**Effects on abstinence of nicotine patch treatment prior to quitting smoking: a parallel, two-arm, pragmatic randomised trial**

**Authors**

The Preloading Investigators

Correspondence to:

Paul Aveyard

Nuffield Department of Primary Care Health Sciences  
University of Oxford  
Radcliffe Primary Care Building

Radcliffe Observatory Quarter

Woodstock Road

Oxford

OX2 6GG

[paul.aveyard@phc.ox.ac.uk](mailto:paul.aveyard@phc.ox.ac.uk)

**ABSTRACT**

**Objectives**

Standard smoking cessation pharmacotherapy is recommended in the post-quit period, but may also facilitate abstinence if used prior to quitting. The objective was to examine the effectiveness and cost-effectiveness of nicotine patch worn for four weeks before a quit attempt.

**Design**

Randomised controlled open-label trial.

**Setting**

Primary care and smoking cessation clinics in England enrolled patients between 13/08/2012 and 10/03/2015.

**Participants**

1792 people, mainly middle-aged and of lower socioeconomic status, who were daily smokers with tobacco dependence.

**Interventions**

Participants were randomised 1:1, using concealed randomly permuted blocks stratified by centre, to either standard smoking cessation pharmacotherapy and behavioural support or the same treatment supplemented by four weeks of 21mg nicotine patch use prior to quitting: ‘preloading’.

**Main outcome measures**

The primary outcome was biochemically confirmed six-month prolonged abstinence and secondary outcomes were prolonged abstinence at four weeks and 12 months.

**Results**

899 people were allocated to the preloading arm and 893 to the control arm. Biochemically validated six-month abstinence, was achieved by 157/899 (17.5%) of the intervention arm and 129/893 (14.4%) of the control arm; difference (95% confidence interval) 3.0% (-0.4% to 6.4%), odds ratio (OR) 1.25 (0.97 to 1.62), p=0.08 in the primary analysis. There was an imbalance between arms in the frequency of use of varenicline for post-cessation medication and planned adjustment for this gave an odds ratio for the effect of pre-loading of 1.34 (1.03, 1.73), p=0.03, difference 3.8% (0.4% to 7.2%). At four weeks, the difference in prolonged abstinence unadjusted for varenicline use was OR 1.21 (1.00 to 1.48), difference 4.3% (0.0% to 8.7%), p=0.05 and adjusted for varenicline use it was OR 1.32 (1.08 to 1.62) p=0.007. At 12 months the OR was 1.28 (0.97 to 1.69), difference 2.7% (-0.4% to 5.8%), p=0.09 unadjusted for varenicline use and after adjustment was OR 1.36 (1.02 to 1.80) p=0.04. 5.9% of participants discontinued preloading because they could not tolerate it. Gastrointestinal symptoms, chiefly nausea, occurred in 4.0% (2.2 to 5.9) more people in the preloading than control arm. There were eight serious adverse events in the preloading arm and eight in the control arm, odds ratio OR of 0.99 (0.36 to 2.75).

**Conclusions**

In the primary analysis there was insufficient evidence to confidently demonstrate that nicotine preloading increases subsequent smoking abstinence. The beneficial effect appears to have been masked by a concurrent reduction in the use of varenicline in people using nicotine preloading and future studies should explore ways to mitigate this unintended effect.

**Registration**

Current Controlled Trials, ISRCTN33031001.

**What this paper adds**

***What is already known on this subject***

Smoking cessation pharmacotherapy is recommended in the period after a quit day. A 2011 meta-analysis reported that using pharmacotherapy prior to quit day may increase abstinence but the data were heterogeneous and there was no clear evidence of long-term benefit.

***What this study adds***

In this trial conducted in a routine health service context, there was no clear evidence that using nicotine patches for four weeks prior to quit improved long-term abstinence. However, the benefit of preloading appears to have been masked by reduced use of varenicline in people allocated to preload, which, being more effective, reduced the overall benefit. After adjusting for this effect, there was clearer evidence of effectiveness.

**INTRODUCTION**

Although there have been several new medications since the 1970s, the paradigm of tobacco cessation treatment has remained largely the same since then, with no major advances in success rates. Treatment comprises behavioural support to motivate and strengthen a person’s resolve to remain abstinent and using medication to reduce the strength of urges to smoke after quit day.

Most adult smokers continue smoking even though they wish to stop because they have developed a drive to smoke. An important cause of this arises from repeated pairing of the behaviour of smoking with stimulation of cholinergic receptors in the midbrain that project to the nucleus accumbens.1 When acted upon, this urge to smoke can remain largely unconscious, but when a person decides to stop smoking it becomes experienced as a craving, typically occurring in response to moods or situations when smoking would normally have occurred. These cravings undermine the success of the large majority of quit attempts.2 All effective smoking cessation medications exert their effect by reducing the intensity of cravings and the most effective medication currently available, varenicline, does so to a greater extent.3 In people who resist the craving, repeated exposure to cues to smoke without actually smoking and the concomitant delivery of nicotine from a cigarette will mean the drive to smoke is unlearnt and craving intensity falls.

If smoking occurs without the reinforcement provided by nicotinic stimulation, the drive to smoke should diminish and, when a person attempts to quit, they should experience less intense craving and be more likely to succeed. One way to block the effect of nicotine from cigarettes is to supply this from a nicotine patch. Doing so desensitises the cholinergic brain receptors meaning they are refractory to further stimulation from the cigarette-supplied nicotine.4 This should reduce the intensity of the urge to smoke while smoking and, crucially, lower dependence will reduce craving intensity if a person makes a quit attempt, facilitating abstinence.

Using a nicotine replacement treatment (or other smoking cessation medications) prior to a quit attempt while smoking normally is called preloading. A systematic review showed some, but not convincing, evidence that nicotine preloading may be effective, with much unexplained heterogeneity between studies.5 Some studies suggested that nicotine preloading doubled the likelihood of achieving abstinence, which, if true, suggests that using nicotine replacement therapy (NRT) used prior to a quit attempt is more effective than when used in the conventional way to support smoking abstinence.6 Other studies suggested preloading had no effect. A partial explanation for the heterogeneity may relate to the form of nicotine replacement used. Smoking while using patches produces higher blood nicotine concentrations than just smoking, but smoking while using short-acting NRT, such as gum, does not.7 There was some but not strong evidence in the review that nicotine patch preloading was more effective than pre-loading with oral NRT. Since then, three more studies using varenicline and bupropion preloading have been conducted with some evidence of a benefit on short-term cessation.8-10 These studies are relevant because they are examining the same hypothetical active ingredient of the preloading interventions as NRT studies, i.e. effects of reduced satisfaction from smoking. Together, these studies have provided modest support that preloading works through reducing the intensity of urges to smoke. 78-12

Given the promise and uncertainty around this novel approach to treating tobacco dependence, we conducted a large trial in a routine health service context to examine the impact of NRT preloading on long-term abstinence and mechanisms of its action.

**METHOD**

**Design**

This was an open-label multicentre pragmatic superiority trial randomised 1:1 to receive or not a nicotine patch for use for four weeks prior to quit day. Participants used standard pharmacotherapy and behavioural support to support cessation thereafter. The primary outcome was prolonged biochemically validated abstinence measured six months after quitting. The protocol is published and it was implemented with one change.11 That is, some participants moved house and were unable to attend in-person to confirm abstinence using exhaled carbon monoxide. We asked such participants to return a supplied saliva swab to measure cotinine or anabasine concentrations to confirm abstinence from smoking. The planned cost-effectiveness analysis will be presented separately. The trial was approved by NRES Committee East Midlands- Leicester, number 12/EM/0014 on 31/01/2012.

**Participants and settings**

In three recruitment centres, Nottingham, Birmingham, and Bristol, GPs spoke to, wrote to, emailed, or texted patients listed as smoking on the electronic health record and invited them to join the trial as a means to stop smoking. The fourth recruitment centre, in London, was an existing NHS smoking cessation clinic, which invited patients seeking treatment to participate in the trial.

Potential participants telephoned the research team to learn more about the trial and were screened for eligibility. If the participant appeared eligible and wanted to participate, we booked an appointment at the patient’s general practice or the smoking cessation clinic to meet the researcher and sent the participant information sheet. At this initial appointment, we again described the trial and obtained consent.

The inclusion criteria were:

* Regularly smoking cigarettes, cigars, and rollup tobacco cigarettes, with or without marijuana aged ≥18 years of age.
* People who would be suitable for preloading in the judgement of the researcher (see below).
* Seeking support to stop smoking from the NHS Stop Smoking Service.
* Willing to set a quit day in four weeks.
* Able to understand and willing to adhere to study procedures.

The exclusion criteria were:

* Pregnant or breastfeeding women.
* People with skin disorders that precluded patch use.
* People who had acute coronary syndrome or stroke in the past three weeks.
* People with an active phaeocromocytoma or uncontrolled hyperthyroidism that would increase the risk of arrhythmias from the nicotine patch.

We judged suitability for preloading by assessing whether potential participants were addicted to smoking using the following criteria, with no cut-offs:

* Failure of previous quit attempts despite use of appropriate pharmacotherapy.
* Time to first cigarette in the morning with earlier use reflecting higher addiction;
* Number of cigarettes smoked per day with a greater number reflecting higher addiction;
* Exhaled carbon monoxide (CO), with higher concentrations reflecting higher addiction.

**Interventions**

***Intervention arm***

In the intervention arm, participants were asked to use a 21mg/24-hour nicotine patch daily for approximately four weeks prior to quit day. If a participant had had problems with overnight use in previous quit attempts, we advised such a participant to wear the patch in waking hours only.

We asked participants to smoke as normal and not reduce consumption. Reduced consumption would probably lower blood nicotine concentration, which could make cigarettes more rewarding and thus undermine the supposed benefits of preloading.13

We referred patients in both arms to the NHS Stop Smoking Service for continuing support with cessation. We asked participants and asked the NHS advisors by letter and in-person to set a quit date between three and five weeks after commencing preloading. We allowed that preloading could continue for up to eight weeks in exceptional circumstances. We also allowed that preloading could restart once, if, for example, when preloading was interrupted because the participant was admitted to hospital. In such cases, participants aimed to complete three to five weeks of preloading from the date of recommencement.

At the first visit, the researcher explained the rationale of preloading and prompted action planning to maximise adherence to the patches. The researcher addressed participants’ concerns about smoking while using patches and advised on how to manage side-effects. The researcher talked through the participant’s daily routine and noted opportunities to use environmental cues to minimise the chance of forgetting to apply the patch daily. We provided a booklet with the same information to reinforce this. Participants commenced using preloading at this visit and we reviewed participants one week after commencing preloading to address concerns and reinforce adherence.

We offered participants lower strength patches at commencement if they reported previous adverse reactions to the 21mg patch, or during the treatment course if they experienced symptoms of nicotine overdose such as nausea, salivation, and pounding heart. We stopped preloading if the patient requested it, it was not possible to alleviate adverse events by reducing the dose, or an intervening health state or contra-indication to preloading emerged.

***Control arm***

We aimed to balance participants’ expectations of success and to assess adverse events in an unbiased way. A placebo would have achieved this but the funder did not allow this so we developed a behavioural intervention. We asked participants to consider their smoking pattern, the triggers for particular cigarettes, and to plan ways to reduce these cues. This is standard in smoking cessation support anyway, so participants in the intervention arm may well have done this later when they enrolled in their NHS stop smoking service. The control arm received a booklet outlining this process, which was similar in length and appearance to the booklet supplied to the intervention arm. As in the intervention arm, participants in the control arm attended and received this support at baseline and one week later. As in the intervention arm, participants in the control arm were also referred to the NHS Stop Smoking Service to commence a quit attempt between three and five weeks after enrolment.

***Standard smoking cessation treatment common to both arms***

In both arms, at the first and second visits, we referred participants to the local stop smoking service, writing a letter to the advisor to ask the advisor to encourage the participant to continue preloading. We asked advisors to ignore the presence or absence of nicotine patch treatment when choosing pharmacotherapy to support the quit attempt. We were concerned that NICE guidance recommends against the concurrent use of NRT and varenicline (which is started a week prior to quit day),14 which advisors often assumed was due to safety concerns. We tried to correct misconceptions in the referral letter, by telephone, and face-to-face discussions with clinicians.

The NHS stop smoking advisors provided weekly behavioural support starting 1-2 weeks prior to quit day and continuing until at least four weeks after quit day and encouraged participants to maintain total abstinence from quit day forward. This support involves planning for the quit day, explanation of how occasional lapses can undermine quitting and encouragement to adopt a ‘not a puff' rule, supervision and facilitation of medication use, advice on and how to deal with temptations to smoke and monitoring of abstinence through carbon monoxide testing. The support is termed withdrawal-orientated therapy.15

**Measures and outcomes**

At baseline, we recorded participants’ smoking history and basic demographic detail. This included two markers of cigarette dependence: the Fagerstrom Test for Cigarette Dependence (FTCD), which measures consumption of cigarettes and difficulty in refraining from smoking, and the concentration of exhaled carbon monoxide (CO).16

We followed up participants on five occasions. We asked participants to return one week after the baseline appointment for the -3-week appointment (so-called because it was about 3 weeks prior to quit day). We assessed occurrence of adverse events and adherence to preloading. We telephoned participants one week after quit day (+1 week), about 6 weeks after baseline, to collect data on adverse events, adherence to preloading, and use of other smoking cessation pharmacotherapy and adherence to it. We obtained data on smoking cessation from the NHS stop smoking service or the participant at +4 weeks. At six and 12 months, we telephoned participants to obtain data on smoking status and health service use. We invited participants who were abstinent to attend to measure the concentration of carbon monoxide (CO) in end-expiratory air using a handheld device to confirm abstinence biochemically. Participants were compensated £15 for their time for attending this meeting.

***Primary outcome***

The primary outcome was six-month prolonged abstinence, defined by the Russell standard criteria.17 This allows a grace period of two weeks following quit day when lapses do not count against abstinence. Thereafter we counted a person as abstinent if they smoked fewer than 5 cigarettes to the six-month assessment and were biochemically confirmed abstinent by an exhaled CO<10 parts per million (ppm).

***Secondary outcomes***

The secondary outcomes were four-week and 12-month Russell standard abstinence and biochemically confirmed 7-day point prevalence abstinence at four weeks, six and 12 months.

***Intensity of urges to smoke***

As the principal hypothesised mechanism of action is that preloading undermines the intensity of urges to smoke, we examined the effect of preloading on this measured at -3 weeks (while on preloading/control) and at +1 week after quit day using the Mood and Physical Symptom Scale -Craving Subscale (MPSS-C, scored 0-5). In the latter assessment, in accord with consensus,18 the analysis was confined to those who were abstinent or still trying to achieve abstinence.

***Adverse events***

Adverse events were defined as newly occurring health conditions or exacerbations of existing conditions. We recorded adverse events that were either serious or of moderate or severe intensity. We assessed adverse events occurring between baseline and one week after quit day, covering the period of preloading and allowing one additional week for adverse events to emerge. Moderate or severe adverse events were defined as those that interfered somewhat or totally with normal functioning. Serious adverse events were defined as hospitalisation, death or life-threatening events, permanent disability, or congenital abnormality. This excluded planned events, such as scheduled surgery. An independent committee assessed serious adverse events and adjudicated whether the event was unrelated, unlikely, possibly, probably, or definitely related to the use of nicotine patches. The committee were blind to treatment allocation and hence also the temporal relation of medication use to the event.

We elicited adverse events from participants in both arms at contacts -3 weeks and at +1 week by asking about new or worsening health problems followed by further enquiry as appropriate. These were coded using MedDRA v19.1. As it can be hard for trial staff and participants to understand the necessity to report adverse events for people in the control arm on no treatment, we also gave participants in both arms a symptom questionnaire. This assessed symptoms of nicotine overdose in the previous 24 hours (such as nausea, excessive salivation) one week after baseline. Participants rated how troubled they had been by the symptoms in the past 24 hours on a scale from ‘not at all’ to ‘very’ or ‘extremely’.

**Sample size**

We estimated that 15% of participants in the control arm would achieve six-month abstinence based on data from similar trials.19-21 We felt that a relative risk of 1.4 was both plausible and would be valuable for patients, implying a 6% absolute difference.5 This gave us a sample size of 893/arm or 1786 in total, to achieve 90% power using χ2 test with Yates’ correction.

**Randomisation**

An independent statistician used Stata to generate a randomisation list stratified by treatment centre and using randomly permuted blocks of varying size using a 1:1 ratio. This was incorporated into an online database and the sequence remained concealed from all research staff until they had entered data to allow randomisation.

**Blinding**

This was an open-label trial so participants, research staff, and NHS Stop Smoking Service personnel knew the arm to which participants were assigned. Blinded follow-up was impractical because staff had been involved in recruitment, but abstinence was biochemically confirmed.

**Statistical analysis**

We followed the Russell standard approach to perform an intention to treat analysis for the abstinence outcome.17 Everyone randomised was included in the denominator, whenever and however smoking abstinence was assessed, and presumed to be smoking if this information was unknown. In the primary analysis, we calculated adjusted odds ratios (OR) using multivariable logistic regression in Stata 14.2 adjusted for the stratification variable (centre). We also calculated the percentage achieving abstinence, the risk difference and risk ratios and 95% confidence intervals using the post-estimation adjrr procedure in Stata v14.2.

In planned sensitivity analysis, we adjusted for two predictors of abstinence to improve precision: longest previous abstinence and degree of addiction measured by strength of urges to smoke at baseline.22-24 Secondly, varenicline is more effective than other pharmacotherapy and commonly used to assist cessation.25 As we anticipated that using nicotine preloading in an open-label trial could deter use of varenicline, we adjusted for use of varenicline after quit day to overcome confounding by this means.

We planned subgroup analyses by including multiplicative interaction terms in the equations above. The presumed mechanism of action of preloading suggests greater benefit from preloading in people more dependent on cigarettes. We used two markers of dependence: baseline FTCD score and exhaled CO concentration added as continuous terms. We also examined whether the effect of preloading was less pronounced in participants using varenicline. Normal use of varenicline involves a week of use before quit day and there is evidence that this may have similar effects to preloading, which could undermine the effect of nicotine preloading.8

We analysed the effect of preloading on urge to smoke (MPSS-C) using a linear regression model with adjustment for baseline MPSS-C score and stratification variables.

The denominator for analysis of adverse events was all those that provided data on such events. The analysis used analogous statistical models to those applied for the primary and secondary outcomes.

**Patient involvement**

We discussed the idea for the study and the proposed methods in a meeting with the UK Centre for Tobacco and Alcohol Studies Smokers Panel. This panel is a standing group of people who smoke or have recently stopped smoking and they agree the study was valuable and gave views on the design that shaped the protocol. After early initial slow recruitment, we returned to eight members of the panel to discuss the letter from GPs to potential participants and participant information leaflet and made some minor amendments as a result. One member of the panel, Dan Griffin, also served on the independent trial steering committee.

**RESULTS**

**Participant flow**

Between 13/08/2012 and 10/03/2015, 3837 people were telephoned about enrolment. In total, 490 (12.8%) were ineligible; the most common reasons were skin problems and that people were unwilling to use preloading patches. We saw 1805 (47.04%) at the initial appointment and 1792 (99.3%) of those were eligible and enrolled. (Figure 1).

**Figure 1 CONSORT flow diagram –**



Footnote:The number analysed for all primary and secondary outcomes is 893 control and 899 intervention and those whose true status was unknown were counted as smoking

One week after baseline we followed up 1702 (95.0%) participants and five weeks after baseline, one week after quit day, we obtained data from 1456 (81.3%) participants. These assessments provided data on adverse events.

We obtained abstinence data on 1585 (88.5%) participants at four weeks, 1461 (81.5%) at six months, and 1389 (77.5%) at 12 months. The proportion successfully followed was similar in each arm. Although 331 (18.5%) participants were not available for the primary outcome assessment at six months, we knew that 97 of this group were smoking at four weeks and could not therefore be classified as abstinent at six months and that 54 never made a quit attempt and likewise could not be classified as abstinent at six months. Thus, altogether, we were certain of the primary outcome in 1612 (90.0%) participants.

**Baseline characteristics**

The majority of participants were middle-aged, half were men and a quarter from minority ethnic groups. The participants had lower levels of educational attainment than the UK average,26 and half were employed. Participants smoked a mean of 18.9 (SD 9.3) cigarettes/day at baseline, and had a mean dependence score indicating moderate addiction, and a mean exhaled CO concentration of 23.7 (SD 12.5). A third had used behavioural support or pharmacotherapy to try to quit in the past six months. Baseline characteristics were well balanced between trial arms (Table 1). The main predictors of abstinence are markers of cigarette dependence, such as the Fagerstrom Test for Nicotine Dependence and exhaled carbon monoxide concentration, and it is reassuring that these were almost exactly balanced by arm. Likewise, demographic variables were balanced, with mean age differing between arms by around a third of a year, exactly the same proportion of males, and people of ethnic groups that were not white British. Education and employment were also balanced by trial arm, with less than 2% difference between the proportions in any category of these variables. The biggest difference appeared in the proportion of people who had used cessation aids in the past six months, with 31.0% (intervention) and 34.0% (control).

**Table 1 Participant characteristics by trial arm**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | Control n=893  n (%) | Intervention n=899  n (%) | Total n=1792  n (%) |
| Age | Mean 48.8 (SD 13.4) | Mean 49.1 (SD 13.3) | Mean 48.9 (SD 13.4) |
| Gender |  |  |  |
| Male | 469 (52.6) | 473 (52.6) | 942 (52.6) |
| Female | 422 (47.3) | 426 (47.4) | 848 (47.4) |
| Ethnicity |  |  |  |
| White – British | 675 (75.6) | 680 (75.6) | 1355 (75.6) |
| White – Irish | 36 (4.0) | 25 (2.8) | 61 (3.4) |
| White – Other | 57 (6.4) | 55 (6.1) | 112 (6.3) |
| White and Black Caribbean | 17(1.9) | 15 (1.7) | 32 (1.8) |
| White and Black African | 3 (0.3) | 5 (0.6) | 8 (0.5) |
| White and Asian | 8 (0.9) | 6 (0.7) | 14 (0.8) |
| Mixed other | 7 (0.8) | 8 (0.9) | 15 (1.8) |
| Indian | 11 (1.2) | 10 (1.1) | 21 (1.2) |
| Pakistani | 9 (1.0) | 6 (0.7) | 15 (0.8) |
| Bangladeshi | 2 (0.2) | 13 (1.5) | 15 (0.8) |
| Asian - Other | 3 (0.3) | 3 (0.3) | 6 (0.3) |
| Black - Caribbean | 29 (3.3) | 34 (3.8) | 63 (3.5) |
| Black - African | 8 (0.9) | 13 (1.5) | 21 (1.2) |
| Black - Other | 4 (0.5) | 3 (0.3) | 7 (0.4) |
| Chinese | 3 (0.3) | 2 (0.2) | 5 (0.3) |
| Other | 12 (1.3) | 14 (1.6) | 26 (1.5) |
| More than one option | 0 | 4 (0.4) | 4 (0.2) |
| Missing | 9 (1.0) | 7 (0.8) | 16 (0.9) |
| Educational qualifications |  |  |  |
| Degree, or equivalent, and above | 201 (22.5) | 218 (24.3) | 419 (23.4) |
| A level, vocational Level 3 and above | 198 (22.2) | 207 (23.0) | 405 (22.6) |
| Other qualifications below A- level or below vocational level 3 | 230 (25.8) | 212 (23.6) | 442 (24.7) |
| Other Qualifications (e.g. foreign) | 52 (5.8) | 52 (5.8) | 104 (5.8) |
| No formal qualifications | 204 (22.8) | 199 (22.1) | 403 (22.5) |
| Missing | 8 (0.9) | 11 (1.2) | 19 (1.06) |
| Occupation |  |  |  |
| Employed | 467 (52.3) | 468 (52.1) | 935 (52.3) |
| Unemployed | 126 (14.1) | 116 (12.9) | 242 (13.5) |
| Looking after home and family | 33 (3.7) | 44(4.9) | 77(4.3) |
| Student | 17 (1.9) | 22 (2.5) | 39 (2.2) |
| Retired | 153 (17.1) | 152 (16.9) | 305 (17.1) |
| Long-term sick or disabled | 26 (2.9) | 26 (2.9) | 52 (2.9) |
| Missing | 4 (0.5) | 8(0.9) | 12 (0.7) |
| Type of cigarette smoked |  |  |  |
| Manufactured cigarettes | 615 (68.9) | 607 (67.5) | 1222 (68.2) |
| Tobacco roll-ups | 272 (30.5) | 284 (31.6) | 556 (31.0) |
| Cigars | 6 (0.7) | 8 (0.9) | 14 (0.8) |
| Cigarettes per day | Mean 18.7 (SD 9.0) | Mean 19.1 (SD 9.6) | Mean 18.9 (SD 9.3) |
| Dependence (FTCD) Mean (SD)\* | 5.2 (2.2) | 5.2 (2.2) | 5.2(2.2) |
| CO reading | Mean 23.8 (SD 12.8) | Mean 23.5 (SD 12.3) | Mean 23.7 (SD 12.5) |
| Longest previous abstinence (days) | Mean 358.4 (SD 750.7) | Mean 442.3 (SD 993.7) | Mean 400.3 (SD 881.4) |
| Smoking cessation support in last 6 months |  |  |  |
| Yes | 304 (34.0) | 279 (31.0) | 583 (32.5) |
| No | 588 (65.9) | 619 (68.9) | 1207 (67.4) |
| Missing | 1 (0.1) | 1 (0.1) | 2 (0.1) |

\* Fagerstrom Test for Cigarette Dependence, scored 0-10, with higher scores representing greater dependence.

**Medication adherence in the preloading arm**

Three quarters of participants used the patch daily during the first week and four fifths did so in the subsequent weeks. During preloading, 49 (5.5%) people discontinued preloading prematurely; most during the first week of treatment.

We assessed medication used after quit day to support abstinence in those making a quit attempt (Table 2). Nicotine patch use was more common in the preloading arm, while varenicline use was more common in the control arm.

**Table 2 Medication used to support cessation among those who made a quit attempt**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Control  (n=738) | Intervention  (n=742) | Total  (n=1480) |
| None | 87 (11.8%) | 61 (8.2%) | 148 (10.0%) |
| Varenicline | 218 (29.5%) | 164 (22.1%) | 382 (25.8%) |
| Bupropion | 6 (0.8%) | 12 (1.6%) | 18 (1.2%) |
| Nicotine patches only | 99 (13.4%) | 169 (22.8%) | 268 (18.1%) |
| Acute nicotine only | 74 (10%) | 44 (5.9%) | 118 (8.0%) |
| Combined nicotine | 156 (21.1%) | 170 (22.9%) | 326 (22.0%) |
| Missing | 113 (15.3%) | 135 (18.2%) | 248 (16.8%) |

Note percentages add to slightly more than 100% because some people used multiple medications

Acute nicotine means oral or nasal forms

**Primary and secondary outcomes**

The primary outcome, biochemically validated six-month abstinence, was achieved by 157/899 (17.5%) of the intervention arm and 129/893 (14.4%) of the control arm, a difference (95% confidence interval) of 3.0% (-0.4% to 6.4%).

The secondary outcomes showed similar modest differences. At four weeks, 319/899 (35.5%) of the intervention arm achieved 7-day point prevalence while 288/893 (32.3%) of the control did so. At twelve months, 126/899 (14.0%) achieved validated prolonged abstinence in the intervention arm while 101/893 (11.3%) achieved it in the control arm. Table 3 presents the primary and secondary outcomes adjusted for centre i.e. the primary analysis.

Adjustment for other predictors of abstinence left the results essentially unchanged but adjustment for the use of post-quit day varenicline use changed the results noticeably; the unadjusted results and was statistically significant at 4 weeks, and 6 and 12 months. The odds ratio went from 1.25 (0.97 to 1.62) to 1.34 (1.03 to 1.73), p=0.03 for the primary outcome (Table 1 Online Appendix and Table 4).

**Table 3 Primary analysis of the primary and secondary outcomes\***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome | Presented as odds ratios Ɨ | | Presented as risk ratios β | | Presented as risk differences β | |
|  | **OR (95%CI)** | **p** | **RR (95%CI)** | **p** | **RD (95%CI)** | **p** |
| Primary outcome |  |  |  |  |  |  |
| 6 month Russell standard | 1.25 (0.97 to 1.62) | 0.08 | 1.21 (0.98 to 1.50) | 0.08 | 3.02 (-0.37 to 6.41) | 0.08 |
| Secondary outcomes |  |  |  |  |  |  |
| 4 weeks Russell standard | 1.21 (1.00 to 1.48) | 0.05 | 1.14 (1.00 to 1.29) | 0.05 | 4.33 (-0.04 to 8.70) | 0.05 |
| 4 week 7-day point prevalence | 1.16 (0.95 to 1.41) | 0.15 | 1.10 (0.97 to 1.25) | 0.15 | 3.22 (-1.15 to 7.59) | 0.15 |
| 6 months 7-day point prevalence | 1.13 (0.90 to 1.41) | 0.31 | 1.10 (0.92 to 1.31) | 0.31 | 1.98 (-1.81 to 5.76) | 0.31 |
| 12 months Russell standard | 1.28 (0.97 to 1.69) | 0.08 | 1.24 (0.97 to 1.58) | 0.09 | 2.71 (-0.37 to 5.78) | 0.08 |
| 12 months 7-day point prevalence | 1.23 (0.97 to 1.54) | 0.08 | 1.17 (0.98 to 1.41) | 0.08 | 3.32 (-0.42 to 7.06) | 0.08 |

\*all participants included in the analysis and assumed to be smoking if true status was unknown and the denominators were 893 control arm to 899 intervention arm

Ɨ Primary form of analysis

β calculated from odds ratios using the adjrr command in Stata

**Table 4 Primary and secondary outcomes expressed as risk ratios (RR) and risk differences (RD) showing the effect of sequential planned adjustment in sensitivity analysis\***

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | Unadjusted | | Adjusted Ɨ | | Adjusted β | | Adjusted α | |
|  | **RD/RR (95%CI)** | **p** | **RD/RR (95%CI)** | **p** | **RD/RR (95%CI)** | **p** | **RD/RR (95%CI)** | **p** |
| Primary outcome:6-month Russell standard | | | | | | | | |
| Estimated risks | 17.5 and 14.4 |  |  |  |  |  |  |  |
| Risk ratio | 1.25 (0.97 to 1.62) | 0.08 | 1.21 (0.98 to 1.50) | 0.08 | 1.21 (0.98 to 1.50) | 0.08 | 1.27 (1.03 to 1.57) | 0.03 |
| Risk difference | 3.02 (-0.37 to 6.41) | 0.08 | 3.02 (-0.37 to 6.41) | 0.08 | 3.03 (-0.37 to 6.43) | 0.08 | 3.80 (0.41 to 7.18) | 0.03 |
| Secondary outcomes | | | | | | | | |
| 4 weeks Russell standard | | | | | | | | |
| Estimated risks | 36.3 and 31.9 |  |  |  |  |  |  |  |
| Risk ratio | 1.14 (1.00 to 1.29) | 0.05 | 1.14 (1.00 to 1.29) | 0.05 | 1.14 (1.00 to 1.29) | 0.05 | 1.19 (1.05 to 1.35) | 0.007 |
| Risk difference | 4.35 (-0.04 to 8.73) | 0.05 | 4.33 (-0.04 to 8.70) | 0.05 | 4.37 (-0.01 to 8.75) | 0.05 | 5.89 (1.60 to 10.19) | 0.007 |
| 4 weeks 7-day point prevalence | | | | | | | | |
| Estimated risks | 35.5 and 32.3 |  |  |  |  |  |  |  |
| Risk ratio | 1.10 (0.97 to 1.25) | 0.15 | 1.10 (0.97 to 1.25) | 0.15 | 1.10 (0.97 to 1.25) | 0.15 | 1.15 (1.02 to 1.31) | 0.03 |
| Risk difference | 3.23 (-1.15 to 7.61) | 0.15 | 3.22 (-1.15 to 7.59) | 0.15 | 3.22 (-1.17 to 7.60) | 0.15 | 4.86 (0.58 to 9.14) | 0.03 |
| 6 months 7-day point prevalence | | | | | | | | |
| Estimated risks | 22.3 and 20.3 |  |  |  |  |  |  |  |
| Risk ratio | 1.10 (0.92 to 1.31) | 0.31 | 1.10 (0.92 to 1.31) | 0.31 | 1.10 (0.92 to 1.32) | 0.28 | 1.15 (0.96 to 1.37) | 0.13 |
| Risk difference | 1.98 (-1.81 to 5.77) | 0.31 | 1.98 (-1.81 to 5.76) | 0.31 | 2.11 (-1.68 to 5.91) | 0.28 | 2.93 (-0.85 to 6.71) | 0.13 |
| 12 months Russell standard | | | | | | | | |
| Estimated risks | 14.0 and 11.3 |  |  |  |  |  |  |  |
| Risk ratio | 1.24 (0.97 to 1.58) | 0.09 | 1.24 (0.97 to 1.58) | 0.09 | 1.24 (0.97 to 1.58) | 0.09 | 1.30 (1.02 to 1.66) | 0.04 |
| Risk difference | 2.71 (-0.37 to 5.78) | 0.08 | 2.71 (-0.37 to 5.78) | 0.08 | 2.66 (-0.43 to 5.75) | 0.09 | 3.31 (0.22 to 6.39) | 0.04 |
| 12 months 7-day point prevalence | | | | | | | | |
| Estimated risks | 22.4 and 19.0 |  |  |  |  |  |  |  |
| Risk ratio | 1.17 (0.98 to 1.41) | 0.08 | 1.17 (0.98 to 1.41) | 0.08 | 1.17 (0.98 to 1.41) | 0.09 | 1.21 (1.01 to 1.45) | 0.04 |
| Risk difference | 3.32 (-0.43 to 7.07) | 0.08 | 3.32 (-0.42 to 7.06) | 0.08 | 3.28 (-0.48 to 7.04) | 0.09 | 3.98 (0.23 to 7.73) | 0.04 |

\*all participants included in the analysis and assumed to be smoking if true status was unknown and the denominators were 893 control arm to 899 intervention arm

Ɨ adjusted for research centre- the primary analysis

β adjusted for research centre, previous longest abstinence, baseline strength of urges to smoke (both continuous following analysis plan)

α adjusted for research centre, previous longest abstinence, baseline strength of urges to smoke (both continuous following analysis plan), and varenicline prescribed at +1 week

**Subgroup analysis**

There was no evidence that people who were classified as more dependent on smoking received a greater benefit from preloading. The p values for multiplicative interaction terms for the effect of preloading in those with higher dependence scores and higher exhaled carbon monoxide were 0.83 and 0.17, respectively. Per unit increase in each variable, the odds ratios were 1.01 (0.90 to 1.14) and 1.01 (0.99 to 1.04), respectively.

There was no evidence that people who used varenicline as their post-cessation medication received less benefit from nicotine preloading than people using other cessation medication. The OR for the effect of preloading compared with control for users of varenicline was 1.42 (0.90 to 2.26) and for non-users was 1.30 (0.95 to 1.77), p=0.74 for the interaction.

**Effect of preloading on urge to smoke**

One week into preloading/control, the urge to smoke had reduced in people using preloading. The mean (SD) MPSS-C score at -3 weeks was 2.1 (0.8) for the preloading arm and 2.6 (0.9) for the control arm, baseline-adjusted difference (95%CI) -0.5 (-0.6 to -0.4). One week after quit day, in those who were abstinent, MPSS-C scores were 1.0 (1.0) for the preloading arm and 1.3 (1.0) for the control arm, difference -0.3 (-0.4 to -0.1) and for those who were still trying to achieve abstinence, the corresponding figures were 1.3 (1.1), 1.5 (1.1), difference -0.2 (-0.4 to -0.1).

**Adverse events**

Spontaneously reported adverse events of moderate or severe intensity were uncommon in both arms. There were eight system or organ class groups where at least 10 participants reported one symptom within that group. Of these, gastrointestinal disorders, general disorders, and nervous system disorders were statistically significantly more common in those using preloading, with absolute differences of 4.0% (2.2 to 5.9), 2.1% (0.7 to 3.5), and 4.5% (2.7 to 6.4) respectively. There were 15 individual symptoms where at least five participants reported that symptom. Of these, nausea occurred in 2.5% (1.1 to 3.8) more people who were preloading and vomiting in 1.2% (0.3 to 2.2). Fatigue was also more common in people preloading by 0.7% (0.1 to 1.2), as were well-recognised adverse effects of nicotine patches, namely abnormal dreams 0.9% (0.2 to 1.6), poor sleep 1.9% (0.9 to 3.0), and headaches 1.2% (0.3 to 2.2). (The full table is presented as Table 2 Online Appendix)

There were 16 serious adverse events during the five-week period, eight in the intervention arm and eight in the control arm, OR of 0.99 (0.36 to 2.75). Of these, one was judged possibly due to preloading: a 64-year old woman in the preloading arm who had an acute coronary syndrome (Table 3 Online Appendix).

One week after baseline, 394 (45.5%) of the intervention arm and 271 (32.4%) of the control arm reported at least one symptom on the symptom questionnaire of symptoms of nicotine excess (p<0.001 for the difference). Of the 12 symptoms, three were statistically significantly more common in the preloading arm: nausea, dizziness, and palpitations. Of these symptoms, the percentages in intervention and control arms with somewhat or very noticeable symptoms were 5.6% and 3.0% dizzy, 3.9% and 1.9% palpitations, 8.1% and 3.1% nausea (Figure 1 Online Appendix).

**DISCUSSION**

**Principal findings**

In this pragmatic open-label trial, there was no strong evidence that four weeks of nicotine patch treatment increased the rate of six-month prolonged abstinence in the primary analysis. Preloading was tested in a clinical setting where smokers could opt to use either NRT or non-nicotine pharmacotherapies for continued cessation treatment after preloading had ended. In a planned analysis adjusted for varenicline use, there was clearer evidence that preloading itself increased the likelihood of achieving abstinence. Preloading reduced the intensity of urge to smoke both prior to and after attempting abstinence, which suggests preloading is an effective treatment. As 95% of participants continued preloading treatment, 80% using it daily, preloading appears well-tolerated. Around 1 in 20 people experienced adverse events caused by preloading that were moderate or severe caused by preloading. There was no evidence of an excess of serious adverse events.

**Strengths and limitations**

This trial has strengths and limitations. It was considerably larger than previous studies on this topic, thus achieving good precision. The pragmatic design makes the results easier to apply to clinical practice; for example, that staff used their judgement to define tobacco dependence avoiding the use of arbitrary cut-offs for cigarettes/day which are not used in clinical practice. Likewise, we included people who had serious co-existing medical conditions, psychiatric disorders, and other substance misuse problems and people from lower socioeconomic groups, reflecting the population of people that seek help to stop smoking. Around 75% of the population were white British, lower than England as a whole, reflecting the cities in which we recruited. However, the likely mechanism of action of preloading is undermining cigarette dependence and this biological action is likely to apply to any dependent smoker, regardless of their ethnic group. Around half of all potential participants who enquired about the trial were not enrolled and this may be thought to indicate poor acceptability of this particular intervention. However, this ratio between enquiries and participation seems to hold in other smoking cessation trials that recruited in the same way but that offered more ‘benign’ interventions, like St John’s wort, or a behavioural intervention in addition to routine care,27 28 so we feel that this is more likely to indicate people’s willingness to quit smoking, quit with support, or attend a schedule of treatment and follow-up visits. While this is unlikely to bias the difference between arms, it may also indicate that not everyone considering supported cessation is prepared to engage with this particular intervention. We had a robust method to assess the occurrence of adverse events. As it is unintuitive for participants on no medication to report apparent side-effects, we trained staff to enquire regardless. We supplemented this approach with a self-completion questionnaire for participants in both arms that concerned symptoms experienced. In the event, both methods revealed similar findings, with nausea emerging as the most frequent adverse effect caused by preloading, albeit the large majority did not experience it. Our trial was the first trial of preloading to assess adverse events to standards defined by Good Clinical Practice and to record serious adverse events. There was only one serious adverse event that was ascribed by an independent committee blinded to allocation as possibly due to preloading, and that was acute coronary syndrome. This was ascribed on the basis that nicotine increases pulse rate, which may predispose to acute coronary syndrome. However, in this person, the nicotine patch had been stopped by the participant two days prior to the event. Nicotine has a half-life of around two hours,29 so even with a skin reservoir, nicotine from the patch though not from smoking would have cleared from the blood and thus not be exerting acute pharmacological effects. The UK Committee on the Safety of Medicines reviewed the cardiac safety of NRT and recommended removal of licence restrictions on use of NRT in people with stable cardiovascular disease and concurrent use while smoking.30 This is based on trials in people with cardiovascular disease and large-scale observational evidence that shows no evidence of an increased risk.31 32 Short-term studies show that high dose nicotine patches up to 63mg/day while smoking exert no greater effect on the cardiovascular system than occurs with smoking alone.33 It therefore seems unlikely that this event was caused by preloading. The open-label design is both a strength and a limitation. Seen as a strength, it suggested an effect of preloading that either promoted the use of nicotine patches for use post-cessation, deterred the use of varenicline, or both. In all other trials of preloading, the investigators controlled the choice of post-cessation medication and therefore this effect was not apparent. Arguably, this effect may occur in routine clinical practice and this has important implications for practice. Seen as a limitation, a placebo would have provided more certainty that participants’ expectations were matched evenly by arm. Inequality of expectations might have influenced participants, but is an unlikely cause of the effect on cessation. The Cochrane Review of NRT contrasts trials where participants were randomised to NRT for post-quit day use or matching placebo; in these studies, the RR was 1.51 (1.39 to 1.63) for long-term abstinence. In studies without blinding, the RR was similar at 1.58 (1.43 to 1.74).6 Perhaps lack of blinding affected participants’ reports of adverse events and urge intensity, though the effects on urge intensity persisted at least a week after the end of treatment. There is in fact evidence that expectations of success were matched in this trial; ratings of confidence in ability to quit one week into preloading/control did not differ significantly by arm. It was also not possible to blind outcome assessors, because the one staff member employed in each centre to perform clinical duties did both recruitment and follow-up. However, smoking abstinence was biochemically validated and this is unlikely to have affected the results.

**Comparison with other studies**

While this trial does not provide strong evidence in itself, there is other evidence that suggests the optimum management of tobacco dependence includes a period of treatment prior to a quit attempt. Since inception of this trial, three further trials have published data on short-term abstinence, two comparing varenicline preloading and one bupropion with standard use.8-10 The RRs (95%CI) for abstinence in these trials were 2.14 (1.14 to 4.00), and 1.35 (0.77 to 2.38) for varenicline (combined 1.78 (1.17 to 2.71)), and 1.70 (1.04 to 2.80) for bupropion. Adding our trial to the previous inconclusive meta-analysis of nicotine patch preloading versus standard use gives an RR of 1.24 (1.07 to 1.43) for long-term abstinence from nicotine patch preloading. Previous trials have reported that preloading reduces the intensity of urges to smoke and smoking consumption in the pre-quit period and that this seems to be part of its mechanism of action.12 What we have shown is that, in line with theory, this reduction of intensity of urges before quitting translates into reduced intensity of urge after quit day. Aside from its theoretical importance, this finding could have implications for smoking cessation practice. Some trials have suggested that response to preloading predicts success in quitting,34 and, if preloading were to be adopted, it may be sensible to continue preloading only in people who experience reduced urges to quit, although randomised trials are needed to confirm this. Our trial is the only trial to be carried out in the context where the therapists who prescribed the preloading (our trial team) were different from those who prescribed the post-cessation support (the NHS Stop Smoking Service). Doing so showed that, on the one hand, preloading can be effective in this context, but its benefit may have been undermined by reduced varenicline use in those allocated to nicotine preload. This effect may have occurred because English (NICE) guidelines, which state ‘Do not offer NRT, varenicline or bupropion in any combination’.35 If so, changing this guidance may overcome this problem and it nicotine preloading might be effective in such a context.

**Implications for policy and practice**

The best estimate of effect is that nicotine preloading could lead to around 3% of people seeking help to quit smoking achieving 12-month prolonged abstinence that might not otherwise have done so. This effect may seem small but current 12 months quit rate in the UK specialist cessation services is 8%,36 and so an additional 3% would represents a worthwhile improvement. A failed quit attempt is likely to cost a person about 3-5 years of life expectancy.22 Thus, around 12 people need to use preloading to gain around a year of life. However, this trial in itself does not provide sufficiently strong evidence to be confident that nicotine preloading is effective, probably because of the reduced use of varenicline that followed preloading. Both observational and randomised trial evidence suggest varenicline used as a medication during the first weeks of abstinence is more effective than nicotine patches alone.25 36 37 It therefore seems important to examine how to mitigate this unintended effect.

**Conclusion**

Nicotine preloading with a 21mg/24hr nicotine patch for four weeks appears efficacious, safe, and well-tolerated, but probably deters the use of varenicline, the most effective cessation medication. If it were possible to overcome this unintended consequence, preloading could lead to a worthwhile increase in long-term smoking abstinence.

**Contributions of authors: (in alphabetical order)**

Writing committee (Study design, data analysis, implementation and interpretation, and study write-up): Marcus Munafo, Nicola Lindson, Peter Hajek, Paul Aveyard, Sarah Lewis, Tim Coleman,.

Study management: including recruitment and follow-up Alia Ataya, Alice Scott, Andy McEwen, Angela Attwood, Anna Phillips, Anne Dickinson, Carmen Wood, Celine Homsey, Clare Randall, Deborah Lycett, Diana Pratt, Doug Coyle, Dunja Przulj, Emma Anderson, Emma Howell, Gurmail Rai, Hayden McRobbie, Jasmine Khouja, Jinshuo Li, Steve Parrott, Jo Perdue, Kate Myers, Katherine Evans, Kathryn Colye, Kayleigh Easey, Khaled Ahmed, Lindsey Lacey, Lizzy Dann, Marcus Munafo, Mark Allen, Megan Fluharty, Megan Hurse, Mike Healy, Miriam Banting, Natalie Bisal, Nicola Lindson, Paul Aveyard,, Peter Hajek, Rachel Adams, Rebecca Anderson, Rhona Alekna, Sarah Lewis, Sarah Tearne, Shahnaz Khan, Sophie Duncombe, Sophie Orton, Subhash Pokhrel, Therese Freuler, Tim Coleman

Chief investigator: Paul Aveyard

Trial Statistician: Sarah Lewis

Guarantors: Paul Aveyard and Sarah Lewis

**Independent trial steering committee**

Michael Ussher (chair), Dan Griffin, Helen Stokes-Lampard, Jane Wright, Lion Shahab, Rumana Omar, Tess Harris. There was no data monitoring and ethics committee.

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**Transparency declaration**

Paul Aveyard affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

**Data sharing**

The authors would be happy to share data where that is in the interests of public health and providing we have not planned similar analyses.

**Ethics approval**

The trial was approved by NRES Committee East Midlands, number 12/EM/0014.

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**Online Appendix**

**Table 1 Primary and secondary smoking cessation outcomes presented as odds ratios for preloading arm versus control (primary analysis)\***

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | Unadjusted | | Adjusted Ɨ | | Adjusted β | | Adjusted α | |
|  | OR (95%CI) | p | OR (95%CI) | p | OR (95%CI) | p | OR (95%CI) | p |
| Primary outcome: |  |  |  |  |  |  |  |  |
| 6 month Russell standard | 1.25 (0.97 to 1.62) | 0.08 | 1.25 (0.97 to 1.62) | 0.08 | 1.26 (0.97 to 1.62) | 0.08 | 1.34 (1.03 to 1.73) | 0.03 |
| Secondary outcomes | | | | | | | | |
| 4 weeks Russell standard | 1.21 (1.00 to 1.48) | 0.05 | 1.21 (1.00 to 1.48) | 0.05 | 1.22 (1.00 to 1.48) | 0.05 | 1.32 (1.08 to 1.62) | 0.007 |
| 4 week 7-day point prevalence | 1.16 (0.95 to 1.41) | 0.15 | 1.16 (0.95 to 1.41) | 0.15 | 1.16 (0.95 to 1.41) | 0.15 | 1.26 (1.03 to 1.54) | 0.03 |
| 6 months 7-day point prevalence | 1.13 (0.90 to 1.41) | 0.31 | 1.13 (0.90 to 1.41) | 0.31 | 1.14 (0.90 to 1.43) | 0.28 | 1.20 (0.95 to 1.51) | 0.13 |
| 12 months Russell standard | 1.28 (0.97 to 1.69) | 0.08 | 1.28 (0.97 to 1.69) | 0.08 | 1.27 (0.96 to 1.69) | 0.09 | 1.36 (1.02 to 1.80) | 0.04 |
| 12 months 7-day point prevalence | 1.22 (0.97 to 1.54) | 0.08 | 1.23 (0.97 to 1.54) | 0.08 | 1.22 (0.97 to 1.54) | 0.09 | 1.28 (1.01 to 1.62) | 0.04 |

\*all participants included in the analysis and assumed to be smoking if true status was unknown and the denominators were 893 control arm, 899 intervention arm

Ɨ adjusted for research centre- the primary analysis

β adjusted for research centre, previous longest abstinence (days, continuous), baseline strength of urges to smoke (continuous, as per analysis plan)

α adjusted for research centre, previous longest abstinence (days, continuous), baseline strength of urges to smoke (continuous, as per analysis plan), varenicline prescribed +1 week

**Table 2 Reported adverse events of moderate or severe intensity in the intervention and control arms**

|  |  |  |  |
| --- | --- | --- | --- |
| Event | Control  (N = 860) | Intervention  (N = 880) | Percentage-point difference (95%CI) |
| Gastrointestinal disorders | 19 (2.2%) | 55 (6.2%) | 4.0 (2.2 to 5.9) |
| Abdominal pain  Diarrhoea  Nausea  Vomiting | 3 (0.3%)  3 (0.3%)  8 (0.9%)  3 (0.3%) | 6 (0.7%)  8 (0.9%)  30 (3.4%)  14 (1.6%) | 0.3 (-0.3 to 1.0)  0.6 (-0.2 to 1.3)  2.5 (1.1 to 3.8)  1.2 (0.3 to 2.2) |
| General disorders | 11 (1.2%) | 30 (3.3%) | 2.1 (0.7 to 3.5) |
| Asthenia  Fatigue | 5 (0.6%)  0 (0.0%) | 10 (1.1%)  6 (0.7%) | 0.6 (-0.3 to 1.4)  0.7 (0.1 to 1.2) |
| Injuries to poisoning to and procedural complications | 8 (0.9%) | 4 (0.5%) | -0.5 (-1.2 to 0.3) |
| Musculoskeletal and connective disorders | 7 (0.8%) | 10 (1.1%) | 0.3 (-0.6 to 1.2) |
| Nervous system | 16 (1.9%) | 56 (6.4%) | 4.5 (2.7 to 6.4) |
| Abnormal dreams  Dizziness  Headache  Poor quality sleep | 1 (0.1%)  6 (0.7%)  3 (0.3%)  3 (0.3%) | 9 (1.0%)  15 (1.7%)  14 (1.6%)  20 (2.3%) | 0.9 (0.2 to 1.6)  1.0 (0.0 to 2.0)  1.2 (0.3 to 2.2)  1.9 (0.9 to 3.0) |
| Psychiatric | 7 (0.8%) | 17 (1.9%) | 1.1 (0.0 to 2.2) |
| Depressed mood | 4 (0.5%) | 5 (0.6%) | 0.1 (-0.6 to 0.8) |
| Respiratory | 21 (2.4%) | 15 (1.7%) | -0.7 (-2.1 to 0.6) |
| Chest infection  Influenza like illness  Nasopharyngitis | 4 (0.5%)  3 (0.3%)  7 (0.8%) | 1 (0.1%)  7 (0.8%)  4 (0.5%) | -0.3 (-0.8 to 0.2)  0.4 (-0.3 to 1.2)  -0.4 (-1.1 to 0.4) |
| Skin and subcutaneous tissue disorders | 4 (0.5%) | 7 (0.8%) | 0.3 (-0.4 to 1.1) |
| Skin irritation | 2 (0.2%) | 5 (0.6%) | 0.3 (-0.3 to 0.9) |

Table reports proportion of people reporting adverse events for any system or organ class term with at least 10 or more participants reporting any single event and any preferred term that had at least five participants reporting it. The denominator includes all who participated either at -3 or +1 week.

**Table 3 Serious adverse events**

|  |  |  |  |
| --- | --- | --- | --- |
| Age and gender | Trial arm | Relevant medical history | Event |
| 68-year-old man | Intervention | Chronic myeloid leukaemia | Hospitalised with chest infection |
| 85-year-old woman | Intervention | Osteoporosis | Hospitalised with pelvic fracture following accidental fall |
| 72-year-old woman | Intervention | None | Hospitalised for aspiration of malignant pleural effusion |
| 65-year old woman | Intervention | Cardiovascular disease, hypertension, pacemaker and history of blackouts | Hospitalised for a blackout |
| 27-year-old woman | Intervention | Psychotic illness, illicit drug use | Hospitalised for psychotic episode following period of illicit drug use leading to anxiety attacks |
| 64-year-old woman | Intervention | None | Acute coronary syndrome |
| 54-year-old woman | Intervention | Angina | Hospitalised with acute coronary syndrome or non-cardiac chest pain |
| 45-year-old woman | Intervention | Self-harming | Hospitalised for increased self-harming and suicidal ideation |
| 68-year-old man | Control | Reflux oesophagitis | Hospitalised with cancer of the oesophagus |
| 55-year-old woman | Control | COPD and type 2 diabetes | Death due to COPD |
| 59-year-old man | Control | Alcohol dependence | Death due to accidental house fire |
| 52-year-old man | Control | Two previous hernia repairs | Hospitalised for hernia repair |
| 47-year-old woman | Control | None | Hospitalised for pyelonephritis |
| 38-year-old woman | Control | Asthma | Hospitalised with chest infection |
| 64-year-old woman | Control | COPD | Exacerbation of COPD |
| 25-year-old man | Control | None | Pneumonia |

**Figure 3 Prevalence and severity of symptoms reported in the last 24 hours reported one week into preloading or control**





