Interventions for smoking cessation

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Antidepressants for smoking cessation (1)

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., blockage of nicotinic-cholinergic receptors) underlying nicotine addiction.

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

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 were searched.

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

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). They used the most rigorous definition of abstinence available in each trial, and biochemically validated rates if available. Where appropriate, they performed meta-analysis using a fixed-effect model.

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 was insufficient evidence that adding bupropion (12 trials, $N = 3487$, RR 1.19, 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). 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), 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).

The authors conclude that 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. Bupropion has been found to be less effective than varenicline, but further research is needed to confirm this finding. Selective serotonin reuptake inhibitors (e.g. fluoxetine) and monoamine oxidase inhibitors have not been shown to aid cessation.

Bupropion initiation prior to quitting smoking (2)

This study evaluated whether 4 weeks of pre-quit bupropion (extended run-in) results in greater pre-quit reductions in smoking rate and greater short-term abstinence than standard 1 week of pre-quit bupropion (standard run-in).

Adult smokers ($n = 95$; 48 females) were randomised to a standard run-in group ($n = 48$; 3-week placebo, then 1-week bupropion pre-quit) or an extended run-in group (4-week pre quit bupropion; $n = 47$). Both groups received group behavioural counselling and 7 weeks of post quit bupropion. Smoking rate (and craving, withdrawal, and subjective effects) was collected daily during the pre-quit period; biochemical data (cotinine and carbon monoxide) were collected at study visits.

During the pre-quit period, the extended run-in group exhibited a greater decrease in smoking rate, compared to the standard run-in group ($p=0.03$). Cigarette craving and salivary cotinine followed a similar pattern, though the latter was evident only among women. Biochemically verified 4-week continuous abstinence rates were higher in the extended run-in group (53%) than the standard run-in group (31%), ($p=0.033$). The extended use of bupropion prior to a quit attempt reduces smoking behaviour during the pre-quit period and improves short-term abstinence rates.

Combination varenicline/bupropion treatment in an adaptive smoking cessation paradigm (3)

This study looked at the efficacy and safety of combination varenicline/bupropion sustained-release (SR) treatment for smokers who were unlikely to achieve abstinence using nicotine patch treatment, based on an assessment of initial smoking reduction prior to the quit date.

A randomized double-blind, parallel group, adaptive treatment trial identified 222 cigarette smokers showing $\leq 50\%$ reduction in smoking after 1 week of nicotine patch treatment. Smokers were randomized to receive 12 weeks of varenicline/bupropion treatment vs. varenicline plus placebo. The primary outcome was continuous smoking abstinence at weeks 8-11 after the target quit date.

Combination varenicline/bupropion treatment increased the abstinence rate relative to varenicline: 39.8% vs. 25.9% (odds ratio [OR], 1.89; 95% CI, 1.07-3.35; $p=0.029$). Male smokers showed a greater effect of combination treatment than female smokers: 50.9% vs. 19.6% for males (OR 4.26; 95% CI, 1.73-10.49; $p=0.002$), and 29.3% vs. 30.6% for females (OR, 0.94; 95% CI, 0.43-2.05; $p=0.87$). Highly dependent smokers also showed a greater effect than smokers with lower levels of dependence: 44.4% vs. 18.6% for highly dependent smokers (OR, 3.51, 95% CI, 1.64-7.51, $p=0.001$), and 31.7% vs. 39.5% for smokers with a lower level of dependence (OR, 0.71, 95% CI, 0.28-1.80, $p=0.47$). Both treatments were well tolerated.

Combination varenicline/bupropion treatment proved significantly more efficacious than varenicline alone for male smokers and for smokers with a high degree of dependence who did not show a sufficient initial response to pre-quit nicotine patch treatment.

The role of nicotine dependence in e-cigarettes' potential for smoking reduction (4)

E-cigarettes (Electronic Nicotine Delivery Systems, or ENDS) are an increasingly popular tobacco product among youth. Some evidence suggests that e-cigarettes may be effective for harm reduction and smoking cessation, although these claims remain controversial. Little is known about how nicotine dependence may contribute to e-cigarettes' effectiveness in reducing or quitting conventional smoking.

A cohort of young adults were surveyed over 4 years (approximate ages 19-23 years). Varying-coefficient models (VCMs) were used to examine the relationship between e-cigarette use and conventional smoking frequency, and how this relationship varies across users with different nicotine dependence levels.

Lifetime, but not recent, e-cigarette use was associated with less frequent concurrent smoking of conventional cigarettes among those with high levels of nicotine dependence. However, non-dependent e-cigarette users smoked conventional cigarettes slightly more frequently than those who had never used e-cigarettes. For those who used e-cigarettes in a cessation attempt, the frequency of e-cigarette use was not associated with reductions in future conventional smoking frequency.

These findings offer possible support that e-cigarettes may act as a smoking reduction method among highly nicotine-dependent young adult cigarette smokers. However, the opposite was found in non-dependent smokers, suggesting that e-cigarette use should be discouraged among novice tobacco users. Additionally, although a substantial proportion of young adults used e-cigarettes to help them quit smoking, these self-initiated

quit attempts with e-cigarettes were not associated with future smoking reduction or cessation.

Individual behavioural counselling for smoking cessation (5)

Individual counselling from a smoking cessation specialist may help smokers to make a successful attempt to stop smoking.

This Cochrane review looked at whether, 1. Individual counselling is more effective than no treatment or brief advice in promoting smoking cessation; 2. Individual counselling is more effective than self-help materials in promoting smoking cessation; and 3. A more intensive counselling intervention is more effective than a less intensive intervention.

Randomised or quasi-randomised trials with at least one treatment arm consisting of face-to-face individual counselling from a healthcare worker not involved in routine clinical care were included. The outcome was smoking cessation at follow-up at least six months after the start of counselling. Two authors extracted data in duplicate. They recorded characteristics of the intervention and the target population, method of randomisation and completeness of follow-up. The most rigorous definition of abstinence was used in each trial, along with biochemically-validated rates where available. In analysis, they assumed that participants lost to follow-up continued to smoke. They expressed effects as a risk ratio (RR) for cessation. Where possible, they performed meta-analysis using a fixed-effect (Mantel-Haenszel) model. They assessed the quality of evidence within each study using the Cochrane 'Risk of bias' tool and the GRADE approach.

They identified 49 trials with around 19,000 participants. Thirty-three trials compared individual counselling to a minimal behavioural intervention. There was high-quality evidence that individual counselling was more effective than a minimal contact control (brief advice, usual care, or provision of self-help materials) when pharmacotherapy was not offered to any participants (RR 1.57, 95% confidence interval (CI) 1.40 to 1.77; 27 studies, 11,100 participants; $I^2 = 50\%$). There was moderate-quality evidence (downgraded due to imprecision) of a benefit of counselling when all participants received pharmacotherapy (nicotine replacement therapy) (RR 1.24, 95% CI 1.01 to 1.51; 6 studies, 2662 participants; $I^2 = 0\%$). There was similar evidence for a small benefit

of more intensive counselling compared to brief counselling (RR 1.29, 95% CI 1.09 to 1.53; 11 studies, 2920 participants; $I^2 = 48\%$). None of the five other trials that compared different counselling models of similar intensity detected significant differences.

The review concluded that there is high-quality evidence that individually-delivered smoking cessation counselling can assist smokers to quit. There is moderate-quality evidence of a smaller relative benefit when counselling is used in addition to pharmacotherapy, and of more intensive counselling compared to a brief counselling intervention.

Declaration of interest

None declared

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