

WHAT IS ALREADY KNOWN ON THIS TOPIC

Survival rates in infants born before 26 weeks' gestation are relatively low

Recent reports from individual centres of improved survival of extremely premature babies are hard to interpret because of inclusion bias and variation in case mix

WHAT THIS STUDY ADDS

By looking at changes in survival over time in a whole population this study provides data free of inclusion bias and case mix effects

Survival rates in infants born at 24 and 25 weeks' gestation have clearly improved in the past 12 years

Survival rates in those born at 23 weeks' gestation have not changed, and intensive care for babies born at 22 weeks remains unsuccessful

and experienced nurses who used the same algorithm throughout collection of data.

Weaknesses

There was a relatively small number of babies born at 22 and 23 weeks' gestation. While this might be why we could not show improving survival in the smallest babies, the similarity of the survival rates at 22 and 23 weeks is compelling. Application of a retrospective calculation of sample size shows that the cohort was large enough to detect a difference of 13% in the survival rates of the infants born at 23 weeks in the two periods.

Our findings concur with the view of Hack and Fanaroff, who suggested in 2000 that the limit of viability had been reached.⁷ Large improvements in the survival to discharge of admitted babies born at 24 and 25 weeks (to 41% and 63%, respectively) in the most recent time period suggests that a blanket policy of not resuscitating these infants is inappropriate. In the

UK a widespread consultation has suggested guidelines for the approach to individual infants based on gestational age.⁸

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Competing interests: None declared.

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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 the sum of the parts and there is no evidence that combination treatment is more effective than either alone.

Trial registration Current Controlled Trials
ISRCTN57852484.

INTRODUCTION

Nicotine replacement therapy is the most commonly used pharmacotherapy for smoking cessation.¹ Three other licensed drugs commonly used are varenicline, a partial nicotinic agonist,² and the antidepressants bupropion and nortriptyline.³

Two trials tested the effectiveness of combining bupropion with nicotine replacement and nortriptyline with nicotine replacement. One trial found no benefit from using nortriptyline compared with nicotine replacement alone,⁴ whereas the other found a noticeable benefit.⁵ 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. Participants could choose from any available nicotine replacement product. Switching products was allowed and in some services participants were given two or more to use simultaneously. This variability necessitated a pragmatic design.⁶

Anyone aged 18 years or older attending a stop smoking service and smoking 10 or more cigarettes a day was eligible. A research nurse attended group meetings and introduced the trial. Interested people were interviewed individually.

Nortriptyline and placebo were provided in identical 25 mg capsules. 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 to be effective.³ The participants took the maximum dose for six weeks and then reduced the dose over a week.

Outcome measures

The primary outcome was prolonged abstinence at six months, confirmed by measurement of salivary cotinine or exhaled carbon monoxide. We included as smokers those lost to follow-up.⁷ 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 and seven day point prevalence abstinence; nicotine withdrawal symptoms; urges to smoke, using the mood and physical

symptoms scale⁸ severity rating of known side effects of nortriptyline; and quality of life using the EQ-5D.⁹

Participants completed a baseline questionnaire for each clinic visit. Smoking status, nicotine withdrawal symptoms, urges to smoke, and side effects were assessed at each visit after quit day by questionnaire. We recorded the concentration of exhaled carbon monoxide measured at the four week visit. We obtained data at six and 12 months by postal questionnaire and telephone. Saliva samples returned by abstinent smokers were analysed for cotinine.

Statistical analysis

An independent statistician generated randomly ordered blocks of two, four, and six, stratified by treating clinician (adviser). Advisers, participants, and study staff carrying out follow-up were blind to allocation.

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 relative risks with 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 follow-up, to examine any changes over time. We used a Mann-Whitney U test to examine 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 abstinence from smoking for the first four weeks.¹⁰ 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 groups using multiplicative interaction terms.

RESULTS

Overall, 901 people (445 nortriptyline arm, 456 placebo arm), recruited from 10 NHS stop smoking services, were seen by 45 different advisers (see bmj.com). Nine (2.0%) people in the nortriptyline arm and 17 (3.7%) in the placebo arm provided no follow-up data. They were analysed as treatment failures. Baseline characteristics were similar between the groups (see bmj.com).

Drug use and side effects

The main choice of drug at all follow-up times was nortriptyline plus nicotine replacement therapy or

placebo plus nicotine replacement therapy, although the proportion of people using these 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 (see [bmj.com](#)).

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 product did not vary much or significantly by trial arm.

Participants in both arms took a median of two capsules of nortriptyline or placebo daily by quit day. A median daily dose of three capsules was consumed thereafter, but with more variation in the nortriptyline arm than placebo arm, a statistically significant effect (see [bmj.com](#)).

Symptoms known to be side effects of nortriptyline were more common and more severe in those taking active drug than placebo. More than 80% of those taking nortriptyline and more than half taking placebo had a dry mouth. More than half experienced constipation and sweating, with small differences between the groups (see [bmj.com](#)). A minority experienced the other side effects. Modelling confirmed these findings (see [bmj.com](#)). Drowsiness, difficulty passing urine, and light-headedness declined less rapidly in the nortriptyline arm than the placebo arm. The decline in severity of dry mouth over time was the same for both groups. For blurred vision the severity was nearly constant for nortriptyline but declined for placebo. The severity of constipation, sweating, and shakiness increased slightly in the nortriptyline arm but declined in the placebo arm.

Those who subsequently stopped nortriptyline or placebo had initial ratings for each of the eight side effects

similar to, and not significantly different from, those who continued treatment.

Abstinence

Data on smoking status were unavailable for 12 (3%) people in the nortriptyline arm and 18 (4%) in the placebo arm by four weeks, 41 (9%) and 65 (14%) by six months, and 52 (12%) and 76 (17%) by 12 months. At six months, however, 89% of those lost after four weeks had not achieved prolonged abstinence at four weeks so were considered treatment failures at six months. Those lost after six months who did not respond to follow-up at 12 months had not achieved prolonged abstinence at six months.

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, but the differences were small and not statistically significant. For the per protocol analysis, the effects in those using nortriptyline plus nicotine replacement or placebo plus nicotine replacement on quit day were similar (table).

Nicotine 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 scale did not differ between groups. These scores declined slightly with time, the decline being similar in each arm (see [bmj.com](#)).

People taking nortriptyline were significantly less likely to score higher on the depression and anxiety scales of the mood and physical symptoms scale (see [bmj.com](#)). An interaction was 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

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)

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

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 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 was similar in both groups and the decline in urges over time was also similar (see bmj.com).

Quality of life

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 for smoking cessation experienced less depression and anxiety early in the quit attempt than those randomised to placebo plus nicotine replacement.¹¹ We found no evidence 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. The point estimate of the effectiveness of combination treatment in one study that gave optimal nortriptyline treatment was less than we observed, however.⁴ Likewise, we allowed combined use of nicotine replacement therapy. Given

that combination therapy is more effective than nicotine replacement alone¹ 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 a single form of nicotine replacement. Finally, some participants did not complete questionnaires on side effects and withdrawal symptoms, which may produce 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, whereas the point estimate in the other trial suggested that combination treatment would be the most effective pharmacotherapy for smoking cessation. When these trials were combined heterogeneity was present ($I^2=56%$). Our study, with three times more participants than both other trials, 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 1.77¹) and nortriptyline compared with placebo (odds ratio 2.34³) is much less than the sum of the parts.

These data show that nortriptyline should not be added routinely to nicotine replacement therapy in smoking cessation clinics, as the effect is small. Many smokers make several attempts to quit and often use different pharmacotherapies in an attempt to overcome their addiction. Although many people stopped nortriptyline in this study, the rate was not higher than in the placebo arm. 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 from the three trials, but as the effect is modest it may be considered only as an option in particular circumstances.

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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 all relevant authorities. 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.

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Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis

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ABSTRACT

Objective To assess the risk of venous thromboembolism in women using hormone replacement therapy by study design, characteristics of the therapy and venous thromboembolism, and clinical background.

Design Systematic review and meta-analysis.

Data sources Medline.

Studies reviewed Eight observational studies and nine randomised controlled trials.

Inclusion criteria Studies on hormone replacement therapy that reported venous thromboembolism.

Review measures Homogeneity between studies was analysed using χ^2 and I^2 statistics. Overall risk of venous thromboembolism was assessed from a fixed effects or random effects model.

Results Meta-analysis of observational studies showed that oral oestrogen but not transdermal oestrogen increased the risk of venous thromboembolism. Compared with non-users of oestrogen, the odds ratio of first time venous thromboembolism in current users of oral oestrogen was 2.5 (95% confidence interval 1.9 to 3.4) and in current users of transdermal oestrogen was 1.2 (0.9 to 1.7). Past users of oral oestrogen had a similar risk of venous thromboembolism to never users. The risk of venous thromboembolism in women using oral oestrogen was higher in the first year of treatment (4.0, 2.9 to 5.7) compared with treatment for more than one year (2.1, 1.3 to 3.8; $P < 0.05$). No noticeable difference in the risk of venous thromboembolism was observed between unopposed oral oestrogen (2.2, 1.6 to 3.0) and opposed oral oestrogen (2.6, 2.0 to 3.2). Results from nine randomised controlled trials confirmed the increased risk of venous thromboembolism among women using oral oestrogen (2.1, 1.4 to 3.1). The combination of oral oestrogen and thrombogenic mutations or obesity further enhanced the risk of venous thromboembolism, whereas transdermal oestrogen did not

seem to confer additional risk in women at high risk of venous thromboembolism.

Conclusion Oral oestrogen increases the risk of venous thromboembolism, especially during the first year of treatment. Transdermal oestrogen may be safer with respect to thrombotic risk. More data are required to investigate differences in risk across the wide variety of hormone regimens, especially the different types of progestogens.

INTRODUCTION

Recent observational studies have shown consistent associations between hormone replacement therapy use and risk of venous thromboembolism in postmenopausal women.^{1w1-w11} These findings were confirmed by randomised controlled trials.^{1w12-w20} We systematically reviewed the risk of venous thromboembolism among users of hormone replacement therapy.

METHODS

We searched Medline from 1974 to 2007 using keywords related to hormone replacement therapy and venous thromboembolism (see bmj.com) and we also back referenced from reviews published after 1970. The quality of the randomised controlled trials was assessed according to several criteria, and the quality of the observational studies was assessed as recommended by the Meta-analysis Of Observational Studies in Epidemiology group.²

We extracted data on route of oestrogen administration, type of oestrogens, unopposed or opposed hormone regimen, duration of treatment and type of venous thromboembolism (idiopathic or secondary, deep vein thrombosis or pulmonary embolism).

Statistical analysis

For each study we used the most adjusted relative risks or odds ratios, with 95% confidence intervals. We

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