Should nortriptyline be used as a first-line aid to help smokers quit: results from a systematic review and meta-analysis
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CRD summary
This review assessed the efficacy of nortriptyline for smoking cessation in motivated individuals who received a behavioural intervention. The authors concluded that nortriptyline increases rates of prolonged abstinence compared with placebo, and is safe and well tolerated. Apart from potential bias in the study selection process, this review was well conducted and the authors' conclusions are likely to be reliable in the short term.

Authors' objectives
To assess the efficacy of nortriptyline for smoking cessation in comparison with placebo and bupropion sustained-release.

Searching
MEDLINE, EMBASE, PsycINFO and CINAHL (all from inception to March 2004) and the Cochrane CENTRAL Register were searched; the search terms were reported. In addition, five online publicly accessible registers of clinical trials were searched. The reference lists of selected studies and reviews, as well as abstract books of five named relevant conferences and symposia from 1999 to March 2004, were also screened. The first authors of identified papers and unpublished trials were contacted for details of additional studies, unpublished studies and ongoing trials. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. The included studies followed up patients for 26 to 64 weeks.

Specific interventions included in the review
Studies that compared nortriptyline, with or without individual or group counselling, with placebo or bupropion hydrochloride sustained-release were eligible for inclusion. All of the included studies used some type of behavioural programme in addition to the study medications. Where stated, nortriptyline was evaluated at a modal dose of 100 mg/day or at a dose that increased from 25 to 75 mg/day. The dose of bupropion evaluated was 300 mg/day. The duration of the medication ranged from 6 to 14 weeks, while the number of behavioural intervention sessions ranged from 4 to 14 over 5 to 11 weeks.

Participants included in the review
Studies of smokers who were motivated to stop smoking were eligible for inclusion. No further details of the included participants were given.

Outcomes assessed in the review
The primary outcome was 6-month or more prolonged abstinence, verified by a biochemical test. The review also assessed abstinence rates in the short term (at the end of treatment), intermediate term (6 months) and long term (at least 12 months), and adverse effects.

How were decisions on the relevance of primary studies made?
One reviewer checked all retrieved references for eligibility.

Assessment of study quality
Studies reported as full papers were assigned a score, ranging from 0 to 11, based on the following items from the Delphi list and the Jadad scale: randomisation method; allocation concealment; description of eligibility criteria; comparability of baseline prognostic factors; (attempted) blinding of the patient, therapist and assessor; verification of success of blinding; loss to follow-up less than 20%; use of intention-to-treat analysis; and reasons for withdrawals. The validity of studies that were reported as abstracts or posters was not assessed. Two reviewers independently assessed validity and any disagreements were resolved by consensus.

Data extraction
Two reviewers extracted the data using a standardised form, but the methods used to resolve any disagreements were not reported. Data on the number of participants with continuous abstinence after at least 6 months were extracted and used to calculate a relative risk (RR) and risk difference (RD), along with a 95% confidence interval (CI). Data to calculate the abstinence percentage (AP) at each time point were also extracted. Participants who had dropped out or were lost to follow-up were classified as smokers.

Methods of synthesis
How were the studies combined?
The studies were pooled using a meta-analysis where at least two studies used comparable interventions and assessed a specific outcome at a comparable follow-up period. A fixed-effect model was used in the absence of statistical heterogeneity, while a random-effects model was used when statistical heterogeneity was found. Pooled RDs and RRs with 95% CIs were calculated.

The authors stated that publication bias was not assessed as only 5 studies were included in the review.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test. The meta-analysis of nortriptyline versus placebo was repeated after excluding one study that used self-reported abstinence rates. The AP rates for each treatment were plotted against time of follow-up and a weighted linear regression was used to estimate the decrease in abstinence rates per month.

Results of the review
Six RCTs met the inclusion criteria, of which five (n=861) provided sufficient data to be included in the meta-analyses.

The 4 studies reported in full scored from 7 to 11 (out of 11 points) for validity. All reported blinding of treatment, three reported blinding of carers, and none reported blinding of the assessor. Two studies reported follow-up greater than 80%.

Nortriptyline versus placebo (4 RCTs, n=641): no statistically significant heterogeneity was found (P=0.37). Nortriptyline significantly increased prolonged (at least 6 months) abstinence rates compared with placebo; the RR was 2.4 (95% CI: 1.7, 3.6) and the RD was 0.11 (95% CI: 0.07, 0.15). The AP decreased significantly faster in the nortriptyline group compared with the placebo group (-1.5% per month versus -0.2%, P<0.01).

Nortriptyline versus bupropion (1 RCT, n=220): the difference in AP between treatments was small but significantly higher with bupropion compared with nortriptyline (45.2% versus 43.1%, P<0.01). At 12 months there was no significant difference in AP between treatments (RR 1.7, 95% CI: 0.7, 4.1).

Adverse effects: significantly more adverse effects were reported with nortriptyline compared with placebo. The most common adverse effects were dry mouth and constipation or gastrointestinal upset.

The study of nortriptyline versus bupropion did not directly compare adverse effects between treatments.

Authors' conclusions
Nortriptyline increases rates of prolonged abstinence compared with placebo and is safe and well tolerated. It may be a
useful alternative to bupropion for smokers who are motivated to quit.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Numerous sources were searched and attempts were made to minimise both publication and language bias. Methods were used to minimise reviewer errors and bias in the assessment of validity and extraction of data, but it was unclear whether similar steps were taken when selecting studies. Validity was assessed using established criteria and the results of the assessment were reported.

Adequate details of each included study were given. Statistical heterogeneity was assessed and the studies were appropriately combined using meta-analysis. The primary outcome was abstinence after at least 6 months but few studies reported longer term data, thus limiting the assessment of long-term abstinence. Apart from potential bias in the study selection process, this review was well conducted and the authors' conclusions are likely to be reliable in the short term. However, the authors cautioned that efficacy may be lower in clinical practice than in the reported studies.

One of the authors received medication (nortriptyline) from the manufacturer for an RCT of nortriptyline versus bupropion.

**Implications of the review for practice and research**

**Practice:** The authors stated that health care professionals should be recommended to prescribe nortriptyline as first-line treatment for smoking cessation.

**Research:** The authors stated that further studies are required to determine the relative efficacy and adverse effects of nortriptyline and bupropion.

**Bibliographic details**

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