

Links Tratamento / intervenções breves

http://talktoyourpatients.org/cme/index.php

http://www.ncsct.co.uk/