The pharmacotherapy of smoking cessation

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ABSTRACT

- The great majority of smokers are chronically dependent on tobacco. This dependence arises from the rituals and sensory associations of smoking that are reinforced, within seconds, by a rapid burst of nicotine from the cigarette.
- All forms of nicotine replacement therapy (NRT) — gum, patches and inhaler — and bupropion are safe and effective for increasing smoking cessation rates in the short and long terms.
- Other than those who are minimally dependent, all patients willing to quit should be offered one of these therapies unless contraindications exist. The effectiveness of drug treatments is multiplied when associated with effective counselling or behavioural treatments.
- While NRT is not recommended during pregnancy or in patients with cardiac disease, if the alternative is smoking NRT is almost certainly safe.
- Combination NRT (more than one therapy) may be indicated in patients who have failed monotherapy in association with withdrawal symptoms.
- There are some specific contraindications to the use of bupropion. Its subsidised availability should not influence prescribers to ignore these.

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IN AUSTRALIA, CIGARETTE SMOKING is the most significant cause of avoidable health harm. To reduce this, individual clinicians should follow the so-called five A's — Ask about smoking; Advise quitting; Assess current willingness to quit; Assist in the quit attempt; and Arrange timely follow-up.[1] While this review focuses on the forms of drug therapy that assist cessation, these treatments should be coordinated with the general and specific support and counselling strategies that are also of proven benefit.[2]

Basic neurobiology of smoking

The great majority of regular smokers are dependent on cigarette smoking, and not simply addicted to nicotine.[3] Smoking is highly contextual and associated with certain rituals. These start with the opening of a packet, followed by the lighting process and then the sight and smell of smoke. After inhaling smoke from a modern cigarette, arterial nicotine levels increase markedly within 15 seconds.[4] This bolus of nicotine activates the brain-reward system by increasing dopamine release.[5] This brain reward system is a common pathway for pleasurable activities (sexual activity, eating) and most drugs of addiction.[6]

This peak in plasma nicotine level, and the transient activation of the reward system, is followed by a gradual fall in nicotine levels into a state of withdrawal[7] that is, in turn, relieved by the next cigarette. Dependence arises from the temporal association of the rituals and sensory inputs with the repeated stimulation and relief of withdrawal.[2] This required association explains why nicotine replacement therapy (NRT) products, that deliver nicotine slowly and do not produce high plasma nicotine levels, have minimal addictive potential.[8]

Nicotine replacement therapy

The aim of NRT is to assist smoking cessation by providing a near-constant level of nicotine above that which is associated with withdrawal. No form of NRT can replicate the rapid nicotine delivery from a cigarette. The NRT formulations available in Australia include gum, patches and oral inhaler. Nicotine nasal spray and a sublingual tablet or lozenge are not presently available in Australia.

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Gum

Gums contain nicotine (2 mg or 4 mg per piece) in a resin base. The gum should be chewed slowly, then left between the cheek and gum. Over the next 20–30 minutes, the gum should be chewed intermittently and repositioned. Because nicotine is poorly absorbed in an acid environment, acid drinks such as fruit juices should be avoided. As smokers may be conscious of the per-piece cost, there may also be a tendency to use an insufficient number of pieces or not to continue with treatment for long enough. It is preferable for patients to use gum on a regular basis. While extra doses may not rapidly increase nicotine levels, the process of their use is a ritual that is in some ways analogous to smoking, and this may be an advantage.

Patches

Nicotine transdermal patches are designed to release nicotine slowly. Immediately after application, there may be relatively rapid transfer of nicotine from the adhesive layer. In steady-state phase, nicotine will exist in the patch, in a skin "reservoir" and in the circulation. The presence of the skin reservoir reduces the rate of decay of plasma levels after the patch is removed. Patches come in a variety of dose strengths from 7 mg to 21 mg, and in preparations designed to be used for 16 or 24 hours.

1: Level-of-evidence codes

Evidence for the statements made in this article is graded according to the NHMRC system[12] for assessing the level of evidence.

- **E1** Level I: Evidence obtained from a systematic review of all relevant randomised controlled trials.
- **E2** Level II: Evidence obtained from at least one properly designed randomised controlled trial.
- **E3$_1$** Level III-1: Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
- **E3$_2$** Level III-2: Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case–control studies, or interrupted time series without a parallel control group.
- **E3$_3$** Level III-3: Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
- **E4** Level IV: Evidence obtained from case-series, either post-test, or pre-test and post-test.

Patches are applied each morning. The 16-hour preparations are useful for smokers who experience insomnia or other nocturnal symptoms. Patches should be applied on a rotational basis to a variety of non-hairy skin sites. Local skin reactions are the commonest adverse effect. This can be minimised by rotation among a number of sites of application, but can be severe enough to require discontinuation.

Inhaler

The inhaler is a plastic cartridge that is inserted into a mouthpiece. Gaseous nicotine is released by deep inhalation through the mouthpiece. Twenty minutes after the first deep inhalation, the device has released about 4 mg of nicotine. This process, as with patches and gums, does not release nicotine rapidly,[9] but it does replicate some of the smoking rituals. After use, the device is spent and cannot be reused or recycled.

Use of NRT in cardiac disease and pregnancy

There is now quite extensive evidence that NRT is safe in patients with stable cardiac disease such as angina pectoris (E1)[10,11] (for an explanation of level-of-evidence codes, see Box 1). Evidence is lacking in acutely unstable patients, but NRT would produce lower peak and cumulative nicotine exposure levels than smoking, without delivering the increased carboxyhaemoglobin and the many other vasoactive compounds in smoke. The issue of NRT use in pregnancy is a vexed one. In one randomised study, NRT by patch did not increase cessation during pregnancy, but did increase birthweight, perhaps by reducing total smoke exposure.[13] The second issue is safety. Prenatal exposures to nicotine have important developmental effects, but, as total nicotine levels are lower with NRT than smoking, if the alternative is active smoking NRT is almost certainly safe in pregnancy.[14]

Because of residual safety concerns, use of NRT in pregnant women should be aimed at those who are moderately or highly dependent and have been unable to quit by other means.[13] NRT is most likely to be effective if combined with high-intensity counselling. Careful supervision of NRT could include monitoring of urinary cotinine levels and use of non-continuous treatment — gum, spray and 16-hour, rather than 24-hour, patches. A key message here is that women contemplating pregnancy should try to quit beforehand, as pregnancy is not a time during which smoking cessation is easy to achieve.[15]

Bupropion

Bupropion was developed and first marketed as an antidepressant. Although it is an effective antidepressant,[16] it is not marketed for this purpose in Australia. Anecdotal observation of spontaneous smoking cessation in depressed smokers[17] led to its further evaluation as an aid to smoking cessation,[18] and the later development of the sustained-release form presently marketed as Zyban (GlaxoSmithKline). The suggested mechanism of action is inhibition of neural reuptake of dopamine or noradrenaline, but this may be simplistic.[19] Bupropion is not related to other classes of antidepressants presently in clinical use. With the exception of nortryptiline, which has a weak effect, these other antidepressants do not increase rates of smoking cessation.[1] There is no evidence that the antidepressant activity of bupropion contributes to its efficacy in smoking cessation.

Dose and administration

Treatment should commence at 150 mg daily for three days, then increase to 150 mg twice daily. The nominal target date for smoking cessation is Day 7 of treatment. However, some smokers lose the desire to smoke before this, and successful, long-term cessation is seen even in those who smoke beyond Day 7.[20] The standard treatment period, subsidised under the Pharmaceutical Benefits Scheme in Australia, is nine weeks.

Side effects, precautions and contraindications

Nausea, insomnia and dry mouth are common early symptoms. The time to peak plasma level is three hours. Therefore, if insomnia is prominent, the evening dose may be taken early, but at least eight hours after the morning dose. Seizures are the major side effect of concern. When bupropion was initially used as an antidepressant, the seizure rate was one in 1000, similar to that with other antidepressant medications. With the slow-release formulation used for smoking cessation, seizures are even less common, but warnings associated with pre-existing conditions and concomitant medication, especially monoamine oxidase inhibitors and drugs that lower the seizure threshold, must be strictly followed.

Bupropion is absolutely contraindicated in patients with a history of epilepsy, and there is a relative contraindication in conditions that might increase the risk of seizures, such as

type 1 or 2 diabetes. If it is to be used in patients with such conditions, it should only be after careful consideration of the risks and alternative treatment options, balanced against the benefits of cessation in the individual. Hypersensitivity reactions are the other adverse effects of concern. Facial oedema has been reported, as has a serum-sickness-like reaction.[21] Adverse cardiovascular effects are rare. At last report, there had been 18 deaths associated with Zyban use reported to the Therapeutic Goods Administration (TGA).[22] At present, bupropion should not be prescribed during pregnancy, as there is insufficient evidence to establish its safety.

Clinical management of the smoker prepared to quit

In counselling smokers about the optimal means to achieve cessation, clinicians should make an assessment of dependence. Box 2 shows the Fagerström test for nicotine dependence, which may be useful and is simple to administer.[23] If there is not the opportunity to apply the Fagerström test, the number of cigarettes smoked daily and the interval between waking and first cigarette will give a rough guide to the degree of dependence. Some long-term smokers do have minimal dependence. They typically smoke small numbers of cigarettes, and may cease smoking for short or longer periods without withdrawal symptoms. This group is worth identifying, as such smokers should be able to quit without pharmacological assistance.

Drug treatments address some of the biochemical aspects of smoking, but are most effective when counselling or behavioural programs are used to redress the associated contextual and ritual elements (E1).[2] The effectiveness of programs and products for smoking cessation needs to be judged against the "natural" rate of smoking cessation that is in the range of 1.5%–3% per year.[24,25] Placebo success rates in all published drug treatment trials are typically higher, about 10%–15% at end of treatment and 5%–10% after one year, as participants are self-selected as interested in quitting and receive at least a minimum level of counselling.

Other than those who are minimally dependent, all smokers trying to quit should be advised to use one of the range of safe, effective treatments available (E1).[1,2] All forms of NRT about double the chance of successful cessation (E1).[26] The number of patients needed to treat to achieve one extra successful quitter is about 10. Patients report a preference for patches over gums, sprays or the inhaler and tend to use patches nearer to the fashion recommended, but these differences do not affect cessation rates.[27]

If the initial treatment is a nicotine patch, 16-hour and 24-hour patches are equally effective (E1). There is a modest increase in success for increases in delivered dose above 20 mg (E1).[28] There is no need to adjust patch dose based on smoking level before cessation.[29] Treatment periods should be at least eight weeks. There is no medical need to taper treatment, but the process of tapering is reassuring to some patients. Smoking while using patches has a trivial safety risk, but above all predicts a very low chance of successful cessation. If a patient is still smoking after seven days, the quit attempt should be terminated, with the intention of trying again at a later time.

2: The Fagerström test for nicotine dependence

Question	Answer	Score
How soon after you wake do you smoke your first cigarette?	Within 5 minutes	3
	5–30 minutes	2
	31–60 minutes	1
	Over 60 minutes	0
Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes	1
	No	0
Which cigarette would you most hate to give up?	The first one in the morning	1
	Any other	0
How many cigarettes per day do you smoke?	10 or less	0
	11–20	1
	21–30	2
	Over 30	3
Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

Score	Rating
0 to 2	Very low dependence
3 to 4	Low dependence
5	Medium dependence
6 to 7	High dependence
8 to 10	Very high dependence

If gum is used, 4 mg doses are associated with greater chance of cessation in smokers with higher dependency.[30,31] Other than those who are minimally dependent, smokers should be advised to use 4 mg pieces (E1). Tapering to 2 mg doses later is intuitively logical, but of unproven benefit. If the nicotine inhaler is chosen, at least six cartridges should be used initially. Tapering the dose is recommended after three months without evidence to support this.

A range of studies have shown that bupropion increases the chance of success 2.1-fold, with the number needed to treat to achieve an extra successful quitter being 7.5.[1] The one comparative study published found that bupropion (150 mg twice daily) produced a higher cessation rate than nicotine patch alone (E2).[32] However, the quit rate with NRT in this study was lower than that generally found in other studies. In a second study, bupropion and NRT by patch were compared for their effect on late quitting from Week 4 onwards.[20] Late quitting was more common with bupropion than NRT but this could be predicted from other studies. The likelihood of successful cessation with bupropion is not reduced in patients previously treated with bupropion.[33]

The choice of recommending NRT or bupropion will rest on individual patient characteristics and preferences. At

present, in Australia, cost is an issue. Bupropion has an advantage in terms of ease of use and is the only smoking cessation agent currently subsidised under the Pharmaceutical Benefits Scheme (some forms of NRT are available on the Repatriation Pharmaceutical Benefits Scheme). Although this presents an economic advantage for the patient, contraindications should never be discounted.

Single-agent versus combination treatments

Current product information advises against concurrent use of different NRT formulations. However, higher abstinence rates are achieved when a patch is combined with *ad libitum* use of either 2 mg gum[34,35] or nasal spray.[36] Although there has been no direct comparison, the benefit derived from combination NRT is greater than that seen with higher-dose patches alone.[37,38] Intuitively, this strategy should be employed in highly dependent smokers, but there is not yet evidence to support this. At present, the use of combination NRT is reasonable in moderate or highly dependent smokers who have failed cessation with monotherapy, particularly if withdrawal symptoms were prominent. The addition of nicotine patches to bupropion has not increased rates of cessation.[32]

Extended therapy

Extension of treatment with bupropion to one year in those abstinent during Week 7 of initial treatment increases abstinence during treatment and delays relapses, but smoking rates are similar one year later (E2).[39] Until there is more evidence, extended therapy should not be prescribed. Many patients who use NRT do so beyond the usual treatment periods. This is unlikely to be harmful, but no benefit has been shown (E1).[2] Generally, smokers should be encouraged to use treatments for 8–12 weeks.

Harm reduction and uncommitted quitters

At any one time, most smokers are not committed to quitting. If prompt cessation is impossible, the principle of harm reduction is to use treatment that may reduce the total number of cigarettes smoked and lead the way to future cessation. The extent to which smoking fewer cigarettes reduces harm is uncertain. In smokers who were also using nicotine sprays, the number of cigarettes smoked was reduced but adverse biomarker exposure was not.[40] Bupropion also reduced smoking in uncommitted quitters with[17] and without[41] depression. In conjunction with counselling support, it may be reasonable to recommend bupropion to the uncommitted quitter.

Smoking cessation and weight gain

Smokers are, on average, underweight. Weight gain is a feature of successful cessation and few smokers will ever return to their precessation weight. Median weight gain is about 2 kg, but around 10% have very large weight increases (more than 12 kg).[42] Despite its intuitive attractiveness, strict dietary restriction reduces cessation rates and should not be initiated during a cessation attempt.[43] Use of NRT or bupropion delays, but does not prevent, weight gain.[44,45] For smokers with particular concerns or who are overweight, it may be better to combine cessation with exercise,[46] and any attempt at weight control by dietary means should be delayed until cessation is consolidated.

3: Important messages for patients

- Stopping smoking will improve your health in the short term and long term, but quitting without some support is almost always unsuccessful
- Drug treatments are safe and effective, especially when combined with the support of your doctor
- It is important for you to think about your lifestyle and how you might change it to help you stay off cigarettes
- Many patients need to try a number of times before they are successful and you should not fear failure. If you do relapse, there will always be another chance.

Mental illness, smoking and cessation

Patients with all major forms of mental illness, particularly major psychoses or those in institutions, have high rates of smoking.[47,48] It has been estimated that just under half of all cigarettes smoked in the United States are smoked by individuals with mental illness.[49] This complex area has recently been reviewed in some detail.[50] There is an incorrect but prevalent view that attempts at controlling smoking in these patients are futile. Bupropion increased cessation rates in a small study of patients with post-traumatic stress disorder (E2),[51] and group therapy with NRT[52] or bupropion[53] has reasonable efficacy in patients with schizophrenia (E2). Patients with depression are as likely as others to quit with NRT[54] or bupropion.[55] There is a risk of relapse of major depression if abstinence is achieved, and these patients should be closely observed (E2).[56] Patients with well controlled major depression should not be switched from an effective therapy to bupropion for the purpose of achieving cessation.

Conclusion

Tobacco dependence is a chronic, relapsing medical illness. Reasonable standard of care now requires that smokers be identified and that proven, effective strategies that will maximise the chance of safe cessation are used. Doctors must therefore become sufficiently familiar with bupropion and one or more forms of NRT to confidently recommend suitable treatment.

Competing interests

M P has conducted clinical trials and received an honorarium from GlaxoSmithKline and support for travel to meetings.

References

1. Fiore MC, Bailey WC, Cohen SJ, et al. Treating tobacco use and dependence. Clinical practice guideline. Rockville, MD: US Department of Health and Human Services, Public Health Service, June 2000.
2. Silagy C, Lancaster T, Stead L, et al. Nicotine replacement therapy for smoking cessation (Cochrane Review). In: The Cochrane Library, Issue 4, 2001. Oxford: Update Software.
3. Balfour DJ, Wright AE, Benwell ME, Birrell CE. The putative role of extra-synaptic dopamine in the neurobiology of nicotine dependence. *Behav Brain Res* 2000; 113: 73-83.
4. Stauffer HP, Riedwyl H. Interaction and pH dependence of effects of nicotine and carbon monoxide in cigarette smoke inhalation experiments with rats. *Agents Actions* 1977; 5-6: 579-588.
5. Zhou FM, Liang Y, Dani JA. Endogenous nicotinic cholinergic activity regulates dopamine release in the striatum. *Nat Neurosci* 2001; 4: 1224-1229.
6. Tomkins DM, Sellers EM. Addiction and the brain: the role of neurotransmitters in the cause and treatment of drug dependence. *CMAJ* 2001; 164: 817-821.
7. Pontieri FE, Tanda G, Orzi G, et al. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature* 1996; 382: 255-257.
8. West R, Hajek P, Foulds J, et al. A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology (Berl)* 2000; 149: 198-202.
9. Schneider NG, Olmstead RE, Franzon MA, Lunell E. The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. *Clin Pharmacokinet* 2001; 40: 661-684.
10. Joseph AM, Norman SM, Ferry LH, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996; 335: 1792-1798.
11. Mahmarian JJ, Moye LA, Nasser GA, et al. Nicotine patch therapy in smoking cessation reduces the extent of exercise-induced myocardial ischaemia. *J Am Coll Cardiol* 1997; 30: 125-130.
12. National Health and Medical Research Council. A guide to the development, implementation and evaluation of clinical practice guidelines. Canberra: NHMRC, AusInfo, 1999.
13. Wisborg K, Henriksen TB, Jespersen LB, Secher NJ. Nicotine patches for pregnant smokers: a randomised controlled trial. *Obstet Gynecol* 2000; 96: 967-971.
14. Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. *Drug Safety* 2001; 24: 277-322.
15. NSW Health. 1999 NSW mothers and babies report. <www.health.nsw.gov.au/public-health/mdc/mdcrep99.pdf> (Accesssed 5 Dec, 2001).
16. Aascher JA, Cole JO, Colin JN, et al. Bupropion: a review of its mechanism of anti-depressant activity. *J Clin Psychiatry* 1995; 56: 395-401.
17. Ferry LH, Robbins AS, Sarlati PD, et al. Enhancement of smoking cessation using the antidepressant, bupropion hydrochloride [abstract]. *Circulation* 1992; 86: I671.
18. Ferry LH, Burchette RJ. Efficacy of bupropion for smoking cessation in non-depressed smokers. *J Addict Dis* 1994; 13: 249.
19. Dong J, Blier P. Modification of norepinephrine and serotonin, but not dopamine, neuron firing by sustained bupropion treatment. *Psychopharmacology (Berl)* 2001; 155: 52-57.
20. Jamerson BD, Nides M, Jorenby DE, et al. Late-term smoking cessation despite initial failure: an evaluation of bupropion sustained release, nicotine patch, combination therapy, and placebo. *Clin Ther* 2001; 23: 744-752.
21. Benson E. Bupropion induced hypersensitivity reactions. *Med J Aust* 2001; 174: 650-651.
22. Therapeutic Goods Administration. Update on bupropion (Zyban SR) - 31 August 2001. <www.health.gov.au/hfs/tga/docs/html/zyban.htm> (Accessed 15 Dec, 2001).
23. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: a revision of the Fagerström tolerance questionnaire. *Br J Addict* 1991, 86: 1119-1127.
24. Centers for Disease Control and Prevention. Smoking cessation during previous year among adults—United States, 1990 and 1991. *MMWR Morb Mortal Wkly Rep* 1993; 42: 504-507.
25. Hatziandreu EJ, Pierce JP, Lefkopoulou M, et al. Quitting smoking in the United States in 1986. *J Natl Cancer Inst* 1990; 82: 1402-1406.
26. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. *BMJ* 2000; 321: 355-358.
27. West R, Hajek P, Nilsson F, et al. Individual differences in preferences for and responses to four nicotine replacement products. *Psychopharmacology (Berl)* 2001; 153: 225-230.
28. Hughes JR, Lesmes GR, Hatsukami DK, et al. Are higher doses of nicotine replacement more effective for smoking cessation? *Nicotine Tob Res* 1999; 1: 169-174.
29. Killen JD, Fortmann SP, Davis L, et al. Do heavy smokers benefit from higher dose nicotine patch therapy? *Exp Clin Psychopharmacol* 1999; 7: 226-233.
30. Herrera N, Franco R, Herrera L, et al. Nicotine gum, 2 and 4 mg, for nicotine dependence. A double-blind placebo-controlled trial within a behavior modification support program. *Chest* 1995; 108: 447-451.
31. Kornitzer M, Kittel F, Dramaix M, Bourdoux P. A double blind study of 2 mg versus 4 mg nicotine-gum in an industrial setting. *J Psychosom Res* 1987; 31: 171-176.
32. Hurt RD, Sachs DPL, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997; 337: 1195-1202.
33. Gonzales DH, Nides MA, Ferry LH, et al. Bupropion SR as an aid to smoking cessation in smokers previously treated with bupropion; a randomized placebo-controlled study. *Clin Pharmacol Ther* 2001; 69: 438-444.
34. Kornitzer M, Boutsen M, Dramaix M, et al. Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. *Prev Med* 1995; 24: 41-47.
35. Puska P, Korhonen H, Vartiainen E, et al. Combined use of nicotine patch and gum compared with gum alone in smoking cessation: a clinical trial in North Karelia. *Tob Control* 1995; 4: 231-235.
36. Blondal T, Gudmundsson LJ, Olafsdottir I, et al. Nicotine nasal spray with nicotine patch for smoking cessation: Randomized trial with six year follow up. *BMJ* 1999; 318: 285-288.
37. Hughes JR, Lesmes GR, Hatsukami DK, et al. Are higher doses of nicotine replacement more effective for smoking cessation? *Nicotine Tob Res* 1999 1: 169-174.
38. Tonnesen P, Paoletti P, Gustavsson G, et al. Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. *Eur Respir J* 1999; 13: 238-246.
39. Hays JT, Hurt RD, Rigotti NA, et al. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. a randomized, controlled trial. *Ann Intern Med* 2001; 135: 423-433.
40. Hurt RD, Croghan GA, Wolter TD, et al. Does smoking reduction result in reduction of biomarkers associated with harm? A pilot study using a nicotine inhaler. *Nicotine Tob Res* 2000; 2: 327-336.
41. Hatsukami D, Rennard S, Malcolm R, et al. A multicenter study examining the effects of Zyban (bupropion HCL SR) vs. placebo as an aid to smoking reduction leading to cessation among smokers unwilling and unable to quit smoking [abstract]. Proceedings, 3rd European Conference of the Society for Research on Nicotine and Tobacco. Society for Research on Nicotine and Tobacco, Middleton WI, USA, 2001.
42. Williamson DF, Madans J, Anda RF, et al. Smoking cessation and severity of weight gain in a national cohort. *N Engl J Med* 1991; 324: 739-745.
43. Hall SM, Tunstall CD, Vila KL, Duffy J. Weight gain prevention and smoking cessation: Cautionary findings. *Am J Public Health* 1992; 82: 799-803.
44. Emont SC, Cummings KM. Weight gain following smoking cessation: a possible role for nicotine replacement in weight management. *Addict Behav* 1987; 12: 151-155.
45. 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: 1195-1202.
46. Kawachi I, Troisi RJ, Rotnitzky AG, Coakley EH. Can physical activity minimize weight gain in women after smoking cessation? *Am J Public Health* 1996; 86: 999-1004.
47. Hughes JR, Hatsukami DK, Mitchell JE, Dahlgren LA. Prevalence of smoking among psychiatric outpatients. *Am J Psychiatry* 1986; 143: 993-997.
48. De Leon J, Dadvand M, Canuso C, et al. Schizophrenia and smoking: an epidemiological survey in a state hospital. *Am J Psychiatry* 1995; 152: 453-455.
49. Lasser K, Wesley Boyd J, Woolhandler S, et al. Smoking and mental illness. A population-based prevalence study. *JAMA* 2000; 284: 2606-2610.
50. McNeill A. Smoking and mental health: a review of the literature. <www.ash.org.uk/html/policy/menlitrev.html> (Accessed 15 Dec 2001).
51. Hertzberg MA, Moore SD, Feldman ME, Beckham JC. A preliminary study of bupropion sustained-release for smoking cessation in patients with chronic post-traumatic stress disorder. *J Clin Psychopharmacol* 2001; 21: 94-98.
52. Addington J, el-Guebaly N, Campbell W, et al. Smoking cessation treatment for patients with schizophrenia. *Am J Psychiatry* 1998; 155: 974-976.
53. Evins AE, Mays VK, Rigotti NA, et al. A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia. *Nicotine Tob Res* 2001; 3: 397-403.
54. Killen JD, Fortmann SP, Kraemer HC, et al. Interactive effects of depression symptoms, nicotine dependence, and weight change on late smoking relapse. *J Consult Clin Psychol* 1996; 64: 1060-1067.
55. Hayford KE, Patten CA, Rummans TA, et al. Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. *Br J Psychiatry* 1999; 174: 173-178.
56. Glassman AH, Covey LS, Stetner F, Rivelli S. Smoking cessation and the course of major depression: a follow-up study. *Lancet* 2001; 357: 1929-1932.

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