Safety of nortriptyline at equivalent therapeutic doses for smoking cessation: a systematic review and meta-analysis

Dhippayom T, Chaiyakunapruk N, Jongchansittho T

CRD summary
The authors concluded that nortriptyline at doses between 75mg and 100mg was not significantly associated with serious adverse events for patients without underlying cardiovascular disease. This was a well-conducted review, but given the variability across studies and small number of studies for the main outcomes these findings should be interpreted with caution.

Authors' objectives
To examine the safety of nortriptyline at doses equivalent to those used in aiding smoking cessation.

Searching
MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, CINAHL, PsycINFO, WHOLIS and ClinicalTrials.gov were searched for English-language studies from inception to November 2008; search terms were reported.

Study selection
Studies of any design that compared nortriptyline at doses between 75mg and 100mg in any indication and with placebo or active control were eligible for inclusion. The incidence of adverse events or withdrawal from the study due to adverse events had to be reported. Outcomes included death associated with adverse effects, cardiovascular adverse effects, other adverse effects and withdrawal due to adverse effects.

Most of the included studies were randomised controlled trials (RCTs); there was one non-randomised trial. Indications for nortriptyline in the included studies were smoking cessation (eight studies), depression (five studies), neuropathic pain (three studies) and schizophrenia (one study). Nortriptyline dose ranged from 75mg to 100mg. The major comparator used was placebo. Comparators with other regimes included sertraline, fluoxetine, amitriptyline and gabapentin. Methods of adverse event monitoring, where stated, varied but in most studies involved routine monitoring. Mean age ranged from 36 to 73 years of age

Two independent reviewers selected studies for the review; disagreements were resolved by reference to a third reviewer

Assessment of study quality
Two independent reviewers assessed study quality using the Jadad scale of randomisation, allocation concealment, blinding, intention-to-treat and follow-up; maximum score 5.

Disagreements were resolved by reference to a third reviewer

Data extraction
Two reviewers independently extracted the number of adverse events to calculate the relative risk (RR) and 95% confidence intervals (CIs).

Disagreements were resolved by reference to a third reviewer

Methods of synthesis
Relative risk and 95% CIs were combined in a meta-analysis using a random-effects model. Heterogeneity between studies was assessed by the Q-test and $I^2$. Sensitivity analysis was undertaken to pool studies that compared nortriptyline
with placebo and those that compared nortriptyline with an active control group as well as removing the non-RCT.

**Results of the review**

Seventeen studies were included in the review (n=2,885 participants): 16 RCTs and one non-randomised trial. Three studies had a quality score of 1 or 2, six studies scored 3, six scored 4 and two scored 5. The randomisation process was not described in 14 trials. Sixteen trials were described as double-blind. The method of double-blinding was only described in eight. Treatment duration ranged from four to 52 weeks.

There were no reports of death or life-threatening adverse events.

Compared with comparator groups, nortriptyline was significantly associated with orthostatic hypotension (RR 3.2, 95% CI 1.9 to 5.4, I²=67%; three studies), but not with other cardiovascular adverse events; sensitivity analyses did not alter these findings. No significant increase in heart rate (two studies, I²=0%) or unspecified cardiovascular events (one study) were observed for nortriptyline-treated patients.

Compared with comparator groups, nortriptyline was significantly associated with the adverse events: anticholinergic-related effects including dry mouth (RR 2.3, 95% CI 2.1 to 2.5; 14 studies), constipation (RR 2.1, 95% CI 1.8 to 2.4), blurry vision (RR 1.9, 95% CI 1.4 to 2.6; five studies), light headache (RR 1.4, 95% CI 1.1 to 1.8; two studies), shaky hands (RR 4.1, 95% CI 2.8 to 5.8; two studies), drowsiness (RR 1.9, 95% CI 1.4 to 2.6; nine studies), dizziness (RR 1.8, 95% CI 1.3 to 2.4; nine studies), gastrointestinal disturbance (RR 1.7, 95% CI 1.3 to 2.1; four studies) and dysgeusia (RR 2.0, 95% CI 1.1 to 3.5; two studies). There was significant heterogeneity for dry mouth (I²=43%), light headache (I²=59%), shaky hand (I²=90%) and gastrointestinal disturbance (I²=66%).

Sensitivity analyses impacted upon outcomes for dizziness and drop-out due to adverse effects, but not on other adverse outcomes.

**Authors' conclusions**

Nortriptyline at doses between 75mg and 100mg was not significantly associated with serious adverse events when administered in patients without underlying cardiovascular disease.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. The search for studies was extensive, but was limited to English-language articles and so language bias may have been introduced. Suitable methods to minimise the risk of reviewer error and bias were applied for all parts of the review process. A quality assessment was conducted using a standard tool. Sufficient primary trial details were reported. Statistical heterogeneity was generally low, but there were few studies for some comparisons and variability across studies was apparent, so the reliability and generalisability of some of the pooled results was uncertain.

This was a well-conducted review and the findings appear to reflect the data, but given the variability across studies and small number of studies for the main outcomes then these findings should be interpreted with caution.

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

**Practice:** The authors stated that nortriptyline should be considered a safe therapeutic option for the management of smoking cessation by policy makers and guideline developers.

**Research:** The authors stated that a systematic review that compared the safety of nortriptyline and bupropion was required.

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