THERAPEUTICS

A nicotine patch plus nicotine nasal spray was more effective than a nicotine patch alone for smoking cessation

Blondal T, Gudmundsson LJ, Olafsdottir I, et al. Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up. *BMJ* 1999 Jan 30;318:285-9.

Question

Is a nicotine patch plus nicotine nasal spray more effective than a nicotine patch alone for smoking cessation?

Design

Randomised, double blind, placebo controlled trial with 6 years follow up.

Setting

Reykjavik, Iceland.

Participants

239 people aged 22-66 years (mean age 42 y, 67% women) who had smoked ≥ 1 cigarette/day for ≥ 3 years. Exclusion criteria were recent myocardial infarction, severe nasal allergy, skin disease, use of smokeless tobacco, current misuse of alcohol, pregnancy, or lactation. Follow up was 98%.

Intervention

Participants were allocated to 5 months of nicotine patches at daily dosages of 15 mg for 3 months, 10 mg for the fourth month, and 5 mg for the fifth month, plus 1 year of either a nicotine nasal spray, 0.5 mg/dose (n = 120), or a placebo spray (n = 119). Group support meetings and individual follow up were provided.

Main outcome measures

Duration and rate of sustained abstinence from smoking were measured from day 1 of smoking cessation. Abstinence was defined as not taking a single puff of a cigarette, not using other forms of tobacco or nicotine drugs, or a carbon monoxide concentration < 10 ppm.

Main results

Participants who received a nicotine patch plus nicotine nasal spray had higher abstinence rates than those who received a nicotine patch plus placebo spray at 15 days (p = 0.004), 6 weeks (p = 0.011), 3 months (p = 0.045), 6 months (p = 0.005), and 1 year (p = 0.001); and a trend towards a higher abstinence rate at 6 years (p = 0.08) (table).

Conclusions

Use of a nicotine patch for 5 months plus nicotine nasal spray for 1 year was more effective than a nicotine patch alone for smoking cessation. Definite differences in sustained abstinence rates at 1 year persisted as a trend at 6 years.

*A nicotine patch plus nicotine nasal spray v a nicotine patch plus placebo spray for abstinence from smoking**

Follow up	Patch and nicotine spray	Patch and placebo spray	RBI (95% CI)	NNT (CI)
15 days	70%	52%	35% (10 to 67)	5 (3 to 17)
6 weeks	51%	34%	48% (9 to 101)	6 (4 to 26)
3 months	37%	25%	48% (1 to 119)	8 (4 to 393)
6 months	31%	16%	96% (21 to 221)	6 (4 to 22)
1 year	27%	11%	148% (40 to 348)	6 (4 to 16)
6 years	16%	8%	92% (-5 to 291)	Not significant

*Abbreviations defined in glossary; RBI, NNT, and CI calculated from data in article.

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Abstract and modified commentary also published in *ACP Journal Club*.

Commentary

Despite higher cigarette prices, tougher anti-smoking laws, and attempts to hold tobacco companies responsible for smoking related medical costs, smoking cessation remains a huge public health challenge. Blondal *et al* point out that nicotine patch treatment alone gives an abstinence rate of only 11% after 1 year. Such results have prompted the search for better single or combination smoking cessation treatments, including combined nicotine patch and spray. Unlike previous studies, Blondal *et al* followed up patients for an extended period of 6 years. Within the first year, the combination treatment led to a higher abstinence rate than did the patch and placebo spray. Few patients used the spray for up to 1 year. Combination treatment showed a trend toward a

higher abstinence rate at 6 years, which suggests a possible long term benefit.

It is unclear whether the higher success rate of combination treatment was because of higher sustained concentrations of nicotine or a brief effect on concentration of the spray delivery system. The spray provides a "quick" dose of nicotine that may relieve temporary cravings associated with relapse of smoking.

Nicotine replacement therapy is one approach to smoking cessation management. Mood is closely related to nicotine consumption. The antidepressant, bupropion, has been shown to be an effective smoking cessation aid.¹ In their well designed, double blind, controlled trial, Jorenby *et al* showed that bupropion, used either alone or in combination with the

nicotine patch, was more effective than the patch alone or placebo for smoking cessation. A direct comparison of the 1 year continuous abstinence rates across the 2 studies shows interesting results: the rate for the patch spray combination in the study by Blondal *et al* was 27%, which is similar to that for bupropion alone (18.4%) or the bupropion patch combination (22.5%) in the study by Jorenby *et al*. Unlike Blondal *et al*, Jorenby *et al* followed up patients for 1 year. The continuous abstinence rate beyond 1 year still needs to be studied. The fact that such high intermediate term continuous abstinence rates can be achieved, however, should prompt physicians to consider bupropion in addition

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Bupropion alone or with a nicotine patch increased smoking cessation rates

Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999 Mar 4;340:685-91.

Question

What is the relative effectiveness of bupropion, a nicotine patch, placebo, and bupropion plus a nicotine patch for smoking cessation?

Design

Randomised, double blind, placebo controlled trial with 1 year follow up.

Setting

4 centres in the US.

Participants

893 people ≥ 18 years of age (mean age 43 y, 52% women) who weighed ≥ 100 lb (≥ 45.4 kg), were motivated to stop smoking, and who smoked ≥ 15 cigarettes/day. Exclusion criteria included serious physical or psychiatric illness, pregnancy, lactation, and previous nicotine replacement therapy. Follow up was 80%.

Intervention

Patients were allocated to 9 weeks of either sustained release bupropion, 150 mg/day for days 1 to 3 and 300 mg/day for days 4 to 63 (n = 244); nicotine patch, 21 mg/day for weeks 2 to 7, 14 mg/day for week 8, and 7 mg/day for week 9 (n = 244); or bupropion plus a nicotine patch (n = 245); or placebo (n = 160). Patients stopped smoking on day 8 and received counselling for 1 year.

Main outcome measures

Self reported point prevalence rate of abstinence in the previous 7 days and carbon monoxide ≤ 10 ppm, and rate of continuous abstinence (abstinence from quit date and carbon monoxide ≤ 10 ppm); withdrawal symptoms; and weight gain.

Main results

Analysis was by intention to treat. At 1 year, compared with the placebo and nicotine patch alone groups, the bupropion groups had higher point prevalence and continuous abstinence rates ($p < 0.001$) (table); no difference existed between the 2 bupropion groups ($p = 0.22$ and $p = 0.61$, respectively). All 3 active treatments led to less severe withdrawal symptoms than placebo in the first 3 weeks ($p < 0.05$). Bupropion plus a nicotine patch led to less weight gain than bupropion alone or placebo in the first 7 weeks ($p < 0.05$).

Conclusion

Compared with placebo or a nicotine patch alone, bupropion alone or with a nicotine patch increased the point prevalence and continuous smoking cessation rates after 1 year.

*Comparison of smoking cessation regimens for point prevalence or continuous abstinence at 1 year**

Abstinence	Regimen	Intervention	Placebo	RBI (95% CI)	NNT (CI)
Point prevalence	Bupropion	30%	16%	94% (31 to 193)	7 (4 to 16)
	Combination†	36%	16%	127% (54 to 240)	5 (4 to 9)
Continuous	Bupropion	18%	6%	228% (69 to 548)	8 (5 to 15)
	Combination†	22%	6%	229% (108 to 681)	6 (4 to 10)

*Abbreviations defined in glossary; RBI, NNT, and CI calculated from data in article and from data provided by the author. †Combination regimen = bupropion plus a nicotine patch.

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to or as an alternative to, nicotine replacement therapy.

Patients in both studies were highly motivated and received adjunctive supportive counselling. These circumstances may not apply to a larger population of people who smoke and have some desire to stop. Extensive supportive counselling is time consuming, expensive, and difficult to obtain without access to properly trained professionals. The feasibility and success of these treatments in usual ambulatory care settings needs to be determined.

Another important question that has yet to be addressed is the effectiveness of antidepressants other than bupropion for smoking cessation. With nicotine replacement therapy already available in patch,

spray, and gum forms, evidence of the effectiveness of other mood altering drugs will add to the smoking cessation management choices available to patients and physicians.

It was the connection between mood and smoking that led eventually to the trial of the antidepressant bupropion as a cessation aid. People with negative affect are more likely to start smoking and less likely to give up.² Affective symptoms are more common among smokers, and their severity is related to the degree of nicotine dependence.³

Although it is unclear how the cessation aids assessed in these 2 studies would perform in a mental health care environment, bupropion could obviously have a dual role among patients with major

depression as both an antidepressant and cessation aid. The overall positive effect of cessation aids in the mental healthcare environment may actually be greater than in the general population because smoking is very common among people with psychiatric illness.

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1 Hurt RD, Sachs DP, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997;337:1195-202.

2 Glassman AH, Covey LS. Smoking and affective disorder. *Am J Health Behav* 1996;30:279-85.

3 Anda RF, Williamson DF, Escobedo IG, et al. Depression and the dynamics of smoking: A national perspective. *JAMA* 1990;264:1541-5.