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Pharmacological Treatments for Smoking Cessation

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CLINICAL QUESTION Among the 3 first-line smoking cessation treatments (nicotine replacement therapy [NRT], bupropion, and varenicline), which is most effective in helping people who smoke achieve and maintain abstinence from smoking for at least 6 months, and what serious adverse events are associated with each?

BOTTOM LINE Higher rates of smoking cessation were associated with NRT (17.6%) and bupropion (19.1%) compared with placebo (10.6%). Varenicline (27.6%) and combination NRT (31.5%) (eg, patch plus inhaler) were most effective for achieving smoking cessation. None of the therapies was associated with an increased rate of serious adverse events.

This summary of the efficacy and harms of pharmacotherapies for smoking cessation incorporates data from 12 Cochrane reviews of 26 different treatments and uses a network meta-analysis to make direct and indirect comparisons of efficacy between the 3 most widely available treatments.[1] We focus on nicotine replacement therapy (NRT), bupropion, and varenicline.

Summary of Findings

All 3 treatments were associated with increased odds of quitting compared with placebo (**Figure**). The odds ratio (OR) for NRT was 1.84 (95% Bayesian credible interval [CrI], 1.71-1.99); bupropion, 1.82 (95% CrI, 1.60-2.06); and varenicline, 2.88 (95% CrI, 2.40-3.47). Direct comparisons between bupropion and NRT showed no difference in efficacy (OR, 0.99 [95% CrI, 0.86-1.13]).

Combination NRT (using 2 NRT formulations simultaneously—eg, patch and inhaler, patch and lozenge) was associated with higher abstinence rates than single NRT formulations. Nicotine replacement therapy patches were similar in efficacy to NRT gum and other NRTs (ie, tablets, lozenges, sprays, and inhalers). However, other NRTs were associated with higher quit rates than NRT gum (OR, 1.21 [95% CrI, 1.01-1.46]).

Varenicline was associated with higher smoking cessation rates compared with single forms of NRT (OR, 1.57 [95% CrI, 1.29-1.91]) and compared with bupropion (OR, 1.59 [95% CrI, 1.29-1.96]). Varenicline and combination NRT were associated with similar smoking cessation rates (OR, 1.06 [95% CrI, 0.75-1.48]).

Absolute cessation rates were 3252 of 30 755 patients (10.6% across 168 groups) for placebo, 5272 of 29 930 patients (17.6% across 143 groups) for NRT, 1347 of 7069 patients (19.1% across 42 groups) for bupropion, and 964 of 3496 patients (27.6% across 15 groups) for varenicline.

There were insufficient data to evaluate the risks of serious adverse events associated with NRT. Among 43 bupropion trials that reported serious adverse events, our estimate of 6 seizures in the bupropion groups (7510 participants) vs none in the placebo groups was lower than the expected rate of 1:1000.[2] A serious adverse event meta-analysis of the bupropion studies demonstrated no increase in neuropsychiatric events (relative risk [RR], 0.88 [95% CI, 0.31-2.50]; 6 studies: bupropion, 4 of 526 patients; placebo, 5 of 524 patients) or cardiovascular events (RR, 0.77 [95% CI, 0.37-1.59]; 10 studies: bupropion, 9 of 2624 patients; placebo, 12 of 2308 patients). Meta-analysis of 14 varenicline trials found no difference between the varenicline and placebo groups (RR, 1.06 [95% CI, 0.72-1.55]; varenicline, 85 of 3984 patients; placebo, 47 of 2349 patients) for the outcome of serious adverse events. Subgroup analyses detected no excess of cardiac events (RR, 1.26 [95% CI, 0.62-2.56]; 14 studies: varenicline, 26 of 3984 patients; placebo, 11 of 2349 patients) or neuropsychiatric events (RR, 0.53 [95% CI, 0.17-1.67]; 14 studies: varenicline, 6 of 3984 patients; placebo, 5 of 2349 patients). The 6 neuropsychiatric events in the varenicline participants were 3 incidents of suicidal ideation (1 considered to be varenicline treatment–related), 1 acute psychotic episode, 1 panic attack, and 1 overdose with seizure (none considered varenicline treatment–related). None of the trials reported attempted or completed suicides.

Discussion

All 3 first-line medications were associated with higher rates of smoking cessation compared with placebo. Varenicline and combination NRT were associated with higher rates of long-term abstinence than bupropion or single formulations of NRT. In this report,

Evidence Profile

No. of studies: 267 (from 12 reviews)

Study years: Published, 1979-2012

No. of patients: 101 804

Sex, race, and age: Unavailable

Settings: Smoking cessation clinics, primary care, antenatal clinics, hospitals; community, workplaces

Countries: Worldwide

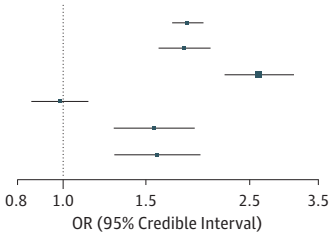
Comparison: Treatment vs placebo; one treatment vs another treatment (direct and indirect comparisons)

Primary outcomes: Smoking abstinence, continuous or prolonged, for at least 6 months; serious adverse events

Secondary outcomes: Other medications; limitations of the evidence base

Figure. Odds Ratios for Smoking Abstinence of 6 Months or More

Comparison (Intervention vs Control)	No. of Studies	Total No. of Individuals	Absolute Quit Rates: Intervention n/N (%)	Absolute Quit Rates: Control n/N (%)	Odds Ratio (95% Credible Interval)
NRT vs placebo	119	51225	4704/27258 (17.3)	2464/23967 (10.3)	1.84 (1.71-1.99)
Bupropion vs placebo	36	11440	1214/6409 (18.9)	535/5031 (10.6)	1.82 (1.60-2.06)
Varenicline vs placebo	15	6293	964/3496 (27.6)	332/2797 (11.9)	2.88 (2.40-3.47)
Bupropion vs NRT	8	2581	191/954 (20.0)	375/1627 (23.0)	0.99 (0.86-1.13)
Varenicline vs NRT	0	0	NA	NA	1.57 (1.29-1.91)
Varenicline vs bupropion	3	1622	174/823 (21.1)	111/799 (13.9)	1.59 (1.29-1.96)



Source: Data have been adapted with permission from the Cochrane Collaboration and Wiley.[1] NA indicates not available; NRT, nicotine replacement therapy (any type, single or combination). Credible interval is the Bayesian equivalent of confidence interval and is interpreted the same way as confidence interval. For varenicline vs NRT, indirect comparison was generated by the network analysis.

none of the therapies was associated with an increased risk of serious adverse events. However, the US Food and Drug Administration (FDA) has a boxed warning for varenicline and bupropion regarding potential risks of neuropsychiatric events. The FDA also warns about the potential for cardiovascular events with varenicline treatment.

Limitations

Although the source reviews of NRT[3] and varenicline[4] are current (2012), the review covering bupropion[5] has not been updated since 2009. However, a sensitivity analysis including 2 bupropion trials after 2009 demonstrated no significant difference for efficacy or harms. The quality of the included studies in the varenicline review was higher than that of the other 2 reviews, attributable largely to improved standards of trial conduct and reporting. Serious adverse events are generally less well reported than smoking cessation rates; hence, findings may be less reliable than those for efficacy.

Comparison of Findings With Current Guidelines

Our findings are consistent with the recommendations of the US guidelines,[6,7] which recommend these medications plus counseling in support of attempts to quit smoking.

Areas in Need of Future Study

Direct comparisons between varenicline and NRTs (single formulation and combination use) would be valuable, focusing on efficacy and harms.

Long-term monitoring of varenicline should continue to clarify the possibility of its implication in neuropsychiatric and cardiovascular events.

ARTICLE INFORMATION

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REFERENCES

1. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev*. 2013;5(5):CD009329. doi:10.1002/14651858.CD009329.pub2.

2. GlaxoSmithKline. Zyban 150 mg prolonged release film-coated tablets: undesirable effects. http://www.medicines.org.uk/emc/medicine/2948#UNDESIRABLE_EFFECTS. Accessed November 26, 2013.

3. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2012;11(11):CD000146. doi:10.1002/14651858.CD000146.pub4.

4. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2012;4(4):CD006103. doi:10.1002/14651858.CD006103.pub6.

5. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2007;(1):CD000031. doi:10.1002/14651858.CD000031.pub3.

6. Fiore M, Jaen CR, Baker TB, et al; Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff. A clinical practice guideline for treating tobacco use and dependence: 2008 update: a US Public Health Service report. *Am J Prev Med*. 2008;35(2):158-176.

7. Centers for Disease Control and Prevention. Smoking and tobacco use: cessation program materials. http://www.cdc.gov/tobacco/quit_smoking/cessation/. Accessed July 23, 2013.