

# Antidepressants for smoking cessation (Review)

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[Intervention Review]

# Antidepressants for smoking cessation

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## ABSTRACT

### Background

There are at least three reasons to believe antidepressants might help in smoking cessation. Firstly, nicotine withdrawal may produce depressive symptoms or precipitate a major depressive episode and antidepressants may relieve these. Secondly, nicotine may have antidepressant effects that maintain smoking, and antidepressants may substitute for this effect. Finally, some antidepressants may have a specific effect on neural pathways (e.g. inhibiting monoamine oxidase) or receptors (e.g. blockade of nicotinic-cholinergic receptors) underlying nicotine addiction.

### Objectives

The aim of this review is to assess the effect and safety of antidepressant medications to aid long-term smoking cessation. The medications include bupropion; doxepin; fluoxetine; imipramine; lazabemide; moclobemide; nortriptyline; paroxetine; S-Adenosyl-L-Methionine (SAME); selegiline; sertraline; St. John's wort; tryptophan; venlafaxine; and zimeledine.

### Search methods

We searched the Cochrane Tobacco Addiction Group Specialised Register which includes reports of trials indexed in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and PsycINFO, and other reviews and meeting abstracts, in July 2013.

### Selection criteria

We considered randomized trials comparing antidepressant medications to placebo or an alternative pharmacotherapy for smoking cessation. We also included trials comparing different doses, using pharmacotherapy to prevent relapse or re-initiate smoking cessation or to help smokers reduce cigarette consumption. We excluded trials with less than six months follow-up.

### Data collection and analysis

We extracted data and assessed risk of bias using standard methodological procedures expected by the Cochrane Collaboration.

The main outcome measure was abstinence from smoking after at least six months follow-up in patients smoking at baseline, expressed as a risk ratio (RR). We used the most rigorous definition of abstinence available in each trial, and biochemically validated rates if available. Where appropriate, we performed meta-analysis using a fixed-effect model.

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## Main results

Twenty-four new trials were identified since the 2009 update, bringing the total number of included trials to 90. There were 65 trials of bupropion and ten trials of nortriptyline, with the majority at low or unclear risk of bias. There was high quality evidence that, when used as the sole pharmacotherapy, bupropion significantly increased long-term cessation (44 trials, N = 13,728, risk ratio [RR] 1.62, 95% confidence interval [CI] 1.49 to 1.76). There was moderate quality evidence, limited by a relatively small number of trials and participants, that nortriptyline also significantly increased long-term cessation when used as the sole pharmacotherapy (six trials, N = 975, RR 2.03, 95% CI 1.48 to 2.78). There is insufficient evidence that adding bupropion (12 trials, N = 3487, RR 1.9, 95% CI 0.94 to 1.51) or nortriptyline (4 trials, N = 1644, RR 1.21, 95% CI 0.94 to 1.55) to nicotine replacement therapy (NRT) provides an additional long-term benefit. Based on a limited amount of data from direct comparisons, bupropion and nortriptyline appear to be equally effective and of similar efficacy to NRT (bupropion versus nortriptyline 3 trials, N = 417, RR 1.30, 95% CI 0.93 to 1.82; bupropion versus NRT 8 trials, N = 4096, RR 0.96, 95% CI 0.85 to 1.09; no direct comparisons between nortriptyline and NRT). Pooled results from four trials comparing bupropion to varenicline showed significantly lower quitting with bupropion than with varenicline (N = 1810, RR 0.68, 95% CI 0.56 to 0.83). Meta-analyses did not detect a significant increase in the rate of serious adverse events amongst participants taking bupropion, though the confidence interval only narrowly missed statistical significance (33 trials, N = 9631, RR 1.30, 95% CI 1.00 to 1.69). There is a risk of about 1 in 1000 of seizures associated with bupropion use. Bupropion has been associated with suicide risk, but whether this is causal is unclear. Nortriptyline has the potential for serious side-effects, but none have been seen in the few small trials for smoking cessation.

There was no evidence of a significant effect for selective serotonin reuptake inhibitors on their own (RR 0.93, 95% CI 0.71 to 1.22, N = 1594; 2 trials fluoxetine, 1 paroxetine, 1 sertraline) or as an adjunct to NRT (3 trials of fluoxetine, N = 466, RR 0.70, 95% CI 0.64 to 1.82). Significant effects were also not detected for monoamine oxidase inhibitors (RR 1.29, 95% CI 0.93 to 1.79, N = 827; 1 trial moclobemide, 5 selegiline), the atypical antidepressant venlafaxine (1 trial, N = 147, RR 1.22, 95% CI 0.64 to 2.32), the herbal therapy St John's wort (hypericum) (2 trials, N = 261, RR 0.81, 95% CI 0.26 to 2.53), or the dietary supplement SAME (1 trial, N = 120, RR 0.70, 95% CI 0.24 to 2.07).

## Authors' conclusions

The antidepressants bupropion and nortriptyline aid long-term smoking cessation. Adverse events with either medication appear to rarely be serious or lead to stopping medication. Evidence suggests that the mode of action of bupropion and nortriptyline is independent of their antidepressant effect and that they are of similar efficacy to nicotine replacement. Evidence also suggests that bupropion is less effective than varenicline, but further research is needed to confirm this finding. Evidence suggests that neither selective serotonin reuptake inhibitors (e.g. fluoxetine) nor monoamine oxidase inhibitors aid cessation.

## PLAIN LANGUAGE SUMMARY

### Do medications used to treat depression help smokers who are trying to quit

#### Background and review questions

Some medications and supplements that have been used to treat depression (antidepressants) have been tested to see whether they also help people who are trying to stop smoking. Two antidepressants, bupropion (Zyban) and nortriptyline, are sometimes prescribed to help with quitting smoking. This review set out to determine if using antidepressants increased people's likelihood of successfully quitting smoking at six months or longer and to determine the safety of using these medications to help quit smoking.

#### Study characteristics

The evidence is current to July 2013. This update includes 24 new studies, and this review includes 90 studies overall. The studies included people who smoked and people who had recently quit smoking. There were 65 trials of bupropion, which is licensed for use as a smoking cessation medication under the trade name 'Zyban'. There were ten trials of nortriptyline which is a tricyclic antidepressant which is not licensed specifically for smoking cessation. We only included studies which measured long term quitting (whether or not people had quit smoking at six months or longer from the start of the study).

#### Key results and quality of evidence

Trials of bupropion (Zyban) for smoking cessation show high quality evidence that it increases the likelihood of a quit attempt being successful after at least six months (44 trials, over 13,000 participants). The side effects of bupropion include insomnia, dry mouth and

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nausea and rarely (1:1000) seizures and perhaps psychiatric problems, but the last is unclear. There is also moderate quality evidence, limited by a relatively small number of included studies and participants, that the antidepressant nortriptyline increases quit rates (six trials, 975 participants). The side effects of this medication include dry mouth, constipation, nausea, and sedation, and it can be dangerous in overdose. Selective serotonin reuptake inhibitor antidepressants (for example, fluoxetine), monoamine oxidase inhibitor antidepressants (for example, selegiline), and the antidepressant venlafaxine have not been shown to help smoking cessation, nor has the herbal therapy St John's wort, or S-Adenosyl-L-Methionine (SAMe), a dietary supplement that is thought to have antidepressant properties.

### **Discussion and considerations**

The way in which bupropion and nortriptyline might work is not fully understood. Both appear to help people quit smoking whether or not they have a history of depression, or have depressive symptoms when they stop smoking. The likelihood of quitting using bupropion or nortriptyline appears to be similar to that for nicotine replacement therapy, but the likelihood of quitting using bupropion appears to be lower than the likelihood of quitting using varenicline.