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Current Approaches to the Management of Smoking Cessation

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Abstract

Smoking remains a widespread intractable behaviour and is a significant cause of morbidity and mortality worldwide. Effective approaches to smoking cessation include behavioural intervention and pharmacotherapy, in particular nicotine replacement therapy (NRT) and sustained-release bupropion (bupropion SR). Pharmacotherapy remains a popular choice of smoking cessation intervention for many smokers, and both NRT and bupropion SR, combined with behavioural interventions, achieve 1.5- to >2-fold increases in smoking cessation rates. Various national and international smoking cessation guidelines have been published recommending effective implementation of smoking cessation strategies. Recommendations include the systematic identification of smokers, assessment of their willingness to quit smoking, provision of advice promoting a cessation attempt, and administration of approved first-line therapies.

In the developed world, smoking represents the single most significant cause of premature death, and smokers of 25 or more cigarettes per day lose an estimated 10 years of their life span.[1] In the US, tobacco use is responsible for 20% of deaths annually,[2] and in the UK smoking is associated with over 120 000 deaths per year in people aged 35 years and over.[3]

Smoking cessation and prevention strategies have tremendous potential to improve public health.[4] For instance, the risk of coronary heart disease has been estimated to decrease by 50% twelve months after smoking cessation. The relative risk of developing other conditions, such as chronic obstructive pulmonary disease, lung cancer and stroke, also decreases with smoking cessation.[5]

Despite the powerful addictive nature of inhaled tobacco smoke, various effective smoking cessation regimens exist. Therapeutic interventions focus on increasing successful smoking cessation through the use of behavioural approaches and/or pharmacotherapy.[6] Approximately 90% of smoking cessation attempts are unassisted (i.e. cold turkey) and are associated with low success rates (3 to 5%).[7]

1. Smoking Cessation Behavioural Interventions

Behavioural strategies for smoking cessation are effective and should be utilised as part of standard medical practice. Interventions range from brief advice to extensive programmes conducted by specialised personnel.[8]

1.1 Brief Interventions

All healthcare professionals and healthcare delivery systems should consistently identify smokers and document smoking status.[9,10] Although 85% of smokers who quit do so without any formal intervention, clinicians are uniquely positioned to

offer assistance and concomitantly reduce smoking-associated morbidity and mortality.[11,12] Including smoking status as part of a patient's vital signs is an effective means of ensuring this assessment is routinely conducted.[13,14]

After the effective identification of smokers, brief advice (3 to 5 minutes) from healthcare professionals is effective at increasing smoking cessation rates.[10,15-19] In the UK, approximately 40% of smokers make some form of attempt to quit each year, and 1 to 3% of smokers refrain from smoking for at least 6 months after receiving advice from a healthcare professional.[10]

Doctors are frequently urged to advise smokers to quit each time they attend for healthcare reasons on the assumption that repeated interventions will promote abstinence.[20] There is some evidence for this, in that repeated physician follow-up of patients trying to quit smoking can double cessation rates.[21] However, despite the fact that people generally have a high regard for physicians' advice, attempted intervention occurs infrequently and in a non-systematic manner.[1,22,23] One reason for this may be that physicians fail to recognise tobacco dependence as a genuine medical disorder and often lack sympathy for a condition that is seen as self-inflicted.[24] In addition, some physicians find the routine repetition of advice frustrating and ineffective.[20]

1.2 Individual and Group Behavioural Therapy

Behavioural therapy programmes, either individual or group-based and led by smoking cessation counselling specialists, are another effective means of increasing smoking cessation rates.[9,10,16,25-27] Behavioural therapy has been studied quite extensively and, for those smokers willing to participate in such programmes, cessation rates are thought to average 20% after 1 year, in the range of 10% to 30%.[21] Smokers are often treated in groups for reasons of efficacy and it is thought that group members can exert peer pressure to motivate each other to maintain an effort to stop smoking.[28] There is a dose-response relationship between success rates and the number of face-to-face sessions and the total contact time between smoker and clinician. However, the optimal number and length of sessions are unknown and vary widely between treatment centres/programmes, but usually comprise between 4 and 8 sessions, of 10 to 30 minutes each at approximately weekly intervals.

1.3 Self-Help Materials

Behavioural intervention methods can also be delivered through self-help materials, including written leaflets and manuals, audiotapes, videotapes, and computer programs. Potentially, these can reach significantly greater numbers of people than interventions delivered by therapists.[16] However, while these materials may provide a small increase in the numbers of smokers quitting,[29] their primary importance may be as an adjunct to clinician advice.[21] There is little evidence to suggest that self-help materials are efficacious without the provision of additional support.[9]

1.4 The Community Pharmacist

The role of the community pharmacy in promoting smoking cessation has also been recognised. Pharmacies are the major point of supply of pharmacological aids and, consequently, the pharmacist is in a key position to encourage and support smokers who wish to stop smoking. Multidisciplinary smoking cessation programmes sometimes encourage pharmacists, as part of the overall programme, to be proactive about smoking cessation.[30]

1.5 Telephone Quitlines

The use of telecommunications to deliver healthcare remains underdeveloped, although it has great potential to improve ambulatory care practice.[31] Acceptable quit rates in adults given direct help through telephone help lines have been reported,[10,32] especially those involving proactive call-back counselling.[33] It has been suggested that telephone counselling is more effective as an ad-

junct to well-defined behavioural programmes rather than as the primary focus of intervention.[34] However, while this is correct, it fails to take into account the fact that many smokers are unwilling to take part in formal behavioural programmes. Moreover, in many areas, there are insufficient programmes to meet the high demand from smokers who do wish to participate. In these cases, telephone quitlines may be an appropriate option.

1.6 Other Treatment Interventions

In addition to behavioural interventions, motivational support, in the form of intra-treatment support from healthcare professionals, and from family, friends, and other community members (i.e. extra-treatment social support), is also useful in helping smokers to quit.[35] Administering computer-generated letters, as a method of encouraging smoking cessation has proven effective.[36] There is also some evidence that exercise can aid smoking cessation.[37,38] The efficacy of acupuncture[39] and hypnotherapy as potential aids in smoking cessation is questionable.[16]

2. Pharmacotherapy in Smoking Cessation

2.1 Nicotine Replacement Therapy

Nicotine dependence is a significant element of tobacco addiction,[40] and so a standard approach to pharmacological-based smoking cessation has been the use of nicotine replacement therapy (NRT).[21]

NRT provides nicotine via a number of delivery systems that reduce or eliminate withdrawal symptoms, thus enabling smokers to stop smoking more easily.[15] As smoking cessation is aided or achieved by partially replacing the nicotine formerly obtained from tobacco, NRT products are often referred to as 'replacement medications'.[41]

Currently, there are six approved formulations of NRT: gum, patches, inhalers, nasal spray, sublingual tablets and lozenges.[8,16] Nicotine-containing gum was the first of these replacement therapies available.[42] However, problems associated with this formulation, including potential underadministration[43] and impaired absorption when taken with coffee or acidic beverages, led to the development of other forms and routes of NRT.[42]

Transdermal patches allow nicotine to be absorbed through the skin,[21] while the nasal spray delivers nicotine more rapidly than any other form of NRT. Despite its name, the inhaler device does not deliver a significant amount of nicotine to the lungs; rather, delivery is achieved buccally as is nicotine delivery from sublingual tablets.[44] Nicotine lozenge (1mg, 2mg and 4mg) is also absorbed buccally, and has a similar pharmacokinetic profile to that of an equivalent dose of gum but delivers more nicotine per labelled dose. Differences in the speed and efficiency with which nicotine delivery occurs allow patients to choose the nicotine form that is most appropriate to their individual needs and preferences.

The use of NRT increases the long-term rates of smoking cessation and relieves cravings for nicotine and the symptoms of nicotine withdrawal.[2] Depending on the particular formulation, patients using NRT are 1.5- to 2.7-times more likely to remain abstinent at 1 year than those using placebo.[42,45-50]

Smoking cessation rates are maximised when NRT products are used as part of combination interventions including behavioural intervention.[51-53] Approximately 20% of smokers given NRT with specialist counselling will remain abstinent for 12 months and up to 10% will remain abstinent if given brief advice from a health professional in addition to nicotine replacement.[54]

Individual NRT formulations have proven efficacy in smokers motivated to make a quit attempt;[15] however, in some smokers who are heavily dependent it may be beneficial to combine NRT products.[44,55,56]

Nicotine replacement therapies are generally very well tolerated. This is underscored by the fact that all six formulations are available from pharmacies without prescription in the UK. The most common adverse effects are localised reactions, particularly skin irritation with patch and

nasal irritation with spray, and do not generally require discontinuation of treatment. Sleep disturbances, which are a feature of withdrawal from tobacco, are also reported with nicotine patches.[21]

2.2 Bupropion and Other Antidepressants

The association between smoking, smoking cessation and depression has been widely investigated,[57-59] and has led to the evaluation of antidepressants for use in smoking cessation therapy.[60-64]

Initial observations that depressed smokers treated with bupropion, an antidepressant, experienced reduced craving for smoking[65] prompted two large randomised prospective trials in which the efficacy and tolerability of a sustained-release formulation of bupropion (bupropion SR; Zyban®)[1] as a smoking cessation agent were demonstrated.[63,66]

Increased smoking cessation rates associated with bupropion SR have been consistently demonstrated.[67,68] Bupropion SR decreases the occurrence of withdrawal symptoms,[15] and efficacy has been reported in combination with behavioural interventions[63,69-71] and in combination with nicotine patches.[66]

Bupropion SR has proven efficacy in people who smoke more than 10 to 15 cigarettes per day who are motivated to stop,[15] approximately doubling the success of smoking cessation.[41] When used as a single agent combined with behavioural interventions, long-term (1 year) abstinence rates of up to 30% can be achieved.[21,72] In one study, significantly higher continuous abstinence rates were achieved with bupropion SR alone or in combination with a nicotine patch than with use of a nicotine patch alone.[66]

Bupropion SR is the first non–nicotine-containing pharmacological agent to be approved for use in smoking cessation and has received regulatory approval in both the US[40] and the European Union.[67]

Unlike NRT, bupropion SR therapy is initiated approximately 1 week prior to a cessation attempt.[44] Treatment with bupropion SR should be accompanied by a motivational support programme highlighting additional information on quitting and relapse prevention.[21]

Bupropion SR is primarily a selective dopamine and noradrenaline re-uptake inhibitor, and it is thought to work by enhancing dopaminergic activity.[73] The drug appears to be equally effective in smokers with or without a past history of depression, suggesting that its efficacy is not due to its antidepressant effect.[44]

Bupropion SR is a useful option for smokers attempting to stop smoking for the first time, and in those who either cannot tolerate NRT, those who prefer non-nicotine treatment,[40] or those in whom NRT has failed.[44]

Treatment with bupropion is generally well tolerated and adverse events observed in clinical trials, including anxiety, dry mouth, headache, insomnia and rash, were mild.[74] However, seizures have been experienced and consequently bupropion is contraindicated in certain groups of patients, for example, in patients who suffer from epilepsy[15] and eating disorders.[8]

Trials of other antidepressant medications for smoking cessation have yielded mixed results. Aside from bupropion SR, nortriptyline, a tricyclic antidepressant, is the only other antidepressant demonstrating evidence of efficacy; however, nortriptyline in not licensed as an aid to smoking cessation.[60,64,67] Doxepin, fluoxetine and moclobemide have also been evaluated as smoking cessation aids without success.[60]

2.3 Clonidine and Mecamylamine

Other smoking cessation treatments have been studied in clinical trials, but their use in smoking cessation remains unlicensed.[30] Mecamylamine, a noncompetitive nicotinic receptor antagonist,[60] which is licensed as an antihypertensive agent,[64] has been studied as a treatment for smoking cessation either alone[75] or as an adjunct to nicotine patches.[76]

1 Tradenames are used for identification purposes only and do not imply endorsement.

Clonidine, an imidazoline used in the management of hypertension,[60,64] has also been reported to have limited efficacy as a smoking cessation therapy.[77-79] It has been recommended as a second-line therapy in US smoking cessation guidelines.[9] However, adverse effects associated with clonidine, such as drowsiness, fatigue and dry mouth, may limit its use, and the drug is likely to play only a second-tier role in smoking cessation.[64]

2.4 Other Smoking Cessation Aids

Smoking may be considered as a form of reducing stress and anxiety, and the potential efficacy of anti-anxiety drugs in smoking cessation has been investigated. Buspirone is associated with decreased nicotine withdrawal symptoms and a reduced urge to smoke,[64] but has not been demonstrated as efficacious for smoking cessation. The efficacy of the opioid antagonists naltrexone and naloxone as smoking cessation aids has also been tested; however, results from studies have been mixed.[64,80]

Lobeline, a nicotine-like alkaloid, has also been used as a form smoking cessation therapy,[60,81] as has silver acetate, which produces an aversive taste when combined with cigarette smoke and functions as a smoking deterrent.[82] However, there is currently insufficient evidence to recommend the use of either lobeline or silver acetate. Glucose has also been identified as a potentially cheap and simple smoking cessation aid with modest efficacy. There is evidence to suggest that chewing glucose tablets can reduce the desire to smoke during periods of cessation.[83-85]

3. Smoking Cessation Guidelines

Over the past 10 years, guidelines have become increasingly common in clinical practice. Such guidelines can ensure improved quality of clinical decisions and quality of care received by patients.[86]

A number of smoking cessation guidelines have been published in recent years. In the US, the Agency for Health Care Policy and Research (AHCPR) published clinical practice guidelines for treating tobacco use and dependence in 1996.[87] These guidelines focus on primary care clinicians, tobacco dependence treatment specialists, and healthcare administrators, insurers and purchasers, and their recommendations are based primarily on meta-analyses of randomised clinical trials.[87]

In 2000, the US Public Health Service also published treatment guidelines with a similar focus to those of the AHCPR.[9] The American Psychiatric Association (APA) Practice Guidelines focus on smokers for whom primary care treatment has failed, psychiatric patients, and patients in smoke-free facilities. Recommendations within this report are based on evaluations of randomised controlled trials and clinical experience and are similar to those of the AHCPR.[88] These guidelines are intended primarily for psychiatrists; however, they may be useful for all clinicians caring for nicotine-dependent patients.

In 1998, the Health Education Authority (HEA) commissioned the development of smoking cessation guidelines for health professionals in the UK.[3] The recommendations within these guidelines were based upon systematic reviews of the Cochrane Collaboration Tobacco Addiction Review Group, AHCPR, and APA guidelines. These guidelines were updated in 2000,[10] and outline ways in which to treat tobacco dependence and reduce the burden of death and illness associated with tobacco use.[10]

In 1998, the UK government released a white paper on tobacco, outlining proposals to help motivated smokers to quit.[89] In April 2002, the National Institute for Clinical Excellence in the UK released a document providing guidance to healthcare professionals on the use of NRT and bupropion for smoking cessation.[50] Guidelines have also been developed and published by the National Health Committee in New Zealand and by the Canadian Task force on Preventive Health Care.[90]

Internationally, World Health Organization recommendations propose core interventions that

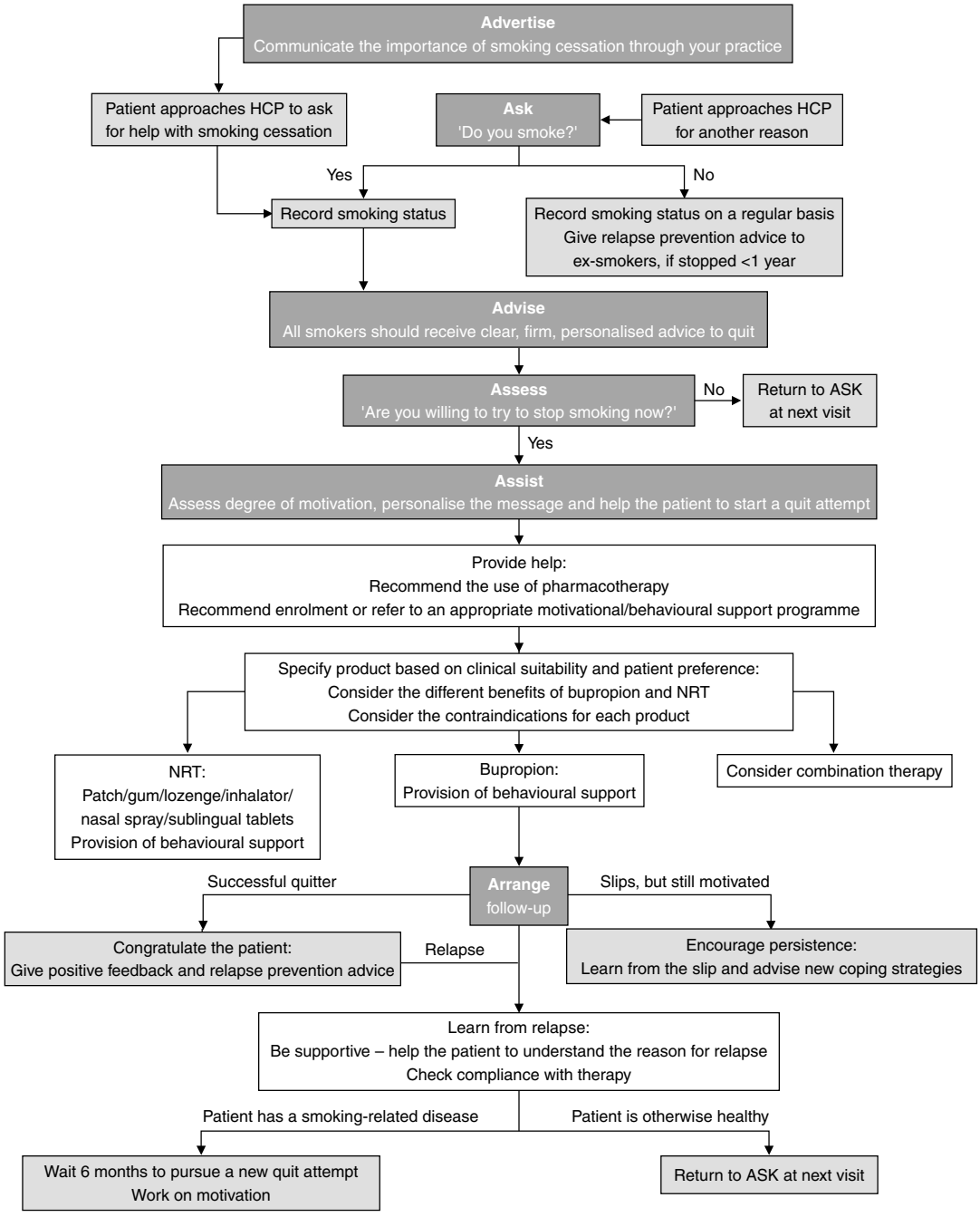

Fig. 1. An illustration of the effective implementation of smoking cessation strategies incorporating approved first-line interventions. **HCP** = healthcare professional; **NRT** = nicotine replacement therapy.

should be integrated into healthcare systems.[19] A number of authoritative reviews and guidelines have been used as the basis for these recommendations, including some of those outlined above.[19]

The first-line smoking cessation interventions generally endorsed in these guidelines include brief advice from healthcare professionals, behavioural therapy, NRT, and bupropion SR. The various guidelines outline the steps necessary to identify smokers, to motivate them to make an attempt to stop smoking, and to support them in quitting successfully through counselling, pharmacotherapy and follow-up.[91] Figure 1 illustrates effective implementation of smoking cessation strategies incorporating approved first-line interventions.

4. Conclusion

As nearly 4 million people globally each year are estimated to die as a result of smoking,[24] reducing the number of current smokers should substantially lower future smoking-related morbidity and mortality.[6]

In general, smokers are dissatisfied with smoking but nevertheless tend to be naive about how easy it will be to stop; this implies that extra urgency is required in promoting smoking cessation.[92] Currently available interventions are efficacious but many smokers seem reluctant to participate in smoking cessation programmes.[4] However, this may be attributed at least in part to the limited availability of such programmes.

Smoking is a chronic condition that requires long-term management;[2] interventions are extremely cost effective,[41] but greatly underused.[2] Tobacco users must not be left to stop smoking on their own and most healthcare professionals are of the opinion that they should help people who are willing to stop smoking.[16]

There is general agreement about what constitutes effective treatment. Physicians should routinely identify smokers, assess their willingness to quit, and advise and assist or refer them to more intensive specialist support.[1,2,91] Recent increases in the number of approved drugs for smoking cessation have given healthcare providers a broad range of treatment approaches.[40] Such pharmacotherapy-based treatment is more effective when accompanied by counselling.[2,44]

Given the proven effectiveness of smoking cessation interventions, failure to identify, advise, and offer pharmacological agents to smokers may soon be judged as deviation from standard care practice.[40] Continued promotion of smoking cessation is necessary and should result in an increase in the numbers of smokers quitting and subsequent reductions in smoking-related morbidity and mortality.

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References

1. Eckert T, Junker C. Motivation for smoking cessation: what role do doctors play? Swiss Med Wkly 2001; 131: 521-6
2. Rigotti NA. Treatment of tobacco use and dependence. N Engl J Med 2000; 346 (7): 506-12
3. Raw M, McNeill A, West R. Smoking cessation guidelines for health professionals: a guide to effective smoking cessation interventions for the healthcare system. Thorax 1998; 53 Suppl 5 (Pt 1): S1-19
4. Lawrence WF, Smith SS, Baker TB, et al. Does over-the-counter nicotine replacement therapy improve smokers' life expectancy? Tob Control 1998; 7: 364-8
5. American College of Chest Physicians, American Thoracic Society, Asia Pacific Society of Respirology, et al. Smoking and health: physician responsibility. Chest 1995; 108 (4): 1118-21
6. Silagy C, Formica N. Place of bupropion in smoking-cessation therapy. Lancet 2001; 357: 1550
7. Hughes JR, Gulliver SB, Fenwick JW, et al. Smoking cessation among self-quitters. Health Psychol 1992; 11 (5): 331-5
8. Rennard SI, Daughton DM. Smoking cessation. Chest 2000; 117 (5): 360S-4S
9. Fiore MC, Bailey WC, Cohen SJ, et al. Treating tobacco use and dependence: clinical practice guidelines. Rockville (MD): US Department of Health and Human Services. Public Health Service, 2000 Jun
10. West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. Thorax 2000; 55: 987-99
11. Fiore MC, Pierce PJ, Remington PL, et al. Cigarette smoking: the clinician's role in cessation, prevention, and public health. Dis Mon 1990; 36 (4): 181-242
12. Russell MAH, Wilson C, Taylor C, et al. Effects of general practitioners' advice against smoking. BMJ 1979; 2 (6184): 231-5
13. Emmons KM. Smoking cessation and tobacco control: an overview. Chest 1999; 116: 490S-2S
14. Fiore MC, Jorenby DE, Schensky AE, et al. Smoking status as a new vital sign: effects on assessment and intervention in patients who smoke. Mayo Clin Proc 1995; 70 (3): 209-13

15. Coleman T. Smoking cessation: integrating recent advances into clinical practice. Thorax 2001; 56: 579-82
16. Lancaster T, Stead L, Silagy C, et al. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. BMJ 2000; 321 (5): 355-8
17. Silagy C, Stead LF. Physician advice for smoking cessation (Cochrane Review). Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; Issue 1. Oxford: Update Software, 2002
18. Rice VH, Stead LF. Nursing interventions for smoking cessation (Cochrane Review). Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; Issue 1. Oxford: Update Software, 2002
19. World Health Organisation (WHO). European partnership to reduce tobacco dependence: WHO evidence based recommendations on the treatment of tobacco dependence. Geneva: WHO, 2001 Jun
20. Butler CC, Pill R, Stott NCH. Qualitative study of patients' perception of doctors advice to quit smoking: implications for opportunistic health promotion. BMJ 1998; 316: 1878-81
21. Prochazka AV. New developments in smoking cessation. Chest 2000; 117 (4): 169S-75S
22. Coleman T, Wilson A. Managing smoking cessation: implementing new guidelines in primary care presents a challenge. BMJ 1999; 318: 138-9
23. Fiore MC, Jorenby DE, Baker TB. Smoking cessation: principles and practice based upon the AHCPR Guidelines, 1996. Ann Behav Med 1997; 19 (3): 213-9
24. McEwen A, West R, Owen L. General practitioners' views on the provision of nicotine replacement therapy and bupropion. BMC Fam Pract 2001; 2: 6
25. Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation (Cochrane Review). Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; Issue 1. Oxford: Update Software, 2002
26. Stead LF, Lancaster T. Group behaviour therapy programmes for smoking cessation (Cochrane Review). Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; Issue 1. Oxford: Update Software, 2002
27. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. A clinical practice guideline for treating tobacco use and dependence. A US Public Health Service Report. JAMA 2000; 283 (24): 3244-54
28. Raw M, McNeill A, West R. Smoking cessation: evidence based recommendations for healthcare systems. BMJ 1999; 318: 182-5
29. Lancaster T, Stead LF. Self-help interventions for smoking cessation (Cochrane Review). Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; Issue 1. Oxford: Update Software, 2002
30. McElnay JC, Maguire TA, Drummond A, et al. Smoking cessation: the contribution of community pharmacy. Drugs 2000; 8 (3): 147-58
31. Friedman RH, Stollerman JE, Mahoney DM, et al. The virtual visit: using telecommunications technology to take care of patients. J Am Med Inform Assoc 1997; 4 (6): 413-25
32. Platt S, Tannahill A, Watson J, et al. Effectiveness of antismoking telephone helpline: follow up survey. BMJ 1997; 314 (7091): 1371-5
33. Borland R, Segan CJ, Livingston PM, et al. The effectiveness of callback counselling for smoking cessation: a randomized trial. Addiction 2001; 96 (6): 881-9
34. Deagle EA, Berigan TR. Adding behavioral therapy to medication for smoking cessation. JAMA 1999; 281 (21): 1983-9
35. Jorenby DE. Smoking cessation strategies for the 21st century. Circulation 2001; 104: 51-2
36. Lennox AS, Osman LM, Reiter E, et al. Cost effectiveness of computer tailored and non-tailored smoking cessation letters in general practice: randomised controlled trial. BMJ 2001; 322: 1-7
37. Bock BC, Marcus BH, King TK, et al. Exercise effects on withdrawal and mood among women attempting smoking cessation. Addict Behav 1999; 24 (3): 399-410
38. Ussher MH, Taylor AH, West R, et al. Does exercise aid smoking cessation?: a systematic review. Addiction 2000; 95 (2): 199-208
39. White AR, Resch KL, Ernst E. A meta-analysis of acupuncture techniques for smoking cessation. Tob Control 1999; 8: 393-7
40. Okuyemi KS, Ahluwalia JS, Harris KJ. Pharmacotherapy of smoking cessation. Arch Fam Med 2000; 9: 270-81
41. Henningfield JE, Fant RV, Gitchell J, et al. Tobacco dependence: global public health potential for new medications development and indications. Ann NY Acad Sci 2000; 909: 247-56
42. Silagy C, Lancaster T, Stead L, et al. Nicotine replacement therapy for smoking cessation (Cochrane Review). Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; Issue 1. Oxford: Update Software, 2002
43. Bohadana A, Nilsson F, Rasmussen T, et al. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: a randomized, double-blind, placebo-controlled trial. Arch Intern Med 2000; 160 (20): 3128-34
44. Hughes JR, Goldstein MG, Hurt RD, et al. Recent advances in the pharmacotherapy of smoking. JAMA 1999; 281 (1): 72-6
45. Abelin T, Ehrsam R, Buhler-Reichert A, et al. Effectiveness of a transdermal nicotine system in smoking cessation studies. Methods Find Exp Clin Pharmacol 1989; 11 (3): 201-14
46. Bolliger CT, Zellweger JP, Danielsson T, et al. Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety. BMJ 2000; 321: 329-33
47. Fiore MC, Smith SS, Jorenby DE, et al. The effectiveness of the nicotine patch for smoking cessation: a meta-analysis. JAMA 1994; 271 (24): 1940-7
48. Gourlay SG, Forbes A, Marriner T, et al. Prospective study of factors predicting outcome of transdermal nicotine treatment in smoking cessation. BMJ 1994; 309: 842-6
49. Schneider NG, Olmstead R, Nilsson F, et al. Efficacy of a nicotine inhaler in smoking cessation: a double-blind, placebo-controlled trial. Addiction 1996; 91 (9): 1293-306
50. National Institute for Clinical Excellence (NICE). Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation. National Institute for Clinical Excellence Technology Appraisal Guidance No. 39, 2002 Apr. Available from URL: www.nice.org.uk
51. Daughton DM, Heatley SA, Prendergast JJ, et al. Effects of transdermal nicotine delivery as an adjunct to low intervention smoking cessation therapy: a randomized, placebo-controlled, double-blind study. Arch Intern Med 1991; 151 (4): 749-52
52. Herrera N, Franco R, Herrera L, et al. Nicotine Gum, 2 and 4mg, for nicotine dependence: a double-blind placebo-controlled trial within a behavior modification support program. Chest 1995; 108 (2): 447-51
53. Hurt RD, Dale LC, Fredrickson PA, et al. Nicotine patch therapy for smoking cessation combined with physician advice and nurse follow-up: one-year outcome and percentage of nicotine replacement. JAMA 1994; 271 (8): 595-600

54. Britton J, Jarvis MJ. Bupropion: a new treatment for smokers. Nicotine replacement treatment should also be available on the NHS. BMJ 2000; 321: 65-6
55. 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: 285-9
56. 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 (1): 41-7
57. Anda RF, Williamson DF, Escobedo LG, et al. Depression and the dynamics of smoking. JAMA 1990; 264 (12): 1541-6
58. Breslau N, Kilbey MM, Andreski P. Nicotine withdrawal symptoms and psychiatric disorders: findings from an epidemiologic study of young adults. Am J Psychiatry 1992; 149 (4): 464-9
59. Breslau N, Kilbey MM, Andreski P. Nicotine dependence and major depression: new evidence from a prospective investigation. Arch Gen Psychiatry 1993; 50 (1): 31-5
60. Benowitz NL, Wilson Peng M. Non-nicotine pharmacotherapy for smoking cessation. Mechanisms and prospects. CNS Drugs 2000; 13 (4): 265-85
61. Barchas JD, Marzuk PM. General psychiatry. JAMA 1998; 280 (11): 961-2
62. Gambassi G, Bernabei R. Antidepressants and smoking cessation. Arch Intern Med 1999; 159: 1257-8
63. 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 (17): 1195-202
64. Covey LS, Sullivan MA, Johnston JA, et al. Advances in non-nicotine pharmacotherapy for smoking cessation. Drugs 2000; 59 (1): 17-31
65. Ferry LH, Burchette RJ. Efficacy of bupropion for smoking cessation in non-depressed smokers. J. Addict Dis 1994; 13: 249
66. 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; 340 (9): 685-91
67. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation (Cochrane Review). Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; Issue 1. Oxford: Update Software, 2002
68. Jarvis MJ, Powell S, Marsh H, et al. A meta-analysis of clinical studies confirms the effectiveness of bupropion SR (Zyban™) in smoking cessation [abstract]. Presented at the 7th Annual Conference of the Society for Research on Tobacco and Nicotine; 2001 Mar 23-25; Seattle (WA)
69. Hays JT, Hurt RD, Rigotti NA, et al. Sustained-release bupropion for pharmacological relapse prevention after smoking cessation: a randomized, controlled trial. Ann Intern Med 2001; 135 (6): 423-33
70. Hertzberg MA, Moore SD, Feldman ME, et al. A preliminary study of bupropion sustained-release for smoking cessation in patients with chronic posttraumatic stress disorder. J Clin Psychopharmacol 2001; 21 (1): 94-8
71. Tashkin DP, Kanner R, Bailey W, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. Lancet 2001; 357: 1571-5
72. Coleman T, West R. Newly available treatments for nicotine addiction: smokers wanting help to stop smoking now have effective treatment options. BMJ 2001; 322: 1076-7
73. Ascher JA, Cole JO, Colin JN, et al. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995; 56: 395-401
74. Holm KJ, Spencer CM. Bupropion: a review of its use in the management of smoking cessation. Drugs 2000; 59 (4): 1007-24
75. Rose JE, Behm FM, Westman EC. Nicotine-mecamylamine treatment for smoking cessation: the role of pre-cessation therapy. Exp Clin Psychopharmacol 1998; 6 (3): 331-43
76. Rose JE, Behm FM, Westman EC, et al. Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. Clin Pharmacol Ther 1994; 56 (1): 86-99
77. Glassman AH, Covey LS, Dalack GW, et al. Smoking cessation, clonidine, and vulnerability to nicotine among dependent smokers. Clin Pharmacol Ther 1993; 54 (6): 670-9
78. Glassman AH, Stetner F, Walsh BT, et al. Heavy smokers, smoking cessation, and clonidine: results of a double-blind, randomized trial. JAMA 1988; 259 (19): 2863-6
79. Hilleman DE, Mohiuddin SM, Delcore MG, et al. Randomized, controlled trial of transdermal clonidine for smoking cessation. Ann Pharmacother 1993; 27 (9): 1025-8
80. Sutherland G, Stapleton J, Russell MAH, et al. Naltrexone, smoking behaviour and cigarette withdrawal. Psychopharmacology 1995; 120 (4): 418-25
81. Dwoskin LP, Crooks PA. A novel mechanism of action and potential use for lobeline as a treatment for psychostimulant abuse. Biochem Pharmacol 2002; 63 (2): 89-98
82. Hymowitz N, Eckholdt H. Effects of a 2.5-mg silver acetate lozenge on initial and long-term smoking cessation. Prev Med 1996; 25 (5): 537-46
83. West R, Willis N. Double-blind placebo controlled trial of dextrose tablets and nicotine patch in smoking cessation. Psychopharmacology 1998; 136 (2): 201-4
84. West R, Courts S, Beharry S, et al. Acute effect of glucose tablets on desire to smoke. Psychopharmacology 1999; 147 (3): 319-21
85. West R. Glucose for smoking cessation: does it have a role? CNS Drugs 2001; 15 (4): 261-5
86. Woolf SH, Grol R, Hutchinson A, et al. Potential benefits, limitations, and harms of clinical guidelines. BMJ 1999; 318: 527-30
87. Fiore MC, Bailey WC, Cohen SJ, et al. Smoking cessation: clinical practice guidelines No 18. Rockville (MD): US Department of Health and Human Services. Public Health Service, Agency for Health Care Policy and Research, 1996. AHCPR publication no.: 96-0692
88. Practice guidelines for the treatment of patients with nicotine dependence. American Psychiatry Association. Available from URL: http//www.psych.org/clin_res/pg_nicotine.cfm [Accessed]
89. Smoking Kills. A White Paper on Tobacco. Available from URL: http://archive.oficial.document.co.uk/document/cm41/4177.htm
90. Silagy CA, Stead LF, Lancaster T. Use of systematic reviews in clinical practice guidelines: case study of smoking cessation. BMJ 2001 Oct; 323 (7317): 833-6
91. Anderson JE, Jorneby DE, Scott WJ, et al. Treating tobacco use and dependence: an evidence-based clinical practice guideline for tobacco cessation. Chest 2002; 121 (3): 932-41
92. Foulds J. Effectiveness of smoking cessation initiatives. BMJ 2002; 324: 608-9

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