Nortriptyline plus nicotine replacement versus placebo plus nicotine replacement for smoking cessation: pragmatic randomised controlled trial

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ABSTRACT

Objective To test the efficacy of nortriptyline plus nicotine replacement therapy compared with placebo plus nicotine replacement therapy for smoking cessation.

Design Pragmatic randomised controlled trial.

Setting National Health Service stop smoking service clinics.

Participants 901 people trying to stop smoking.

Interventions Participants chose their nicotine replacement product, including combinations of nicotine replacement therapy, and received behavioural support. Nortriptyline was started one to two weeks before quit day, with the dose increased from 25 mg to 75 mg daily for eight weeks and reduced if not tolerated.

Main outcome measures Primary outcome was prolonged confirmed abstinence at six months. Secondary outcomes were prolonged abstinence at 12 months, drug use, severity of side effects, nicotine withdrawal symptoms, and urges to smoke.

Results 72 of 445 (16%) people using nortriptyline and 55 of 456 (12%) using placebo achieved prolonged abstinence at six months (relative risk 1.34, 95% confidence interval 0.97 to 1.86). At 12 months the corresponding values were 49 (11%) for nortriptyline and 40 (9%) for placebo (1.26, 0.84 to 1.87). 337 (79%) people in the nortriptyline arm and 325 (75%) in the placebo arm were taking combination treatment on quit day, median 75 mg per day in both groups. More people in the nortriptyline arm than in the placebo arm took lower doses. The nortriptyline arm had noticeably higher severity ratings for dry mouth and constipation than the placebo arm, with slightly higher ratings for sweating and feeling shaky. Both groups had similar urges to smoke, but nortriptyline reduced depression and anxiety. Overall, withdrawal symptom scores did not differ.

Conclusions Nortriptyline and nicotine replacement therapy are both effective for smoking cessation but the effect of the combination is less than either alone and evidence is lacking that combination treatment is more effective than either alone.

Trial registration Current Controlled Trials ISRCTN57852484.

INTRODUCTION

Treatments aimed at smoking cessation are among the most cost effective interventions in health care. Most people treated in a single treatment episode, however, eventually return to smoking. Most of those who do return to smoking relapse while receiving treatment, and therefore more effective interventions are needed.

Nicotine replacement therapy is the most commonly used pharmacotherapy, almost doubling the odds of smoking cessation. Three other licensed drugs are commonly used worldwide. Varenicline is a partial nicotinic agonist and is probably the most effective treatment. Bupropion and nortriptyline are both antidepressants and about double the odds of smoking cessation. The odds ratio for nortriptyline compared with placebo is 2.34 (95% confidence interval 1.61 to 3.41), with fewer than 10% of people withdrawing because of side effects.

Nicotine withdrawal symptoms are aversive psychological and physical symptoms that occur on smoking cessation. Effective drugs for smoking cessation reduce the severity of withdrawal symptoms, and it is believed that this effect underlies their efficacy. Nicotine replacement therapy probably increases cessation rates by reducing the symptoms of nicotine withdrawal and abstinence induced urges to smoke. Selective serotonin reuptake inhibitors reduce the occurrence of nicotine withdrawal symptoms. Symptoms include low mood and depression, but also others such as restlessness and increased appetite. Selective serotonin reuptake inhibitors probably reduce nicotine withdrawal symptoms and urges to smoke more effectively than nortriptyline but do not improve cessation rates. Nortriptyline possibly increases smoking cessation rates partly or wholly by means other than reducing the severity of withdrawal symptoms and suppressing urges to smoke.

Bupropion and nortriptyline increase levels of noradrenaline in the synapse by blocking reuptake. Smoking affects noradrenergic transmission, with rebound changes on cessation. It may therefore be logical to combine nicotine replacement therapy with...
bupropion or nortriptyline, which may have different and complementary means by which they enhance cessation. This has been tested in two trials. One found no benefit of nortriptyline plus nicotine replacement therapy compared with nicotine replacement therapy alone, whereas the other found a noticeable benefit (odds ratio 2.62, 95% confidence interval 1.06 to 6.44). If this were the true effect, nicotine replacement therapy plus nortriptyline would be more effective than varenicline. These trials totalled 318 people. Given the heterogeneity of results and potential size of benefit in these trials we carried out a placebo controlled trial to test the efficacy of combination treatment compared with nicotine replacement therapy alone for smoking cessation.

METHODS

The trial took place in the UK National Health Service stop smoking service, which runs specialist and primary care services. In the specialist clinics stop smoking advisers provide group support as seven one hour weekly sessions. The NHS stop smoking service trains primary care nurses to provide shorter one to one sessions, with a more flexible schedule with several contacts. The NHS supplied the nicotine replacement therapy for the study, allowing participants to choose from all available products. Switching products was allowed and in some services participants were given two or more types of nicotine replacement therapy to use simultaneously. This variability necessitated a pragmatic design.

Anyone aged 18 years or older attending a stop smoking service and smoking 10 or more cigarettes a day was eligible. We excluded those with a contra indication or caution to nortriptyline or contraindication to nicotine replacement therapy and those taking a drug that interacted with nortriptyline. A research nurse attended stop smoking groups and briefly introduced the trial. Interested people were then interviewed individually. We were therefore unable to count the number of people who were eligible and declined participation or were ineligible. About one third of participants in the group were interviewed, however, and about one fifth of those were excluded, mainly because they were taking other antidepressants.

Nortriptyline and placebo were provided in 25 mg capsules, maximum daily dose 75 mg. One to two weeks before quit day participants used 25 mg of either drug for three days, 50 mg for four days, and 75 mg thereafter, a dose found effective in previous trials. The participants took the maximum dose for six weeks and then reduced the dose over a week. Participants were posted the whole course of drugs from a central pharmacy. We ensured that the batch had arrived or introduced the trial. Interested people were then enrolled and we sometimes reduced the dose because of side effects. We telephoned all participants to ensure that they were using the treatment, were happy taking the treatment, and attended as many stop smoking courses as possible later into the cessation attempt.

Outcome measures

The primary outcome was prolonged abstinence at six months—defined, as is usual, as no smoking at all between day 15 after quit day and the six month follow up, confirmed by cotinine concentration in saliva or exhaled carbon monoxide concentration. We followed the Russell standard, including as smokers those lost to follow-up. The secondary outcomes were confirmed seven day point prevalence abstinence at 26 weeks and 52 weeks, and prolonged abstinence at 26 weeks. We also measured prolonged abstinence at four weeks; seven day point prevalence abstinence; nicotine withdrawal symptoms; urges to smoke, using the mood and physical symptoms scale; and quality of life using the EQ-5D.

The research nurse gave participants a baseline questionnaire containing questions on history of smoking, which they were asked to return at subsequent clinic visits. Smoking status, nicotine withdrawal symptoms, urges to smoke, and side effects were assessed at each clinic visit after quit day by questionnaire distributed and collected by the NHS adviser. Clinics stopped behavioural support four weeks after quit day and we recorded the concentration of exhaled carbon monoxide measured at that visit. We obtained data at six and 12 months by postal questionnaire and telephone follow-up, with several attempts made to contact unavailable participants. Abstinence was confirmed by urine collection using gas chromatography at ABS Laboratories, London.

Fig 1 | Flow of participants through trial
concentration less than 10 ppm or salivary cotinine concentration less than 15 ng/ml on each occasion.\textsuperscript{17}

**Statistical analysis**

At the time the trial was planned only the study showing a benefit of nortriptyline plus nicotine replacement therapy had been published,\textsuperscript{11} with an odds ratio of 2.62. We conservatively assumed an odds ratio of 1.80, with a six month prolonged abstinence rate of 10% in the nicotine replacement therapy only group. On these assumptions of a type I error rate of 5% and 80% power, we needed 430 participants in each arm. We aimed for 900 participants in total.

An independent statistician generated the randomisation schedule in Stata. We used block randomisation, with randomly ordered block sizes of two, four, and six, stratified by stop smoking adviser. Study nurses recruited participants, and the study administrator (who had not met the participants) allocated participants in sequence against the list for each adviser. Only the administrator and the pharmacist knew the allocation. Advisers, participants, and study staff carrying out follow-up were blind to allocation. Nortriptyline tablets were encapsulated, and identical powder filled capsules provided the placebos.

We calculated the proportion of people using each possible combination of drug as a proportion of all still attempting to quit at each of the four weeks of clinic follow-up, calculating $\chi^2$ statistics for the differences. We calculated the median number of capsules taken per day, testing differences with a Mann-Whitney U test. For abstinence we used the intention to treat approach, calculating risk differences and 95% confidence intervals and relative risks and 95% confidence intervals using the Mantel Haenszel approach for stratified analyses. The analysis of differences in the occurrence of side effects and withdrawal symptoms was done only on those who took nortriptyline and nicotine replacement therapy for all four weeks of clinical follow-up to examine whether side effects or withdrawal symptoms changed over time, as expected. Those with intolerable symptoms, however, could stop treatment and such people would be excluded. Therefore we used a Mann-Whitney U test to examine

### Table 1 | Baseline characteristics of people allocated to nortriptyline plus nicotine replacement therapy or to placebo plus nicotine replacement therapy for smoking cessation. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nortriptyline group (n=445)</th>
<th>Placebo group (n=456)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)*</td>
<td>43.2 (11.5)</td>
<td>44.0 (12.4)</td>
</tr>
<tr>
<td>Women*</td>
<td>206 (46)</td>
<td>213 (46)</td>
</tr>
<tr>
<td>Ethnic group:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>337 (94)</td>
<td>338 (94)</td>
</tr>
<tr>
<td>Mixed</td>
<td>4 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (1)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Missing</td>
<td>9 (3)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Educational attainment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>152 (42)</td>
<td>185 (52)</td>
</tr>
<tr>
<td>Diploma</td>
<td>101 (28)</td>
<td>94 (26)</td>
</tr>
<tr>
<td>Degree</td>
<td>46 (13)</td>
<td>34 (10)</td>
</tr>
<tr>
<td>Other</td>
<td>61 (17)</td>
<td>46 (13)</td>
</tr>
<tr>
<td>Smoking variables:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) cigarettes per day</td>
<td>21.4 (8.1)</td>
<td>21.4 (8.1)</td>
</tr>
<tr>
<td>Roll-up smokers</td>
<td>34 (9)</td>
<td>34 (10)</td>
</tr>
<tr>
<td>Cigar smokers</td>
<td>1 (0.3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Pipe smokers</td>
<td>1 (0.3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Mean (SD) nicotine dependence score (range 0-10)\textsuperscript{‡}</td>
<td>5.4 (2.1)</td>
<td>5.4 (2.2)</td>
</tr>
<tr>
<td>Mean (SD) age started smoking</td>
<td>16.4 (4.2)</td>
<td>16.4 (4.2)</td>
</tr>
<tr>
<td>Live with a smoker</td>
<td>129 (36)</td>
<td>143 (40)</td>
</tr>
<tr>
<td>Median (interquartile range)longest previous quit attempt (days)</td>
<td>60 (7-180)</td>
<td>42 (6-180)</td>
</tr>
<tr>
<td>Psychological variables:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of depression§</td>
<td>230 (64)</td>
<td>204 (57)</td>
</tr>
<tr>
<td>Mean (SD) anxiety score (range 0-21)¶</td>
<td>8.0 (3.8)</td>
<td>7.5 (3.7)</td>
</tr>
<tr>
<td>Mean (SD) depression score (range 0-21)¶</td>
<td>4.9 (3.5)</td>
<td>4.7 (3.6)</td>
</tr>
</tbody>
</table>

182 people did not return baseline questionnaires and are excluded from percentages.

*Data available for all participants.

†Main source of tobacco.

‡Fagerstrom test for nicotine dependence.\textsuperscript{18}

§Two weeks of pervasive low depressed mood and two weeks of lost interest, past diagnosis of depression, or past prescription of antidepressants for depression.

¶Hospital anxiety and depression scale: normal population mean (SD) for anxiety is 6.1 (3.8) and for depression is 3.7 (3.1). Score 0-7 is normal, 8-10 borderline, ≥11 caseness.\textsuperscript{20}
whether initial severity of side effects was worse in those who stopped treatment than those who continued. For withdrawal symptoms we included only those maintaining complete abstinence from smoking for the first four weeks, as is standard.\textsuperscript{18} We accommodated the repeated weekly measures of side effects, withdrawal symptoms, and quality of life by random effects regression of observations nested within individuals, assuming a normal distribution for the error function for means and using ordered proportional odds models for individual symptoms measured on Likert-type scales. We entered time as days and days squared and we tested whether the change in symptoms over time differed between users of nortriptyline and users of placebo using multiplicative interaction terms.

### RESULTS

Overall, 901 people (445 nortriptyline arm, 456 placebo arm) were enrolled between November 2003 and June 2005 (fig 1). They were recruited from 10 NHS stop smoking services and were seen by 45 different advisers. Forty one were seen in primary care and 860 by specialists. Of these, 9 (2.0%) people in the nortriptyline arm and 17 (3.7%) in the placebo arm did not attend clinics after the initial appointment and therefore provided no follow-up data. They were assumed not to have attempted to quit and were analysed as treatment failures. Baseline characteristics were well balanced between the groups (table 1).

### Drug use and side effects

The main choice of drug at all treatment follow-up periods was combination nortriptyline plus nicotine replacement therapy or placebo plus nicotine replacement therapy, although the proportion of people using the combinations decreased from 77% on quit day to 57% by week 4. This was mainly as a result of an increase in the proportion of people using nortriptyline only or placebo only (from 3% to 8%) and nicotine replacement therapy only (from 13% to 25%). Treatment choices did not vary by trial arm (table 2).

The patch was the main nicotine replacement product used—around 70% of those using nicotine replacement at every assessment used the patch, with a further 15% using combination nicotine replacement therapy—mainly patch plus an oral product. The remaining 15% used the other types of nicotine replacement therapy. The proportions using each choice of nicotine replacement product did not vary much or significantly by trial arm (table 2).

Participants in both arms were taking a median of two capsules of nortriptyline or placebo daily by quit day, indicating that they were still escalating the dose.
The median dose consumed thereafter was three capsules daily, but with more variation in the number in the nortriptyline arm than placebo arm, a statistically significant effect (table 3). At week 4, 44 (22%) of those in the nortriptyline arm were not using nortriptyline, 15 (8%) were taking one capsule daily, 20 (10%) were taking two capsules daily, and 121 (61%) were taking three capsules daily.

Five people were admitted to hospital while taking nortriptyline or placebo (four in placebo arm, one in nortriptyline arm), of whom two (one in each arm) were admitted with collapse or palpitations that were judged possibly caused by treatment although no final diagnosis was reached in either case. Occurrence of symptoms known to be side effects of nortriptyline were more common and more severe in those taking active drug rather than placebo. (The exception was difficulty passing urine, experienced by fewer than 6% of participants.) More than 80% of those taking nortriptyline had a dry mouth, but so did more than

Fig 2 | Side effects in people using nortriptyline plus nicotine replacement therapy and placebo plus nicotine replacement therapy for at least four weeks
Table 4 | Severity of side effects in patients using nortriptyline plus nicotine replacement therapy for smoking cessation

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Odds ratio (95% CI)</th>
<th>P value for effect modification by time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>1.16 (0.93 to 1.45)</td>
<td>0.021</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6.67 (5.12 to 8.69)</td>
<td>0.55</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>0.54 (0.41 to 0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.06 (1.66 to 2.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difficulty passing urine</td>
<td>0.28 (0.19 to 0.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sweating</td>
<td>1.37 (1.11 to 1.68)</td>
<td>0.002</td>
</tr>
<tr>
<td>Light headedness</td>
<td>1.10 (0.88 to 1.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shaky</td>
<td>1.28 (1.00 to 1.65)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

...halff taking placebo. More than half experienced constipation and sweating, but the differences between nortriptyline and placebo were small (fig 2). A minority experienced the other side effects. Modelling confirmed these findings (table 4). The symptoms of drowsiness, difficulty passing urine, and light headedness declined less rapidly for people using nortriptyline than for those using placebo. For dry mouth, the decline in severity over time was the same for nortriptyline and placebo. For blurred vision the severity was nearly constant for nortriptyline but declined for placebo. The severity of constipation, sweating, and shakiness increased slightly in people using nortriptyline but declined in people using placebo.

Those who started nortriptyline or placebo but subsequently stopped had initial ratings for each of the eight side effects similar to, and not significantly different from, those who continued treatment. This was true of those who stopped nortriptyline or stopped placebo.

Effect on abstinence

Some people were lost to follow-up. By four weeks no data on smoking status were available for 12 (3%) people in the nortriptyline arm and 18 (4%) in the placebo arm. By six months the corresponding values were 41 (9%) and 65 (14%) and by 12 months were 52 (12%) and 76 (17%). At six months, however, 89% of those lost after four weeks had not achieved prolonged abstinence at four weeks so were by definition treatment failures at six months. All those lost after six months who did not respond to follow-up at 12 months had not achieved prolonged abstinence at six months. Loss to follow-up lowered only point prevalence abstinence rates.

For the intention to treat analysis, people using nortriptyline plus nicotine replacement therapy were slightly more likely to stop smoking on every measure at every follow-up than those using placebo plus nicotine replacement therapy, but the differences were small and not statistically significant. For the per protocol analysis, the effects in those using nortriptyline plus nicotine replacement therapy or placebo plus nicotine replacement therapy on quit day were similar (table 5).

The quit rate in people treated by specialists was about double that in those treated in general practice (statistically significant), as reported in a recent similar trial. Variation in quit rate was notable although not statistically significant among stop smoking services. In neither case, however, did these variables modify the effect of nortriptyline or placebo on the outcome.

Effects on withdrawal symptoms

The majority of respondents experienced most withdrawal symptoms, but predominantly these were mild. The mean score for combined symptoms on the mood and physical symptoms-M scale (range 1-5) did not differ between groups. These scores declined slightly with time, the decline being similar in each arm (figs 3 and 4 and table 6).

Each withdrawal symptom was measured on an ordinal five point scale of severity, and the outcome
was expressed as an odds ratio. These odds ratios express the likelihood of scoring progressively one category higher on the scale in those taking nortriptyline compared with those taking placebo. People taking nortriptyline were significantly less likely to score higher on the depression and anxiety scales of the mood and physical symptoms scale (table 6). An interaction was, however, found with time, such that the difference was greatest on quit day (odds ratio 0.15 for depression and 0.35 for anxiety) and declined with time so that there was almost no difference by four weeks. The effect was different for hunger, irritability, and poor concentration. Early in the quit attempt nortriptyline reduced the occurrence of these symptoms. Severity ratings declined for all three symptoms over time, but the decline was slight in the nortriptyline arm and significantly more pronounced in the placebo arm, such that ratings on these were lower for placebo

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**Fig 3** Withdrawal symptoms in abstinent smokers taking nortriptyline plus nicotine replacement therapy or placebo plus nicotine replacement therapy for at least four weeks.
at four weeks. Nortriptyline had no effect on poor sleep and restlessness and the decline in severity ratings on both variables over time was similar in the nortriptyline and placebo groups.

Urge to smoke (mood and physical symptoms scale-C score-M) was similar in both groups and the decline in urges over time was also similar (fig 4 and table 6).

Effects on quality of life
The mean (SD) quality of life score was 0.86 (0.21) at baseline, measured on a scale from zero (dead) to one (full health), but no detectable differences were found between nortriptyline and placebo. Over the first four weeks the difference in the EQ-5D between the nortriptyline arm and placebo arm was 0.00 (95% confidence interval −0.02 to 0.02). Quality of life scores did not vary significantly over time and this was not modified by nortriptyline or placebo. The difference between the nortriptyline arm and placebo arm at six months was 0.02 (−0.02 to 0.05) and at 12 months was −0.02 (−0.06 to 0.02).

DISCUSSION
Participants randomised to nortriptyline plus nicotine replacement therapy for smoking cessation experienced less depression and anxiety early in the quit attempt when the risk of return to smoking is at its highest than those randomised to placebo plus nicotine replacement therapy.32 Contrary to expectations, no evidence was found that this led to greater abstinence. Overall, symptoms of nicotine withdrawal and urges to smoke were similar in those treated with nortriptyline plus nicotine replacement compared with those receiving nicotine replacement alone. The results were not changed on a per protocol analysis. Many people stopped taking nortriptyline or placebo and, to a lesser extent, nicotine replacement therapy, despite continuing to attempt to quit, but rates of discontinuation were similar in each arm and seem not to have been affected by severity of side effects, which differed noticeably only for dry mouth and constipation.

We adopted a pragmatic design, consistent with our aim to test nortriptyline in the NHS. This led to an unbiased estimate of the degree to which the drug might help in routine care but did not provide optimum conditions for any benefit to be apparent. For example, in a previous study, dose of nortriptyline was titrated on blood level over several weeks prior to quitting before abstinence began,10 whereas in our study, many participants had not reached maximum dose by quit day. Blood assays are not, however, practical in most health systems’ smoking cessation clinics, where many staff are not clinically trained. The point estimate of the effectiveness of combination treatment in the study using dose titration was less than we observed, however.10 Likewise, we allowed combined use of nicotine replacement therapy. Given that combination nicotine replacement therapy is more effective than nicotine replacement therapy alone,3 this might have reduced the scope for additional benefit of nortriptyline plus nicotine replacement. The relative risks were, however, similar in those using combination nicotine replacement therapy compared with those using nicotine replacement therapy alone. Finally, some participants who were attending clinics did not complete questionnaires on side effects and withdrawal symptoms, which may produce bias. Non-completion was caused by NHS advisers not distributing the questionnaires, not patient factors, so it is unlikely to be a major source of bias.

The Cochrane review of antidepressants for smoking cessation includes two trials of nortriptyline plus nicotine replacement therapy compared with nicotine replacement therapy alone.3 One trial showed almost no effect of the combination over single treatment,
No effects were found on withdrawal symptoms and urges to smoke overall. Anxiety and depression were reduced early in the quit attempt with combined treatment abstinence from smoking at six months, but this was not statistically significant. Nortriptyline plus NRT compared with NRT alone led to a modest increase in prolonged abstinence from smoking at six months. In routine practice many people stop nortriptyline or nicotine replacement therapy. Although nortriptyline alone has a place in smoking cessation clinics the data show that the efficacy of combination treatment is slight and should not be used routinely.

We thank the stop smoking services in South Birmingham, Warwickshire, Buckinghamshire, Gwent, Herefordshire, Coventry, Sandwell, Walsall, Wolverhampton, and Black Water Valley and Hart.

**Contributors:** PA and MM wrote the protocol, with contributions from Robert Walton and Mark Drury. CJ, SF, AP, and PA ran the study. Mike Bradburn (statistician, Cancer Research UK Medical Statistics Unit) prepared the randomisation schedule. PA, AP, and CJ analysed the data with help from Michelle Qume. PA drafted the paper, with help from all authors. PA is the guarantor.

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**Competing interests:** PA has done consultancy work for the pharmaceutical and biotechnology industry that has led to payments to him and his institution. This includes work for companies providing smoking cessation treatment, including nicotine replacement therapy. MM has received consultancy income from the European Network for Smoking Prevention and has provided scientific consultancy services through the University of Oxford ISIS Innovation to the National Audit Office and G-Notics.

**Ethical approval:** We obtained approval from the multicentre research ethics committee and all local research ethics committees for the areas in which our trial took place. We obtained a clinical trials authorisation from the Medicines and Healthcare products Regulatory Agency. We obtained approval from all NHS research and development offices of the primary care organisations for the areas in which our trial took place.

**Provenance and peer review:** Not commissioned, externally peer reviewed.

In summary, combining nortriptyline with nicotine replacement therapy led to reductions in anxiety and depression on stopping smoking and a modest and non-significant improvement in prolonged abstinence at six months. In routine practice many people stop nortriptyline or nicotine replacement therapy. Although nortriptyline alone has a place in smoking cessation clinics the data show that the efficacy of combination treatment is slight and should not be used routinely.


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