

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.¹ Most people treated in a single treatment episode, however, eventually return to smoking.²⁻⁴ 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.⁴ Three other licensed drugs are commonly used worldwide. Varenicline is a partial nicotinic agonist and is probably the most effective treatment.² Bupropion and nortriptyline are both antidepressants and about double the odds of smoking cessation.³ 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.³

Nicotine withdrawal symptoms are aversive psychological and physical symptoms that occur on smoking cessation.⁵ 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.⁶ Selective serotonin reuptake inhibitors reduce the occurrence of nicotine withdrawal symptoms.⁷ 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 nortriptyline⁸ but do not improve cessation rates.³ 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.⁹ 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,¹⁰ whereas the other found a noticeable benefit (odds ratio 2.62, 95% confidence interval 1.06 to 8.44).¹¹ 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.¹² 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.¹³

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 contraindication 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.³ 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 arranged for another to be dispensed. We tried to enhance adherence to nortriptyline. We provided written information to participants. Stop smoking advisers were trained in managing drugs, although they remained unfamiliar and hesitant to mention it. We encouraged participants with concerns to ring the trial nurse, and we sometimes reduced the dose

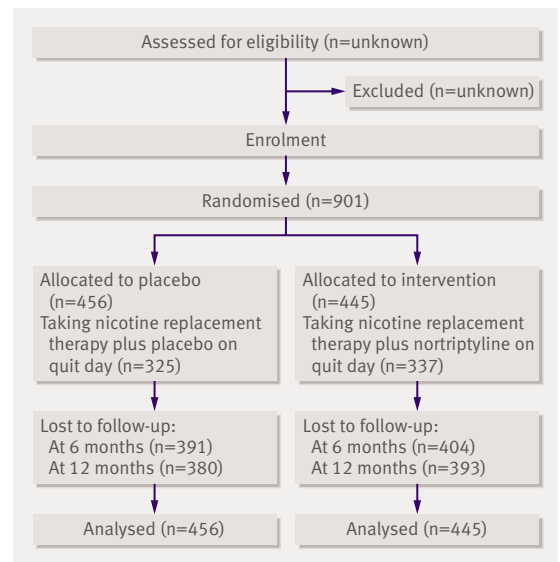


Fig 1 | Flow of participants through trial

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.¹⁴ The secondary outcomes were confirmed seven day point prevalence abstinence at 26 weeks and 52 weeks, and prolonged abstinence at 52 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 scale¹⁵ severity rating of known side effects of nortriptyline; and quality of life using the EQ-5D.¹⁶

The research nurse gave participants a baseline questionnaire containing questions on history of standard 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. Abstinent smokers posted back saliva samples, which were analysed for cotinine using gas chromatography at ABS Laboratories, London. Confirmation of abstinence was defined as an exhaled carbon monoxide

concentration less than 10 ppm or salivary cotinine concentration less than 15 ng/ml on each occasion.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,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 χ^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

Variables	Nortriptyline group (n=445)	Placebo group (n=456)
Mean (SD) age (years)*	43.2 (11.5)	44.0 (12.4)
Women*	206 (46)	213 (46)
Ethnic group:		
White	337 (94)	338 (94)
Mixed	4 (1)	2 (1)
Black	3 (1)	6 (2)
Asian	7 (2)	5 (1)
Missing	9 (3)	8 (2)
Educational attainment:		
Secondary school	152 (42)	185 (52)
Diploma	101 (28)	94 (26)
Degree	46 (13)	34 (10)
Other	61 (17)	46 (13)
Smoking variables:		
Mean (SD) cigarettes per day	21.4 (8.1)	21.4 (8.1)
Roll-up smokers	34 (9)	34 (10)
Cigar smokers	1 (0.3)	2 (1)
Pipe smokers	1 (0.3)	2 (1)
Mean (SD) nicotine dependence score (range 0-10)‡	5.4 (2.1)	5.4 (2.2)
Mean (SD) age started smoking	16.4 (4.2)	16.4 (4.1)
Live with a smoker	129 (36)	143 (40)
Median (interquartile range) longest previous quit attempt (days)	60 (7-180)	42 (6-180)
Psychological variables:		
History of depression§	230 (64)	204 (57)
Mean (SD) anxiety score (range 0-21)¶	8.0 (3.8)	7.5 (3.7)
Mean (SD) depression score (range 0-21)¶	4.9 (3.5)	4.7 (3.6)

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.¹⁹

§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.²⁰

Table 2 | Use of drugs for smoking cessation by trial arm by time. Values are numbers (percentages) of participants unless stated otherwise

Variable	Unknown	Drug plus nicotine replacement	Drug only	Nicotine replacement only	No drug	Total*	χ^2 , P value†
Quit day:							
Nortriptyline	19 (4.5)	337 (79.3)	11 (2.6)	51 (12.0)	7 (1.6)	425	2.21, 0.70
Placebo	24 (5.6)	325 (75.2)	14 (3.2)	59 (13.7)	10 (2.3)	432	
Week 1:							
Nortriptyline	19 (4.6)	312 (75.7)	18 (4.4)	55 (13.3)	8 (1.9)	412	2.59, 0.63
Placebo	23 (5.5)	299 (71.2)	19 (4.5)	67 (16.0)	12 (2.9)	420	
Week 2:							
Nortriptyline	18 (4.5)	264 (66.7)	21 (5.3)	83 (21.0)	10 (2.5)	396	2.89, 0.58
Placebo	22 (5.5)	266 (66.2)	27 (6.7)	72 (17.9)	15 (3.7)	402	
Week 3:							
Nortriptyline	16 (4.3)	237 (63.4)	25 (6.7)	87 (23.3)	9 (2.4)	374	4.02, 0.40
Placebo	22 (5.7)	230 (59.1)	28 (7.2)	91 (23.4)	18 (4.6)	389	
Week 4:							
Nortriptyline	15 (4.2)	212 (58.9)	30 (8.3)	90 (25.0)	13 (3.6)	360	3.02, 0.56
Placebo	22 (5.9)	208 (55.6)	31 (8.3)	92 (24.6)	21 (5.6)	374	

*Denominators are all those where quit attempt lasted to this point.

†For difference between arms, $df=4$.

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.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.

Table 3 | Number of 25 mg capsules of nortriptyline or placebo used by trial arm by time

Variable	Median (interquartile range)*	z score, P value†
Quit day:		
Nortriptyline	2 (2-3)	-0.22, 0.83
Placebo	2 (2-3)	
Week 1:		
Nortriptyline	3 (2-3)	-1.05, 0.29
Placebo	3 (3-3)	
Week 2:		
Nortriptyline	3 (2-3)	-3.08, 0.002
Placebo	3 (3-3)	
Week 3:		
Nortriptyline	3 (2-3)	-2.78, 0.006
Placebo	3 (3-3)	
Week 4:		
Nortriptyline	3 (1-3)	-2.66, 0.008
Placebo	3 (2-3)	

*Among those using trial drug at this point.

†Difference between trial arms (Mann-Whitney U test).

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 at any time.

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

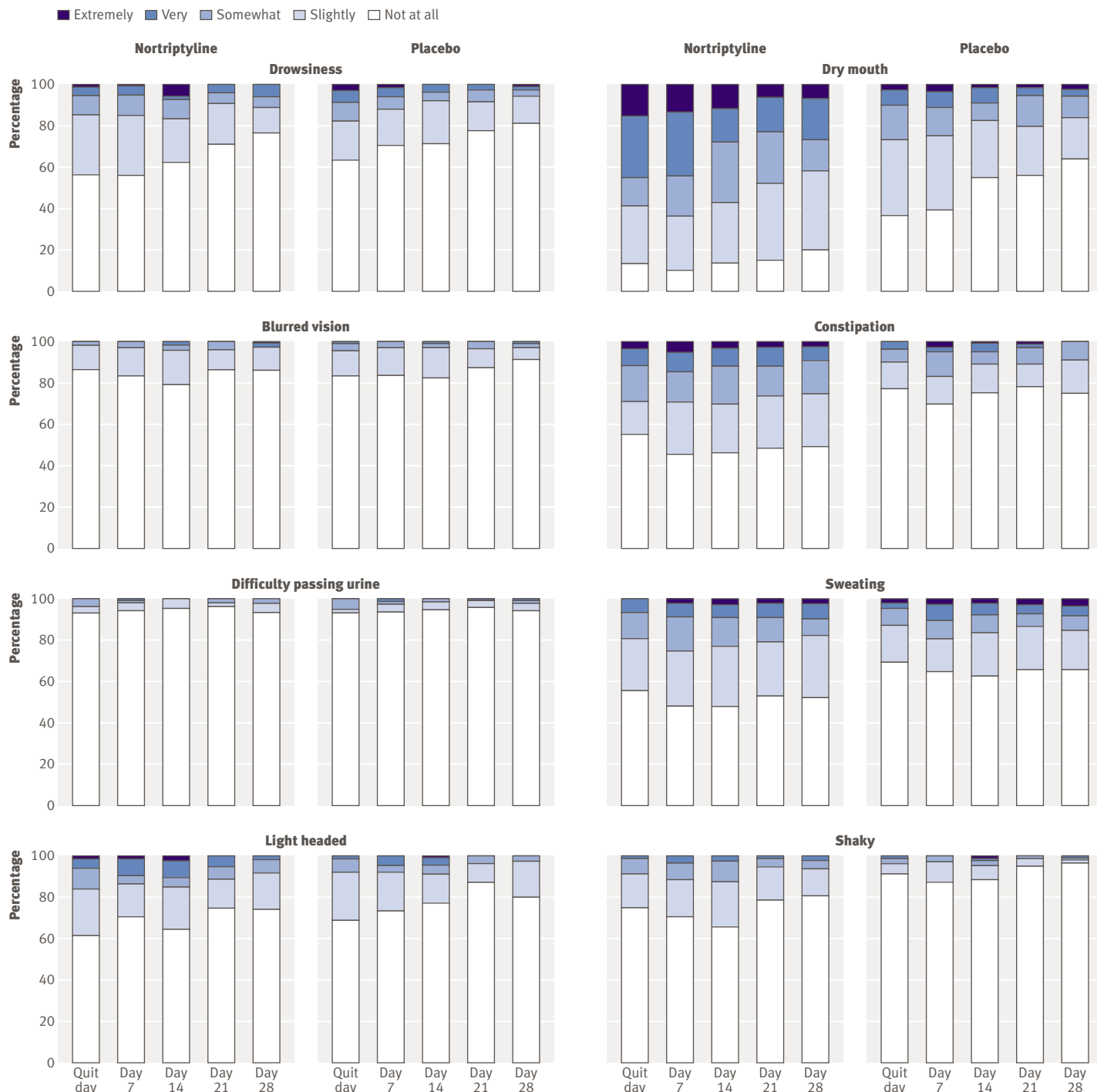


Fig 2 | Side effects in people using nortriptyline plus nicotine replacement therapy and placebo plus nicotine replacement therapy for at least four weeks

Table 4 | Severity of side effects in patients using nortriptyline plus nicotine replacement therapy for smoking cessation

Side effect	Odds ratio (95% CI)	P value for effect modification by time
Drowsiness	1.16 (0.93 to 1.45)	0.021
Dry mouth	6.67 (5.12 to 8.69)	0.55
Blurred vision	0.54 (0.41 to 0.70)	<0.001
Constipation	2.06 (1.66 to 2.56)	<0.001
Difficulty passing urine	0.28 (0.19 to 0.43)	<0.001
Sweating	1.37 (1.11 to 1.68)	0.002
Light headedness	1.10 (0.88 to 1.38)	<0.001
Shaky	1.28 (1.00 to 1.65)	<0.001

half 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.²¹ 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

Table 5 | Prolonged and point prevalence confirmed abstinence from smoking at follow-up in patients using nortriptyline plus nicotine replacement therapy or placebo plus nicotine replacement therapy. Values are numbers (percentages) of participants unless stated otherwise

Variable	Intention to treat analysis				Per protocol analysis			
	Nortriptyline group (n=445)	Placebo group (n=456)	Difference % (95% CI)	Relative risk (95% CI)	Nortriptyline group (n=337)	Placebo group (n=325)	Difference % (95% CI)	Relative risk (95% CI)
Prolonged abstinence:								
4 weeks	220 (49.4)	211 (46.3)	3.2 (-3.4 to 9.7)	1.07 (0.92 to 1.22)	197 (58.5)	186 (56.0)	1.2 (-6.3 to 8.8)	1.04 (0.91 to 1.19)
6 months	72 (16.2)	55 (12.1)	4.1 (-0.4 to 8.7)	1.34 (0.97 to 1.86)	67 (19.9)	46 (14.2)	5.7 (0.0 to 11.4)	1.40 (1.00 to 1.98)
12 months	49 (11.0)	40 (8.8)	2.2 (-1.7 to 6.1)	1.26 (0.84 to 1.87)	44 (13.1)	33 (10.2)	2.9 (-2.0 to 7.8)	1.29 (0.84 to 1.97)
Point prevalence abstinence:								
4 weeks	283 (63.6)	270 (59.2)	4.4 (-2.0 to 10.7)	1.07 (0.97 to 1.19)	247 (73.3)	224 (68.9)	4.4 (-2.5 to 11.3)	1.06 (0.96 to 1.17)
6 months	75 (16.9)	57 (12.5)	4.4 (-0.3 to 9.0)	1.35 (0.98 to 1.85)	69 (20.5)	48 (14.8)	5.7 (-0.1 to 11.5)	1.39 (0.99 to 1.94)
12 months	59 (13.3)	48 (10.5)	2.7 (-1.5 to 7.0)	1.26 (0.88 to 1.80)	52 (15.4)	40 (12.3)	3.1 (-2.1 to 8.4)	1.25 (0.85 to 1.84)

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

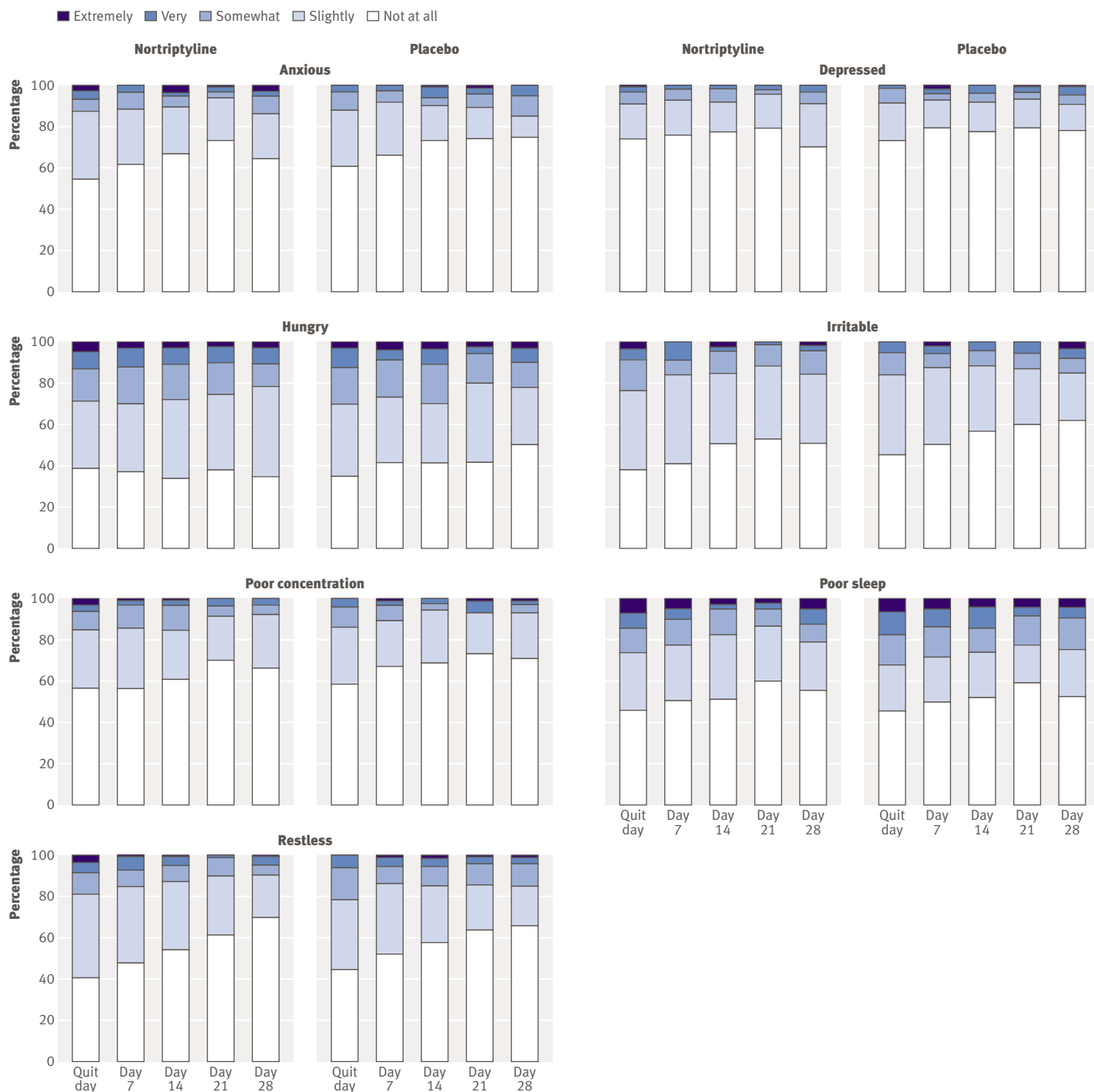


Fig 3 | Withdrawal symptoms in abstinent smokers taking nortriptyline plus nicotine replacement therapy or placebo plus nicotine replacement therapy for at least four weeks

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) was similar in both groups and the decline in urges over time was also similar (fig 4 and table 6).

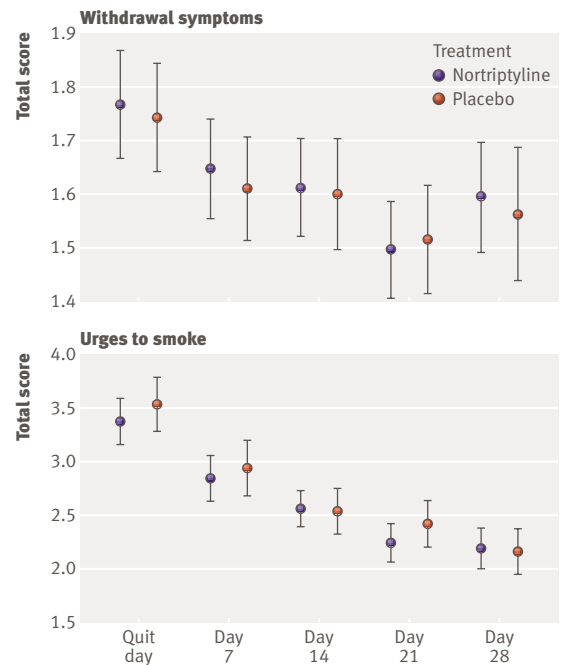
Effects on quality of life

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.²² 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



Withdrawal scored 1-5, urges scored 1-6

Fig 4 | Total score of nicotine withdrawal symptoms and urges to smoke (95% confidence interval) by treatment allocation for smoking cessation

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 alone⁴ 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,

Table 6 | Likelihood of marking higher severity ratings in mood and physical symptoms score and effect modification of nortriptyline plus nicotine replacement therapy by time

Variable	Odds ratio (95% CI)	P value for effect modification*
Mood and physical symptoms score-M:	0.40 (-0.40 to 1.20)†	0.47
Anxiety	0.78 (0.62 to 0.98)	<0.001
Depression	0.57 (0.45 to 0.72)	<0.001
Hunger	1.25 (1.01 to 1.54)	0.022
Irritable	1.17 (0.94 to 1.44)	0.008
Poor concentration	0.84 (0.67 to 1.05)	<0.001
Poor sleep	0.84 (0.68 to 1.04)	0.44
Restless	0.87 (0.70 to 1.08)	0.29
Mood and physical symptoms score-C (urge to smoke)	-0.14 (-0.61 to 0.33)†	0.63

*df=2.
†Mean (95%CI).

WHAT IS ALREADY KNOWN ON THIS TOPIC

One trial suggests that nortriptyline plus nicotine replacement therapy (NRT) is more effective than NRT alone for smoking cessation

Another trial produced a contradictory result but both trials are too small to give a reliable effect size

WHAT THIS STUDY ADDS

Nortriptyline plus NRT compared with NRT alone led to a modest increase in prolonged abstinence from smoking at six months, but this was not statistically significant

Anxiety and depression were reduced early in the quit attempt with combined treatment

No effects were found on withdrawal symptoms and urges to smoke overall

whereas the point estimate in the other trial suggested that combination treatment would be the most effective pharmacotherapy for smoking cessation. Unsurprisingly, when these trials were combined there was heterogeneity ($I^2=56\%$). Our study, with three times more participants than both other trials combined, is compatible with a small beneficial effect of combination treatment, which is not statistically significant. The study shows, however, that efficacy of nicotine replacement therapy compared with placebo (odds ratio 1.77⁴) and nortriptyline compared with placebo (odds ratio 2.34³) is much less than the sum of the parts. The same seems to be true for bupropion, with the overall effect estimate of bupropion plus nicotine replacement therapy compared with nicotine replacement therapy alone showing evidence of modest efficacy (odds ratio 1.37, 95% confidence interval 0.65 to 2.91) and heterogeneity between studies ($I^2=67\%$).³ These clinical data show that the mechanisms by which these antidepressants achieve efficacy for smoking cessation largely overlap the actions of nicotine.

These data show that nortriptyline should not be added routinely to nicotine replacement therapy in smoking cessation clinics as the effect, if any, is small. Many smokers, however, make several attempts to quit and often use different pharmacotherapies each time in an attempt to overcome their addiction. In the international tobacco treatment guidelines nortriptyline is suggested as a first line or second line treatment.²³ In the United Kingdom, tricyclics are not often used for treatment of depression because of concerns about toxicity in overdose and side effects.²⁴ Although many people stopped nortriptyline in this study, the rate was not higher than in the placebo group. This parallels findings from the other nortriptyline trials, where generally fewer than 10% of people stopped treatment because of side effects, and the rate was generally similar in active treatment and placebo groups.³ We found few serious problems of routine use of nortriptyline in smoking cessation clinics, and side effects seem tolerable. The effect estimate suggests some effect of adding nicotine replacement therapy to nortriptyline treatment from the three trials, but as the effect is modest it may be considered only as an option in particular clinical circumstances.

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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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-Nostics.

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.

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