Nicotine preloading for smoking cessation: the Preloading RCT

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Scientific summary

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Background

Nicotine preloading means using nicotine replacement therapy (NRT) prior to quitting smoking while continuing either to try to smoke the same amount or to smoke freely. It is quite distinct from the licensed indication for NRT, which is called 'cut down to quit', where people who feel that they cannot set a quit day reduce their cigarette consumption with the aid of NRT. With preloading, users are working towards a quit day and, in the past, have used NRT for 2–4 weeks prior to this quit day.

In a systematic review and meta-analysis in 2011, we compiled all of the previous studies of the effectiveness of preloading and also looked at what evidence was available showing how preloading was exerting an effect on people to increase the chance of abstinence. There were several possible mechanisms of action; knowing the mechanism of action is important, partly to help with future studies to maximise benefit and partly to allow therapists to monitor the effect of preloading in clinical practice and either modify the treatment dose or abandon preloading. This review found a relative risk (RR) of 1.05 [95% confidence interval (CI) of 0.92 to 1.19] for achieving short-term abstinence with preloading, with a high level of heterogeneity ($I^2 = 69\%$; $p = 0.002$). The effect on long-term abstinence was given by a RR of 1.16 (95% CI 0.97 to 1.38), with a lower level of heterogeneity ($I^2 = 36\%$; $p = 0.14$). However, patches may be more effective because using a patch while smoking can lead to higher blood concentrations of nicotine than smoking alone; this may reduce the drive to smoke more than other forms of NRT that do not result in higher nicotine levels. The patch studies did show stronger evidence that patch preloading was effective, with a RR of 1.26 (95% CI 1.03 to 1.55) for longer-term abstinence. There was some evidence that preloading reduced the positive feelings that people get from smoking and the urge to smoke but no study had carried out a full mediation analysis.

Objectives

We, therefore, planned to carry out a trial to investigate the effectiveness of preloading, investigate its mechanisms of action and examine its cost-effectiveness.

Methods

Four centres, Nottingham, Birmingham, Bristol and London, recruited participants to the trial. In three centres, general practitioners (GPs) in local practices spoke to, wrote to, e-mailed or texted patients listed as smokers on the electronic health record to inform them about the trial. GPs encouraged their patients who wished to quit smoking with the help of pharmacotherapy and behavioural support to enrol in the trial and interested people telephoned the trial team. The fourth centre was a NHS Stop Smoking Service and offered trial enrolment to people seeking help to quit or who responded to advertisements in the press. Participants were eligible for the trial if they were seeking help to stop smoking and showed signs of dependence on smoking, such as finding it difficult to stop smoking, smoking at least one cigarette per day, having a high level of exhaled carbon monoxide (CO) or smoking soon after waking. We excluded people who could not tolerate nicotine patch glue on their skin, were pregnant or breastfeeding, had had a stroke or myocardial infarction in the last 3 weeks or had uncontrolled hyperthyroidism or phaeochromocytoma.

An independent statistician generated a randomisation list stratified by trial centre. Participants were randomised to either the preloading group or the control group by investigators using a database that concealed the next allocation until after enrolment. In the preloading group, participants used a

21 mg/24 hour nicotine patch for between 3 and 5 weeks prior to a planned quit day and received behavioural support at baseline and 1 week later to support adherence. Dose adjustments downwards in the event of adverse effects were allowed. To ensure commitment to the trial and the quit attempt, we provided equivalent-intensity behavioural support for the control group, designed to help them prepare for abstinence.

During preloading, we ensured that participants made an appointment with their local NHS Stop Smoking Service and set a quit date within the desired time window. Participants were free to use any medication to support their quit attempt. In the case of bupropion and varenicline (Champix®; Pfizer Inc., New York, NY, USA), normal use to support a quit attempt starts about 1 week before the quit date and, therefore, necessitates concurrent use with preloading. We knew from experience that this would deter NHS Stop Smoking advisors from prescribing these medications as National Institute for Health and Care Excellence guidance recommends not using these medications concurrently with preloading. We provided support for services and participants to try to prevent this from happening because varenicline is more effective than other medications and the trial results would be confounded if this effect occurred. NHS Stop Smoking Services provided behavioural support and medication as standard to participants in both arms.

The primary outcome was 6 months' prolonged abstinence assessed using the Russell Standard criteria. This allows a grace period of 2 weeks after quit day during which lapses do not count against abstinence and no more than five lapses thereafter, which are validated by measurement of exhaled CO levels. The secondary outcomes were 4-week and 12-month abstinence, both 7-day point prevalence abstinence, and Russell Standard abstinence.

We assessed adverse events (AEs) in the weeks between enrolment and 1 week after quit day. We collected information on serious adverse events (SAEs) (deaths or unplanned hospitalisations) and asked participants 1 week after treatment started and 1 week after treatment ended about AEs that they may have suffered; we reported on events of moderate severity or above (i.e. those that interfere to some extent with normal functioning). We also asked participants in both arms to complete a checklist of symptoms of excessive nicotine use 1 week after commencing treatment.

Based on the proportion of people achieving 6-month prolonged abstinence in previous UK-based trials, we determined that a trial of 1786 participants would have 90% power to detect a RR of 1.4, increasing the 6-month abstinence rate from 15% to 21%. We used binary logistic regression to examine the outcomes, with the addition of a term for centre to account for stratified randomisation. In a planned adjunct to the main analysis, we adjusted for two predictors of achieving abstinence and use of varenicline as post-cessation pharmacotherapy. We also examined whether or not the use of varenicline reduced the apparent effect of preloading, because its actions mimic those of nicotine preloading, and whether or not the relative effect of nicotine preloading would be greater in people with a higher level of dependence, as measured at baseline.

For the cost-effectiveness analysis, we used a NHS and personal and social care perspective. At baseline and 6 and 12 months, we assessed participants' use of health and social care services over the previous 6 months, including services to assist with smoking cessation. At these assessments, we also recorded participants' use of prescribed medication. At the follow-ups to 1 week past quit day, we assessed participants' use of nicotine preloading and their use of other pharmacotherapy to try to stop smoking. We costed these using standard sources for health services or the Prescription Cost Analysis database. For the analysis, we imputed missing data using the multiple imputation technique. We calculated incremental cost-effectiveness ratios (ICERs) relative to the control group for achieving 6- and 12-month abstinence, using bootstrapping to examine uncertainties.

We modelled the long-term effectiveness of preloading using the EQUIPTMOD model. This examines the likelihood that the cohort of people enrolled will develop the major smoking-related illnesses, given that participants either stop smoking or continue smoking and taking account of the natural quit rate. The

model includes data on the quality-adjusted life-years (QALYs) that accrue from these illnesses and the costs of treating them. We used this to determine the total health service spend and the total number of QALYs accruing as a result of the intervention relative to the control condition.

For the mediation analysis, we collected data 1 week after baseline (1 week after starting preloading) on the positive and negative rewards from smoking, urges to smoke, smoke inhalation (exhaled CO concentration), addiction score and cigarette consumption. Using the Baron and Kenny method, we examined the effect of preloading on change in the mediator variable. We also examined the association between the mediators and the outcome of abstinence. Finally, we examined the effect of treatment status on smoking abstinence while controlling for potential mediators. Although the primary hypothesis of this analysis related to features of tobacco dependence, we tested three other competing hypotheses: (1) that the effect was the result of increased confidence in the ability to quit, (2) that the effect was the result of improving adherence to cessation medication and (3) that the effect occurred because preloading produced an aversive smoking experience.

Results

Between 13 August 2012 and 10 March 2015, 1792 participants were enrolled in the study. AEs were recorded 1 week after baseline and 5 weeks later; 1702 (95.0%) and 1456 (81.3%) participants provided data at these assessments respectively. We obtained data on 1585 (88.4%) participants at 4 weeks, 1461 (81.5%) at 6 months and 1389 (77.5%) at 12 months. The proportion successfully followed up was similar in each group. For abstinence outcomes, we imputed, following the Russell Standard procedure, that people who were not followed up were smoking, but we knew from the earlier follow-up that 151 people who were not followed up at 6 months (primary outcome) were already smoking. Thus, altogether, we were certain of the primary outcome in 1612 (90.0%) participants.

The mean [standard deviation (SD)] age of participants was 48.9 (13.4) years. Men constituted 52.6% of the population and 75.6% identified as white British. The proportion of participants with advanced levels of education was lower than the UK average. Fifty-two per cent were in employment. Participants smoked a mean of 18.9 (SD 9.3) cigarettes per day at baseline and had a mean nicotine dependence score that indicated a moderate level of addiction. One-third (32.5%) of participants had used behavioural support or pharmacotherapy to try to quit in the past 6 months. The baseline characteristics were well balanced between the trial arms.

One week after baseline, nearly three-quarters of participants in the active group reported using the patch daily, whereas > 80% reported using the patch daily in the subsequent 3 weeks of preloading. During preloading, 49 (5.5%) people discontinued preloading prematurely.

The primary outcome, biochemically validated 6-month abstinence, was achieved by 157 (17.5%) participants in the intervention group and 129 (14.5%) participants in the control group, a difference of 3.0 percentage points (95% CI –0.4 to 6.4 percentage points). The odds ratio (OR) was 1.25 (95% CI 0.97 to 1.62; $p = 0.081$). After adjustment for use of post-cessation varenicline, the OR was 1.34 (95% CI 1.03 to 1.73; $p = 0.028$).

The secondary outcomes showed similar modest differences. At 4 weeks, 319 (35.5%) participants in the intervention group achieved 7-day point prevalence abstinence, whereas 288 (32.3%) participants in the control group did so. At 12 months, 126 (14.0%) participants in the intervention group achieved validated prolonged abstinence, whereas 101 (11.3%) participants in the control group achieved validated prolonged abstinence. The ORs were similar, showing no significant difference in the primary analysis but, again, adjustment for use of varenicline revealed a statistically significant benefit of preloading. There was no evidence that the benefit of preloading depended on whether or not varenicline had been used to assist cessation or on how dependent on smoking participants were at baseline.

Adverse events were uncommon in both groups. Around 4% of participants suffered AEs that are well established in people who use a patch after cessation (sleep disturbance and headaches) and an additional 4% experienced nausea, which most people using the patch after smoking cessation do not experience. The checklist of symptoms of nicotine toxicity revealed a similar pattern of a small excess of AEs in the preloading group: 5.6% and 3.0% were somewhat or very dizzy in the intervention and control groups, respectively, 3.9% and 1.9%, respectively, had palpitations and 8.1% and 3.1%, respectively, experienced nausea.

There were nine unexpected hospitalisations or deaths (SAEs) in the intervention group and eight in the control group during the 5-week observation period, giving an OR of 1.12 (95% CI 0.42 to 3.03). Of these, one was judged to be potentially the result of preloading: an acute coronary syndrome suffered by a 64-year old woman.

In total, the intervention cost amounted to £59 per participant in the intervention group and £11 per participant in the control group. At 6 months, the adjusted difference in overall cost was £22 (95% CI –£160 to £259). The ICER was £710 (95% CI –£13,674 to £23,205) per additional person achieving 6-month prolonged abstinence. At 12 months, preloading showed lower overall costs and improved abstinence, leading to a dominance over the control group, but with a wide degree of uncertainty (95 % CI –£135,032 to £7125).

Over the long term, participants' total discounted health-service spend in the preloading group was projected to be £13,111 compared with £13,177 in the control group. This would accrue 17.977 discounted life-years and 14.300 QALYs in the preloading group compared with 17.957 life-years and 14.267 QALYs in the control group. Thus, preloading was dominant, improving long-term health while reducing overall health-service spend. Changing the relapse rate and reducing the discount rate did not change the results and probabilistic sensitivity analysis revealed an 80% chance of dominance and a 93% chance of cost-effectiveness at a willingness-to-pay threshold of £20,000 per QALY.

Although there was evidence that many possible mediators were influenced by preloading, only three potential mediators were associated with abstinence: (1) noticing a reduction in urges to smoke before quitting, (2) a reduced CO level before quitting, which is a marker of a reduced rate of smoking and (3) a reduced intensity of urges after cessation. Together, in an analysis adjusted for the effect of varenicline, these changes explained 78% of the effect of preloading on 6-month abstinence. There was no evidence that the effect of preloading was mediated through increased confidence, improved medication adherence or an aversion to smoking.

Conclusions

There is evidence that nicotine preloading is modestly effective at increasing long-term smoking abstinence, but its impact in the current NHS is limited. This is because using nicotine preloading reduces the use of varenicline, which is the most effective smoking cessation pharmacotherapy. Preloading appears to be safe and it is well tolerated, with only 1 in 20 or fewer people experiencing AEs because of it. Preloading appears to have a similar cost per quitter as the control intervention and, as such, is likely to be cost neutral. In the long term, it improves health and is likely to be cost saving.

The main mechanism of action of preloading appears to be that it reduces the intensity of urges to smoke and this leads to reduced consumption, undermining the learnt drive to smoke. After quit day, this reduced drive means that the intensity of cravings for cigarettes is reduced and, hence, the chance of abstinence is increased. The pre-quit changes could allow treating clinicians to monitor the effectiveness of preloading and adjust treatment to improve outcomes or abort preloading prematurely if it is proving unhelpful.

Further research needs to identify if changes to guidelines and advice to patients can change the choice of post-quit medication. Varenicline preloading looks likely to be equally or more effective than NRT and clinical trials to examine this would be helpful.

Trial registration

This trial is registered as ISRCTN33031001.

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