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[Intervention Review]

Nicotine receptor partial agonists for smoking cessation

Kate Cahill[1], Nicola Lindson-Hawley[1], Kyla H Thomas[2], Thomas R Fanshawe[1], Tim Lancaster[1]

[1]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK. [2]School of Social and Community Medicine, University of Bristol, Bristol, UK

Contact address: Nicola Lindson-Hawley, Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, UK. nicola.lindson-hawley@phc.ox.ac.uk.

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ABSTRACT

Background

Nicotine receptor partial agonists may help people to stop smoking by a combination of maintaining moderate levels of dopamine to counteract withdrawal symptoms (acting as an agonist) and reducing smoking satisfaction (acting as an antagonist).

Objectives

To review the efficacy of nicotine receptor partial agonists, including varenicline and cytisine, for smoking cessation.

Search methods

We searched the Cochrane Tobacco Addiction Group's specialised register for trials, using the terms ('cytisine' or 'Tabex' or 'dianicline' or 'varenicline' or 'nicotine receptor partial agonist') in the title or abstract, or as keywords. The register is compiled from searches of MEDLINE, EMBASE, and PsycINFO using MeSH terms and free text to identify controlled trials of interventions for smoking cessation and prevention. We contacted authors of trial reports for additional information where necessary. The latest update of the specialised register was in May 2015, although we have included a few key trials published after this date. We also searched online clinical trials registers.

Selection criteria

We included randomised controlled trials which compared the treatment drug with placebo. We also included comparisons with bupropion and nicotine patches where available. We excluded trials which did not report a minimum follow-up period of six months from start of treatment.

Data collection and analysis

We extracted data on the type of participants, the dose and duration of treatment, the outcome measures, the randomisation procedure, concealment of allocation, and completeness of follow-up.

The main outcome measured was abstinence from smoking at longest follow-up. We used the most rigorous definition of abstinence, and preferred biochemically validated rates where they were reported. Where appropriate we pooled risk ratios (RRs), using the Mantel-Haenszel fixed-effect model.

Main results

Two trials of cytisine (937 people) found that more participants taking cytisine stopped smoking compared with placebo at longest follow-up, with a pooled risk ratio (RR) of 3.98 (95% confidence interval (CI) 2.01 to 7.87; *low-quality evidence*). One recent trial comparing cytisine with NRT in 1310 people found a benefit for cytisine at six months (RR 1.43, 95% CI 1.13 to 1.80).

One trial of dianicline (602 people) failed to find evidence that it was effective (RR 1.20, 95% CI 0.82 to 1.75). This drug is no longer in development.

We identified 39 trials that tested varenicline, 27 of which contributed to the primary analysis (varenicline versus placebo). Five of these trials also included a bupropion treatment arm. Eight trials compared varenicline with nicotine replacement therapy (NRT). Nine studies tested variations in varenicline dosage, and 13 tested usage in disease-specific subgroups of patients. The included studies covered 25,290 participants, 11,801 of whom used varenicline.

The pooled RR for continuous or sustained abstinence at six months or longer for varenicline at standard dosage versus placebo was 2.24 (95% CI 2.06 to 2.43; 27 trials, 12,625 people; *high-quality evidence*). Varenicline at lower or variable doses was also shown to be effective, with an RR of 2.08 (95% CI 1.56 to 2.78; 4 trials, 1266 people). The pooled RR for varenicline versus bupropion at six months was 1.39 (95% CI 1.25 to 1.54; 5 trials, 5877 people; *high-quality evidence*). The RR for varenicline versus NRT for abstinence at 24 weeks was 1.25 (95% CI 1.14 to 1.37; 8 trials, 6264 people; *moderate-quality evidence*). Four trials which tested the use of varenicline beyond the 12-week standard regimen found the drug to be well-tolerated during long-term use. The number needed to treat with varenicline for an additional beneficial outcome, based on the weighted mean control rate, is 11 (95% CI 9 to 13). The most commonly reported adverse effect of varenicline was nausea, which was mostly at mild to moderate levels and usually subsided over time. Our analysis of reported serious adverse events occurring during or after active treatment suggests there may be a 25% increase in the chance of SAEs among people using varenicline (RR 1.25; 95% CI 1.04 to 1.49; 29 trials, 15,370 people; *high-quality evidence*). These events include comorbidities such as infections, cancers and injuries, and most were considered by the trialists to be unrelated to the treatments. There is also evidence of higher losses to follow-up in the control groups compared with the intervention groups, leading to a likely underascertainment of the true rate of SAEs among the controls. Early concerns about a possible association between varenicline and depressed mood, agitation, and suicidal behaviour or ideation led to the addition of a boxed warning to the labelling in 2008. However, subsequent observational cohort studies and meta-analyses have not confirmed these fears, and the findings of the EAGLES trial do not support a causal link between varenicline and neuropsychiatric disorders, including suicidal ideation and suicidal behaviour. The evidence is not conclusive, however, in people with past or current psychiatric disorders. Concerns have also been raised that varenicline may slightly increase cardiovascular events in people already at increased risk of those illnesses. Current evidence neither supports nor refutes such an association, but we await the findings of the CATS trial, which should establish whether or not this is a valid concern.

Authors' conclusions

Cytisine increases the chances of quitting, although absolute quit rates were modest in two recent trials. Varenicline at standard dose increased the chances of successful long-term smoking cessation between two- and three-fold compared with pharmacologically unassisted quit attempts. Lower dose regimens also conferred benefits for cessation, while reducing the incidence of adverse events. More participants quit successfully with varenicline than with bupropion or with NRT. Limited evidence suggests that varenicline may have a role to play in relapse prevention. The most frequently recorded adverse effect of varenicline is nausea, but mostly at mild to moderate levels and tending to subside over time. Early reports of possible links to suicidal ideation and behaviour have not been confirmed by current research.

Future trials of cytisine may test extended regimens and more intensive behavioural support.

PLAIN LANGUAGE SUMMARY

Can nicotine receptor partial agonists, including cytisine and varenicline, help people to stop smoking?

Background

When people stop smoking they experience cravings to smoke and unpleasant mood changes. Nicotine receptor partial agonists aim to reduce these withdrawal symptoms and the pleasure people usually experience when they smoke. The most widely-available treatment in this drug type is varenicline, which is available world-wide as an aid for quitting smoking. Cytisine is a similar medication, but is only available in Central and Eastern European countries and through internet sales.

Study characteristics

We searched for randomised controlled trials testing varenicline, cytisine or dianicline. We found 39 studies of varenicline compared to placebo, bupropion or nicotine patches. We also found four trials of cytisine, one of which compared it to nicotine replacement therapy. We include one trial of dianicline, which is no longer in development, and so not available to use as a quitting aid. To be included, trials had to report quit rates at least six months from the start of treatment. We preferred the strictest available definition of quitting, and results which had been biochemically confirmed by testing blood or bodily fluids.We conducted full searches up to May 2015, although we have also included several key trials published after that date.

Key findings

From the information we found (27 trials, 12,625 people), varenicline at standard dose more than doubled the chances of quitting compared with placebo. Low-dose varenicline (four trials, 1266 people) roughly doubled the chances of quitting, and reduced the number and severity of side effects. The number of people stopping smoking with varenicline was higher than with bupropion (five trials, 5877 people) or with NRT (eight trials, 6264 people). Based on the evidence so far, we can calculate that varenicline delivers one extra successful quitter for every 11 people treated, compared with smokers trying to quit without varenicline.

The most common side effect of varenicline is nausea, but this is mostly at mild or moderate levels and usually clears over time. People taking varenicline appear to have about a 25% increased chance of a serious adverse event, although these include many which are unrelated to the treatment. We also note that more people were lost from the control groups than from the varenicline groups by the end of the trials, which may mean that the count of events in the control groups is lower than it should be. After varenicline became available to use, there were concerns that it could be linked with an increase in depressed mood, agitation, or suicidal thinking and behaviour in some smokers. However, the latest evidence does not support a link between varenicline and these disorders, although people with past or current psychiatric illness may be at slightly higher risk. There have also been concerns that varenicline may slightly increase heart and circulatory problems in people already at increased risk of these illnesses. The evidence is currently unclear whether or not they are caused or made worse by varenicline, but we should have clearer answers to these questions when a further study is published later this year.

Quality of the evidence

The varenicline studies were generally of high quality, providing evidence that we consider to be reliable and robust. We rate the quality of the evidence comparing varenicline with NRT as moderate quality (we are reasonably confident of the stability of the evidence), since in some of them the participants knew which treatment they were receiving (i.e. non-blinded open-label trials). We judge the evidence from the cytsine trials to be of low quality (we have limited confidence in the evidence), as there are only two trials, with relatively low numbers included.