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# Advances in Non-Nicotine Pharmacotherapy for Smoking Cessation

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## Abstract

Progress in understanding the pharmacological nature of tobacco addiction, along with the modest success rates achieved by the nicotine replacement therapies, has provided the major impetus for the development of non-nicotine drugs as smoking cessation aids. This article reviews evidence from controlled trials of several non-nicotine medications for the treatment of nicotine dependence.

Clonidine was the first non-nicotine medication to show efficacy for smoking cessation in multiple studies, but its effect was found to be limited at best. Positive results across several trials have been consistently demonstrated for amfebutamone (bupropion). Encouraging results have also been observed for nortriptyline and moclobemide. Studies of combined treatments using non-nicotine medications (amfebutamone, mecamylamine, oral dextrose) with nicotine replacement therapy suggest increased efficacy relative to treatments using one or the other treatment strategy alone.

Thus, available evidence indicates that non-nicotine drug treatments offer a promising panoply of therapeutic strategies for the addicted smoker.

Treatments for addictive disorders have evolved with our understanding of the pharmacology of drug dependence. The history of smoking cessation treatments exemplifies this association. The earliest perception about persistent tobacco use was its repetitive, conditioned and habit-like character. This view gave rise to the emphasis on behavioural change methods which marked smoking cessation treatments shortly after the first US Surgeon General's Report on smoking in 1964.[1] These treatments helped smokers who had been unable to stop smoking on their own to learn specific techniques for managing nicotine withdrawal symptoms, coping with smoking cues, and developing new behaviours to take the place of smoking. However, these treatments based on behavioural precepts alone tended to benefit only a small minority of would-be quitters.[2]

Research on the use of medications for helping smokers actually began as early as the 1930s. Uncontrolled observations with lobeline, an alkaloid with physiological effects similar to those of nicotine, had suggested some promise for its ability to reduce craving for tobacco.[3] Building on the notion that lobeline acted as a chemical nicotine substitute, several studies of lobeline followed. However, none of these studies demonstrated treatment gains beyond those seen with placebo.[4] This evidence of poor efficacy for lobeline, as well as for a number of other drugs (meprobamate, dexamfetamine, ephedrine) that were tested during this early period, turned researchers' attention to nicotine replacement.

The 2 decades that followed the first US Surgeon General's Report[1] witnessed advances in knowledge of the physiological effects of regular tobacco use, as well as the central role of nicotine as the main pharmacological ingredient in tobacco. These advances culminated in the 1988 US Surgeon General's Report, which recognised chronic tobacco use as a form of addictive behaviour.[5] The successful use of methadone in the treatment of opiate addiction in the early 1960s generated an interest in nicotine replacement as a form of smoking cessation treatment. Methadone treatment had demonstrated that craving and propensity to relapse to an initial drug of abuse could be diminished by the use of a second drug. Nicotine replacement therapy (NRT), initially with nicotine gum, subsequently with the nicotine patch, and later with the nicotine inhaler and nasal spray, has consistently proven efficacious when compared with placebo.[6,7] Despite this demonstrated efficacy, the number of quitters amongst users of NRT has also been relatively low. In controlled clinical trials, abstinence rates have hovered around the 30% mark at the end of treatment and at 20% 6 months to 1 year later.[7,8]

The limited success of NRT was only one of several factors which spurred renewed interest in non-nicotine pharmacotherapies for smoking. Laboratory research had led to increased knowledge of the neurobiological nature of tobacco dependence, as effects of nicotine on brain function were observed in animal and human studies. In clinical and epidemiological studies, research demonstrating the strong association between the propensity to nicotine dependence and psychiatric illness had begun to emerge. These developments provided a rationale

for testing the benefit of drugs previously known for their antidepressant or anxiolytic effects as aids for addicted smokers.

This paper examines current knowledge about the efficacy of several promising non-nicotine medications as smoking cessation aids either alone or in combination with NRT. Its focus is on studies that yielded encouraging, even if not conclusive, results and to highlight their implications on the future direction of smoking cessation treatment research. For the most part, attention has been restricted to the evidence from placebo-controlled trials which were published in full manuscript form. For a comprehensive examination of non-nicotine medications that have been studied to date, regardless of their outcome or manner of publication, readers are referred to recent reviews by Cinciripini et al.,[9] Henninfield et al.[10] and Hughes et al.[11] To identify relevant studies for this paper, a Medline search for the period 1970 to 1999 was conducted, and other investigators in the field were consulted. While the use of adjunctive smoking cessation counselling is noted where appropriate, we have not attempted to control for such clinical support in this analysis because of substantial differences in the level and type of clinical intervention between trials.

## 1. Non-Nicotine Medications Used Alone

### 1.1 Clonidine

Clonidine is an $\alpha_2$-noradrenergic agonist which was initially used for the treatment of hypertension, and was subsequently found to diminish symptoms of both opiate and alcohol withdrawal syndromes. Glassman and colleagues[12] demonstrated its efficacy for reducing nicotine craving and withdrawal symptoms in heavy cigarette smokers who had been abstinent for 24 hours. These encouraging results led to a randomised trial for smoking cessation in which 71 smokers were assigned to receive either clonidine or placebo for 4 weeks with adjunctive individual behaviour therapy.[13] In this study, the clonidine dose was slowly titrated upward from 0.05mg until reaching the therapeutic level of 0.15 mg/day taken in divided doses, at which point individuals were instructed to stop smoking. The dosage was adjusted according to the appearance of adverse effects or severe tobacco withdrawal discomfort, with the maximum dose of 0.4 mg/day taken by a few participants. The success rate among clonidine-treated smokers was more than twice that of the placebo-treated group, demonstrating for the first time the efficacy of a non-nicotine pharmacological agent as an aid in smoking cessation.

There have been 2 review papers on controlled trials of clonidine as a smoking cessation aid (see table I). Covey and Glassman[24] performed a meta-analysis of end-of-treatment results from 9 trials reported between 1987 and 1989. Combined odds ratios (OR) for success, which accounted for differences in the sample size among trials, indicated that smokers treated with clonidine were significantly more likely to quit smoking than those treated with placebo. The meta-analysis also indicated that clonidine efficacy was increased when it was delivered via a skin patch compared with oral administration, and when clonidine treatment was accompanied by behaviour therapy. This study also observed that clonidine was more helpful for female smokers than males in those studies that stratified the data by gender.[13,25,26] This finding was subsequently replicated in a trial of 300 smokers by Glassman and colleagues.[27]

In the second review of clonidine trials, Gourlay and Benowitz[15] not only observed a significantly higher long term quit rate (table I) with clonidine but also noted the high frequency of adverse effects during clonidine therapy. They concluded that although clonidine may be helpful for quitting smoking in the short term, possibly because of its ability to alleviate nicotine withdrawal symptoms, its benefit may be limited to smokers who experience high levels of agitation and anxiety when they stop smoking.

In general, the effect of clonidine on smoking cessation has not proved as robust as the nicotine replacement products. In addition, the adverse effects associated with clonidine use, such as drows-

**Table I.** Short- and long-term nicotine abstinence rates and odds ratios (OR) with 95% confidence intervals (CI) in clinical trials of non-nicotine medications, 1990 to 1998[a]

| Treatment | No. of smokers | Short term[b] | | Long term[b] | |
|---|---|---|---|---|---|
| | | % quit | OR, 95% CI | % quit | OR, 95% CI |
| **Non-nicotine medications alone** | | | | | |
| ***Clonidine*** | | | | | |
| Covey & Glassman,[14] 1990 | | | | NA | NA |
| Active | 9 studies | 39 | 2.4 (1.7-32.8)[c] | | |
| Placebo | n = 813 | 21 | | | |
| Gourlay & Benowitz,[15] 1995 | | | | | |
| Active | 4 studies | NA | | 31 | 2.0 (1.3-3.0)[c] |
| Placebo | n = 189 | | | 17 | |
| ***Amfebutamone (Bupropion) SR*** | | | | | |
| Hurt et al.,[16] 1997 | | | | | |
| 300 mg/day | 156 | 44 | 3.4 (2.2-5.7) | 23 | 2.0 (1.1-3.5) |
| 150 mg/day | 153 | 39 | 2.7 (1.6-4.5) | 23 | 2.0 (1.2-3.6) |
| 100 mg/day | 153 | 29 | 1.7 (1.0-2.9) | 20 | 1.7 (0.9-3.0) |
| Placebo | 153 | 19 | | 12 | |
| ***Moclobemide*** | | | | | |
| Berlin et al.,[17] 1995 | | | | | |
| Active | 44 | 48 | 2.4 (1.0-5.9) | 25 | 1.8 (0.6-5.1) |
| Placebo | 44 | 27 | | 16 | |
| ***Nortriptyline*** | | | | | |
| Hall et al.,[18] 1998 | | | | | |
| Active | 99 | 55 | 3.2 (1.8-5.9) | 31 | 1.7 (0.9-3.3) |
| Placebo | 100 | 27 | | 21 | |
| Prochazka et al.,[19] 1998 | | | | NA | NA |
| Active | 108 | 14 | 5.5 (1.6-19.7) | | |
| Placebo | 106 | 3 | | | |
| ***Buspirone*** | | | | | |
| Cinciripini et al.,[20] 1995 | | | | | |
| Total sample: | | | | | |
| Active | 50 | 90 | 1.7 (0.5-5.8) | 27 | 1.5 (0.6-3.8) |
| Placebo | 51 | 84 | | 20 | |
| High anxiety subjects only: | | | | | |
| Active | 25 | 88 | 4.8 (1.1-19.7) | 12 | 0.5 (0.11-2.3) |
| Placebo | 28 | 61 | | 23 | |
| **Non-nicotine medications combined with nicotine patch (NP)** | | | | | |
| ***Mecamylamine*** | | | | | |
| Rose et al.,[21] 1998 | | | | | |
| Active + NP | 24 | 50 | 5.0 (1.3-19.1) | 38 | 13.8 |
| Placebo + NP | 24 | 17 | | 4 | (1.6-120.0) |
| ***Oral dextrose*** | | | | | |
| West & Willis,[22] 1998 | | | | | |
| Active + NP | 77 | 38 | 2.3 (1.2-4.6) | NA | NA |
| Active + placebo P | 80 | 35 | 1.9 (0.9-3.6) | | |
| Placebo + NP | 80 | 29 | 1.4 (0.7-2.7) | | |
| Placebo + placebo P | 71 | 21 | | | |
| ***Amfebutamone SR*** | | | | | |
| Jorenby et al.,[23] 1999 | | | | | |
| Active + NP | 245 | 67 | 4.0 (2.6-6.0) | 36 | 3.0 (1.8-4.9) |
| Active + placebo P | 244 | 60 | 2.9 (1.9-4.4) | 30 | 2.3 (1.4-3.9) |
| Placebo + NP | 244 | 48 | 1.8 (1.2-2.7) | 16 | 1.1 (0.6-1.8) |
| Placebo + placebo P | 160 | 34 | | 16 | |

a The placebo or placebo-placebo group is the reference group (OR = 1.0) in each study.

b Short-term rates are based on end-of-treatment data. Long-term rates are based on 12-month data with the exception of Gourlay and Benowitz[15] (6 months) and Hall et al.[18] (64 weeks).

c Data are common odds ratios from combined studies.

**NA** = data not available; **P** = patch; **SR** = sustained release.

iness, fatigue and dry mouth, may limit its effective use. For these reasons, clonidine is likely to play only a second-tier role in the treatment of nicotine addiction.

### 1.2 Antidepressants

Although clonidine proved to have a limited impact as a smoking cessation aid, certain unexpected observations from the clonidine studies by Glassman and colleagues regarding the association between smoking, smoking cessation and depression, suggested the value of antidepressants for smoking cessation therapy. At the outset of the first clonidine smoking cessation study,[13] the researchers had excluded smokers with evidence of present psychiatric illness, such as depression, schizophrenia or dependence on some other drug. Smokers with a history of major depression that had fully resolved at least 6 months before the study were not excluded. On average, smokers with a history of major depression had been free of any depressive illness for more than 4 years. Analysis of the data revealed that 60% of the participants had a past episode of major depression, which was highly unexpected as this figure was several times greater than rates of 10 to 20% for lifetime major depression observed in studies of the general population.[28] The data were further examined to determine if smoking cessation was influenced by a history of depression. This analysis produced a second surprising finding, replicated in other studies,[29,30] that smokers with a history of depression were less likely to succeed in their smoking cessation efforts than smokers without a history of depression.

Two other findings from the initial clonidine smoking cessation data suggested a rationale for using antidepressant treatments as an aid to quitting. Examining only those smokers who received placebo in order to control for confounding effects of clonidine, the researchers observed that: (i) among the symptoms reported by quitters during the first week, depressed mood was the strongest predictor of who would resume smoking by the end of the four-week trial; and (ii) smokers with a history of major depression were more likely to report depressed mood during the abstinence period than were smokers without a history of depression (75 *vs* 30%, $p < 0.05$).[14]

These series of findings, i.e. an association between past depression and smoking, the adverse influence of past depression on the ability to stop smoking, the propensity of those with past depression to re-experience depression during the nicotine withdrawal period, and the tendency of depressed mood during nicotine withdrawal to prevent a successful cessation outcome, prompted speculation that antidepressants might be useful in smoking cessation. In fact, the effects of antidepressants on smoking cessation had been examined earlier by Sellers et al.[31] in a study of the effect of certain selective serotonin (5-hydroxy tryptamine; 5-HT) reuptake inhibitors (SSRIs) [i.e. citalopram and zimeldine] on spontaneous alcohol consumption. Although no marked effect of the SSRIs on smoking cessation was observed, it should be noted that the purpose of those trials was to examine the effects of SSRIs on alcohol consumption and no efforts at promoting nicotine abstinence were involved.

#### *1.2.1 Amfebutamone (Bupropion)*

Amfebutamone (bupropion), originally marketed for the treatment of depression, represents the first potent non-nicotine pharmacological treatment for tobacco dependence. After extensive testing, and on the strength of the findings from considerable data (described in this section), amfebutamone sustained release (SR), was approved by the US Food and Drug Administration in 1997 as a treatment for nicotine dependence. Amfebutamone is listed in Pregnancy Category B which indicates that while no adverse effects on fetal development have been observed in animal studies of amfebutamone, no data from humans are available.

The mechanism by which amfebutamone assists smokers in their efforts to quit is not clear, but it is thought to be related to both noradrenergic and dopaminergic activity. It is hypothesised that the dopaminergic activity of amfebutamone affects the reward pathways and that the noradrenergic activity of amfebutamone plays a role in the emergence of

nicotine withdrawal symptoms. Amfebutamone has also been found to interact with nicotine receptors. In a dose-dependent fashion, amfebutamone blocks the antinociceptive effect of nicotine in mice.[32] This finding was replicated by Fryer and Lukas[33] who established that amfebutamone produces an acute functional blockade of human nicotinic receptors. These researchers suggest that amfebutamone functions by noncompetitive inhibition at the nicotinic receptor site and posit a role for these receptors in smoking cessation strategies.

On the basis of the published association between depression and cigarette smoking, researchers began to test whether an antidepressant could be an effective smoking cessation aid in a sample of heavy smokers. At the Veterans Memorial Center in Loma Linda, California, USA, Ferry[34] selected amfebutamone since, among the antidepressants on the market, it had the most clear-cut activity on the dopamine system. In the first study, 42 male smokers were given either amfebutamone 300 mg/day or placebo in a double-blind trial. The outcome for patients treated with amfebutamone in this trial was strikingly positive. To control for a potential confound due to possible over-representation of smokers with depression, Ferry conducted a second and enlarged trial which excluded smokers with a history of depression. In a sample of 190 non-depressed smokers who attended weekly group counselling over a 4-week period and received either amfebutamone 300 mg/day or placebo, amfebutamone was again demonstrated to be efficacious in helping smokers to quit.[35]

Since these early trials by Ferry and her colleagues, the efficacy of amfebutamone has been evaluated in 2 multi-site placebo-controlled trials: a dose-response study by Hurt et al.[16] and a nicotine patch-comparison study by Jorenby et al.[23] which assessed the sustained release formulation in conjunction with brief individual counselling.

The dose-response study was conducted at 3 centres, involved 615 smokers, and consisted of a 7-week treatment phase with follow-up through 1 year. Self-report of smoking cessation was confirmed using exhaled carbon monoxide levels. Three dosages of amfebutamone SR were evaluated: 100 mg/day, 150 mg/day and 300 mg/day. The primary efficacy variable was continuous quitting for the last 4 weeks of treatment (weeks 4 to 7). This time-line allowed 1 week for the drug to reach steady-state plasma concentrations and 2 weeks for cessation. As noted in table I, a clear dose response was demonstrated with the 2 higher dose groups showing clear superiority over placebo. At 1-year follow-up, participants in the 2 highest dosage groups reported significantly higher rates of smoking cessation than those in the placebo group (300mg = 23.1%, 150mg = 22.9%, placebo = 12.4%). The differences from placebo in cessation rates observed for the 300mg and 150mg dosage levels were both statistically significant ($p < 0.01$ and $p < 0.02$, respectively). Of additional interest, this study found that amfebutamone attenuated weight gain among the patients who had quit smoking; once treatment ceased, however, these differences between the active and placebo groups were not maintained.[16,36]

Only 2 adverse events from amfebutamone, insomnia and dry mouth, were observed at an incidence of 5% greater than with placebo. The incidence of premature discontinuation due to an adverse event (8%) was also low. The most common adverse events leading to premature discontinuation were tremor and rash. Although amfebutamone is associated with a low rate of seizures, none occurred in these smoking cessation studies.

#### *1.2.2 Nortriptyline*

Nortriptyline, a widely prescribed and well-established tricyclic antidepressant, was tested as a smoking cessation aid on the basis of its ability to inhibit the neuronal uptake of noradrenaline (norepinephrine). In the first of 2 published smoking cessation trials of nortriptyline, Hall and colleagues[18] at the San Francisco Veterans Affairs Medical Center in California, USA, examined the effects of nortriptyline and cognitive-behavioural therapy on smokers with and without a history of major depression. 199 smokers of 10+ cigarettes per day received nortriptyline or placebo for 12 weeks at an initial dose of 50mg, titrated up to 100 mg/day. Counselling began at week 4, and participants selected a

quit date at week 5. Self-reported abstinence rates at 1 year, verified by cotinine concentrations and carbon monoxide levels, were 31% for nortriptyline recipients and 21% for placebo recipients ($p < 0.05$). The positive effect of nortriptyline was observed regardless of a history of major depression. The researchers also found that nortriptyline recipients experienced a greater decrease in depressive symptoms and fatigue during the first week after quitting than placebo recipients.[18]

In a second study, Prochazka and his colleagues[19] also observed a significant benefit of nortriptyline over placebo for achieving nicotine abstinence among 214 smokers. In this double-blind study in which nortriptyline was tested in combination with a behavioural intervention, the cessation rate at 6 months for those who received nortriptyline was 14% (15/108) compared with 3% (3/106) among those who received placebo ($p = 0.003$) (table I).

#### 1.2.3 Moclobemide

Moclobemide is a monoamine amine oxidase (MAO) inhibitor, a class of antidepressant that is associated with enhanced dopamine activity.[37] The potential of MAO inhibitors as a smoking cessation aid was suggested by Fowler and colleagues,[38] who observed that levels of MAO-B in the brains of living smokers were 40% lower than levels measured in the brains of non-smokers or former smokers. Subsequently, another study reported that among dependent smokers, those with a past depression do not have lower MAO activities than those without such a history;[39] this finding suggests that smoking itself, and not depression, is associated with reduced MAO activities.[40]

To examine the efficacy of a MAO inhibitor to enhance smoking cessation, Berlin et al.[17] administered moclobemide or placebo, with minimal adjunctive clinical support, to a sample of 88 smokers in a parallel group design. 50 (57%) participants had a history of major depression. The investigators found a higher self-reported abstinence rate at the end of treatment, and 6 months later, among those who received moclobemide than among those who received the placebo (table I). Survival analysis indicated a significant difference in abstinence rates between moclobemide and placebo in the 6-month analysis ($p < 0.05$), and a difference that approached significance in the 12-month analysis ($p < 0.09$). However, when abstinence was biologically verified by serum cotinine concentrations, the differences between treatment conditions in both the 6- and 12- month analyses were no longer significant ($p < 0.13$ and $p < 0.12$, respectively). Further research to clarify this interesting, albeit ambiguous, result is warranted.

#### 1.2.4 Other Antidepressants

Trials of other antidepressants as smoking cessation aids have been reported with generally promising but as yet inconclusive results. Edwards and his colleagues[41] were the first group of researchers to test an antidepressant in a controlled smoking cessation trial. Their study of 19 smokers found encouraging results for doxepin as measured by a reduction in the number of cigarettes smoked as well as by a higher quit rate in doxepin recipients compared with those who received placebo. However, these findings have not undergone replication.

In addition, a large multi-site study of the SSRI fluoxetine has been conducted. While a first report of this trial did not indicate a measurable benefit of fluoxetine for smokers,[42] a post-hoc stratified analysis of those treated at the Brown University in Rhode Island, USA site found a positive fluoxetine effect at the higher dosage of 60 mg/day among smokers with high scores on the Hamilton Depression Scale at baseline.[43] Although fluoxetine does not seem to be efficacious for broad groups of smokers, it could exert a specific benefit for smokers who are susceptible to depression.

### 1.3 Anxiolytics

Smoking has long been interpreted as a form of 'stress management', or a means of reducing anxiety. As a result, a number of efforts have been made to investigate the potential efficacy of anti-anxiety drugs as an aid to smoking cessation. However, the benzodiazepine diazepam was not found to be superior to placebo in a 3-arm smoking cessation trial of 300 smokers conducted in China (although the

abstinence rate was significantly higher among the third arm of clonidine recipients).[44] In addition to the traditional sedatives (i.e. barbiturates and benzodiazepines), there have been trials of other sedative-like drugs, including both β-blockers and certain specific serotonin receptor drugs. The most widely tested of these compounds is buspirone, a non-sedating, non-addicting compound which became available in the 1980s for the treatment of anxiety.

#### 1.3.1 Buspirone

Recent research has suggested that buspirone is a selective agonist primarily for the serotonin 5-$HT_{1A}$ receptor, with lesser dopamine $D_2$ receptor activity.[45,46] It is indicated for the management of anxiety disorders or the short term relief of anxiety symptoms. Buspirone is pharmacologically unrelated to benzodiazepines, barbiturates or other potentially habituating sedative-hypnotic agents, and a withdrawal syndrome has not been observed in patients receiving buspirone for an extended period of time.[47] As with amfebutamone, buspirone is listed in Pregnancy Category B, although no well-controlled studies among pregnant women have been performed. Individuals who have taken buspirone report dizziness (12%), nausea (8%), headache (6%), nervousness (5%) and lightheadedness (3%) as the most common adverse effects.[48]

Early uncontrolled studies of buspirone as a smoking cessation agent had indicated that it decreased nicotine withdrawal symptoms and reduced the urge to smoke.[49] However, 4 placebo-controlled trials of buspirone did not find that its use resulted in significant relief of withdrawal symptoms compared with placebo.[20,50-52]

With regard to its effect on cessation, 5 placebo-controlled trials of buspirone have been reported.[20,50-53] Each study enrolled generally healthy volunteers who lacked underlying active mood disorders. Three of the trials reported a short term benefit of buspirone.[20,50,53] The duration of buspirone therapy ranged from 4 to 12 weeks with participants receiving 2 to 4 weeks of treatment prior to smoking cessation, and the average treatment dosage varied from 15 mg/day to 45 mg/day. Two trials reported adjunctive group behavioural treatment,[20,51] the 3 others did not.[50,52,53] The Profile of Mood States Anxiety/Tension scale was used to score anxiety levels in these studies.

Two of the trials stratified the sample by level of anxiety reported at baseline. In a double-blind study, Cinciripini et al.[20] randomised 101 community health volunteers to buspirone or placebo. The trial involved a 4-week pre-medication period with a target dosage of 45 mg/day (maximum dosage of 60 mg/day). Patients then received the medication for an additional 8 weeks in conjunction with 1 month of weekly behavioural therapy. Overall, there was no significant effect of buspirone (see table I). While the very high short term cessation rates observed in this study are quite remarkable, the 1-year follow-up witnessed a decline to levels more typically observed in smoking cessation trials (across the sample, 27% for buspirone, 20% for placebo).

Stratification of the sample by high or low anxiety score at baseline revealed a somewhat better effect of buspirone compared with placebo among those with high anxiety 1 month after the medication was withdrawn (88 *vs* 61%, $p < 0.05$) [table I]; however, this difference was not apparent at 3 months (16 *vs* 26%) or at 1 year (12 *vs* 23%) [table I]. The investigators concluded that buspirone enhanced short term cessation rates only in those smokers who were already generally anxious and then only for as long as they remained in treatment.[20]

Schneider and colleagues[52] stratified smokers post-hoc by level of anxiety in their analysis of buspirone efficacy. The 1-year survival analysis of data obtained from 100 smokers showed no differences overall in quit rate between active and placebo groups, and, unlike the study by Cinciripini et al.,[20] no interaction between high or low anxiety rating and drug condition. However, the anxiety scores reported by the participants overall and the cut-off scores indicating high or low anxiety were lower in this second study than those reported in the study of Cinciripini. Thus, it is possible that different populations of smokers were actually studied in the trials conducted by Cinciripini et al.[20]

and Schneider et al.,[52] which could possibly explain their inconsistent results.

At present, there is not sufficient evidence to support the general usefulness of buspirone as a smoking cessation aid; nevertheless, buspirone may be helpful for smokers with a high level of anxiety.

### 1.4 Opioid Antagonists

The notion that endogenous opioids are involved in the reinforcing properties of nicotine prompted researchers to test the efficacy of the opioid antagonists naltrexone and naloxone as smoking cessation aids. Naltrexone has been approved in the US for the treatment of alcohol dependence, based in part on findings from 2 placebo-controlled, 12-week trials of the drug (50 mg/day) in alcohol-dependent patients enrolled in alcohol treatment programmes.[54,55]

A number of studies on the effects of naltrexone or naloxone on smoking behaviour in humans have been conducted, with mixed results. Two studies of the shorter-acting opioid antagonist naloxone found that it reduced ad libitum smoking,[56,57] while 2 others failed to demonstrate this effect.[58,59] In a double-blind controlled trial, 14 smokers received naltrexone 50 mg/day or placebo on 4 days, separated by a 10-day washout period.[60] This study found that naltrexone reduced craving, urges to smoke, restlessness and increased eating, but did not exert an appreciable effect on smoking behaviour.

More recently 2 studies have reported findings from controlled trials of naltrexone in conjunction with behavioural counselling.[61,62] Neither study pointed to a significant effect of naltrexone, although one found that naltrexone was helpful for the subgroup of smokers with a history of major depression.[61] The placebo-controlled study by Covey et al.[61] examined the effect of naltrexone in 80 smokers. This study found a trend towards an advantage of naltrexone for smoking cessation relative to placebo. The end-of-treatment abstinence rate among the actively treated group was 46% compared with 26% among those who received placebo (OR = 2.5; $p < 0.10$). Stratified data analysis indicated that naltrexone enhanced abstinence at end-of-treatment among female smokers with past major depression, a subgroup which has been identified in other studies to be at high risk of smoking cessation failure. Of further interest, this specific benefit of naltrexone over placebo for women with past major depression persisted 6 months later (OR = 2.4, $p < 0.05$). Although this finding requires further testing, it offers some suggestive evidence for naltrexone as an alternative medication for helping smokers quit when administered in conditions similar to those in this study. These conditions included a dosage of 50 to 75 mg/day, supportive behavioural counselling, and a high level of motivation to quit.

It is worth noting that the researchers observed a significantly higher drop-out rate before quit day among the smokers who received naltrexone than those on placebo (25 *vs* 5%, $p < 0.02$). Those who were unable to tolerate the drug reported drowsiness, disorientation, spaciness, nausea, abdominal pain, and concentration problems. Among the 68 participants who persisted through to quit day, the proportions of those reporting adverse effects were higher among naltrexone than placebo recipients for concentration difficulty (79 *vs* 53%, $p < 0.03$) and dry mouth (61 *vs* 28%, $p < 0.01$). Whether further trials will confirm the observations from the small sample who participated in this study remains to be seen.

The study by Wong et al.[62] at the Mayo Clinic in Rochester, Minnesota in the US examined the effect of naltrexone administered alone or in combination with nicotine in 100 smokers. Naltrexone was administered at a daily dose of 50mg. At the end of a 12-week treatment, the abstinence rate among smokers who had received naltrexone alone was not appreciably different than in smokers who had received the placebo.

## 2. Non-Nicotine Medications Combined with Nicotine Replacement Therapy

Despite the ability of nicotine replacement agents to significantly improve smoking cessation rates compared with placebo, it had become evident that NRT still left the majority of its users unable to quit smok-

ing successfully. This modest outcome prompted a number of investigations into whether or not abstinence rates could be improved through the combination of theoretically promising non-nicotine pharmacotherapies and the nicotine substitutes. Rose et al.,[21] among others, have suggested that combining a nicotine receptor antagonist, such as mecamylamine, with the nicotine patch offers the advantage of insulating an individual from the reinforcing effect of the abused drug, while minimising withdrawal symptoms and adverse effects. The efficacy of mecamylamine, amfebutamone and oral dextrose when administered with the nicotine patch has been examined.

### 2.1 Mecamylamine

Mecamylamine had been marketed as an antihypertensive for many years before its discontinuation in 1996. Its action is to block the peripheral and CNS effects of nicotine. Although some laboratory studies have shown that smokers may attempt to override this nicotine blockade,[63,64] it has also been noted[65] that smokers are often highly motivated to comply with antagonist therapy. The therapeutic potential of mecamylamine for smoking cessation was suggested in an open-label trial of 14 smokers which found that mecamylamine at dosages averaging 26.7 mg/day substantially decreased nicotine withdrawal symptoms.[66] In this trial, 30% of participants stopped smoking completely within the 21-day study period. However, intolerable adverse effects including constipation and urinary retention resulted in a high (36%) drop-out rate. These researchers subsequently re-tested mecamylamine using a comparison administrations schedule of 3 weeks (high dose) versus 6 weeks (low dose).[67] Although the difference was not statistically significant, fewer smokers in the low dose group than the high dose group reported total cessation (22 *vs* 33%, respectively).

After showing that mecamylamine was well tolerated at lower dosages of 2.5 to 10 mg/day,[64] this research group evaluated its effects when administered at this lower dosage concurrently with the nicotine patch.[21] The investigators reasoned that by occupying specific receptors that would otherwise be acted upon by nicotine from smoking cigarettes, nicotine delivered by an alternative route and mecamylamine would work in concert to attenuate the rewarding effects of cigarette smoking, suppress withdrawal symptoms, and, in so doing, facilitate smoking abstinence. 48 smokers of at least 20 cigarettes/day over the last 2 years, aged 20 to 40 years, were enrolled. All received the nicotine patch, beginning at a dose of 21mg. Half received mecamylamine, the other half received placebo. The rate of continuous abstinence throughout the first 7 weeks after cessation was significantly higher in the mecamylamine group than in the placebo group (50 *vs* 16.7%, $p < 0.015$). The advantage of mecamylamine was still observed at the sixth month (37.5 *vs* 12.5%, $p < 0.05$) ) and twelfth month (37.5 *vs* 4.2%, $p < 0.004$) follow-up points (see table I).

This study also observed that mecamylamine attenuated negative affect, craving for cigarettes and increased appetite even before smoking cessation began. Furthermore, only 3 participants dropped out of the study, and adverse effects were minimal.

Research is being conducted to examine the effect of mecamylamine when administered through the same patch delivering nicotine. The tolerability and efficacy of mecamylamine for smokers older than 40 years of age also remains to be determined.

### 2.2 Oral Dextrose

This intervention is based on the premise that the urge to smoke arises in part from a mislabelling of a physiological 'desire' for carbohydrates.[68] West et al.[69] had reported that, compared with a placebo, dextrose tablets could reduce urges to smoke. This finding was replicated in a 4-week double-blind trial in 308 smokers to test the effects of oral dextrose 3g in combination with the nicotine patch on nicotine abstinence.[22] The observed end-of-treatment abstinence rates in the 4 study groups were as follows: dextrose + nicotine patch 38%, dextrose + placebo patch 35%, placebo tablet + nicotine patch 29%, placebo tablet + placebo patch 21% (table I). The authors found that dextrose tablets, whether alone or in combination with a 15mg nicotine patch,

produced significantly greater rates of abstinence ($p < 0.01$) than placebo tablets. There was no significant difference between the groups receiving dextrose or placebo in their ratings of the palatability of the tablets and, interestingly, in the amount of weight gained during the treatment period.

### 2.3 Amfebutamone

The efficacy of amfebutamone SR 300 mg/day administered with or without the nicotine patch (21 mg/day) was examined in 893 smokers who were treated at 4 sites.[23] The 4 treatment conditions evaluated were: amfebutamone SR + nicotine patch, amfebutamone SR + placebo patch, placebo tablet + nicotine patch, and placebo tablet + placebo patch. The study design was similar to the dose-response study by Hurt et al.[16] with the exception that 2 weeks were added to the treatment phase (9 weeks total) to allow for tapering of the patch: 14mg during week 8 and 7mg during week 9. The point-prevalence abstinence rates at 4 weeks were significantly higher in all 3 treatment groups (48%, 60% and 67%, respectively, for nicotine patch, amfebutamone SR, and amfebutamone SR + nicotine patch) than in the placebo group (34%; $p = 0.005$, $p < 0.001$; and $p < 0.001$, respectively; see table I). Thereafter, only amfebutamone SR and amfebutamone SR + nicotine patch were significantly different than placebo. At 12 months, the abstinence rates were 16% for placebo and 16% ($p = 0.84$), 30% ($p < 0.001$) and 36% ($p < 0.001$) for nicotine patch, amfebutamone SR, and amfebutamone SR + nicotine patch, respectively (table I). Both amfebutamone SR and the combination produced significantly higher abstinence rates than the nicotine patch ($p < 0.001$ for both). Although the abstinence rates were highest with the combination treatment, they were not significantly different from amfebutamone alone either in the short term or after 1 year.

As with the dose-response study,[16] amfebutamone treatment attenuated weight gain during treatment.[23] The most common adverse events were insomnia and headache.[23,36]

## 3. Comparative Efficacy of Non-Nicotine Medications for Smoking Cessation

For the purpose of this review, OR and 95% confidence intervals (CI) were calculated for individual studies using data provided in the published manuscripts, with the exception of 3 papers which reported the OR (Covey and Glassman;[24] Gourlay and Benowitz;[15] and Jorenby et al.[23] for short term data). For each study, the placebo group was used as the reference point (OR = 1.0). We did not include the doxepin study because of the small study sample (n = 20). Data from the buspirone trial by Schneider et al.[52] were also not included because the survival data presented therein did not permit us to extract quit rates at time points comparable to those of the other studies.

### 3.1 Non-Nicotine Medications Alone

Four agents – clonidine, nortriptyline, moclobemide and amfebutamone – were found to have significant efficacy at the end-of-treatment as demonstrated by 95% CI for the point estimates that exclude 1. Similarly, statistically significant long term efficacy was demonstrated for amfebutamone 300mg and 150mg,[16] and for clonidine.[15] Among these monotherapy trials, we find the evidence for amfebutamone the most impressive for a number of reasons: (i) the OR for a successful outcome in the study reported by Hurt et al.[16] are statistically significant both at the end of active treatment (7 weeks) as well as in the long term (52 weeks); (ii) a dose-response effect on the likelihood of cessation was demonstrated; and (iii) the trial was conducted in multiple study sites with a large total sample. The 2 studies of nortriptyline observed short term effects that were similar or greater in magnitude than in the amfebutamone dose-response study,[16] but the long term usefulness of the nortriptyline is less clear. In the study by Hall et al.[18] the OR for long term abstinence (64 weeks) fell short of the threshold of statistical significance (OR = 1.7, 95% CI = 0.9 to 3.3). In the trial reported by Prochazka et al.,[19] nortriptyline was highly beneficial (OR =

5.5) at the end of treatment but long term quit rates were not reported. For clonidine, the combined OR for short term[14] and for long term[15] abstinence were significant; however, these data were not derived from the same individuals.

### 3.2 Non-Nicotine Medications Used with Nicotine Replacement Therapy

The evidence from studies of non-nicotine medications administered in conjunction with nicotine patch or placebo patch indicates that for each drug, efficacy relative to placebo is increased when it is combined with nicotine replacement. In the mecamylamine + nicotine patch study by Rose and colleagues[21] in which all participants used the nicotine patch, those who also received mecamylamine had significantly higher abstinence rates than those who received the placebo. Interestingly, this advantage appeared to be stronger 1 year later. The mecamylamine + nicotine patch combination was associated with a lower 1-year reduction in the abstinence rate (from 50 to 38%) than was the placebo plus nicotine patch combination (from 17 to 4%). West and Willis[22] also observed an improved response with dextrose plus nicotine compared with the double-placebo arm (OR = 2.3). Oral dextrose with placebo patch was more effective than placebo alone (OR = 1.9); however, this difference did not reach statistical significance.

Based on the 12-month data from the amfebutamone SR + nicotine patch trial,[23] smokers who received the amfebutamone SR + nicotine patch combination were 3 times (OR = 3.0) more successful than those who received the placebo pill and the placebo patch. This effect (relative to placebo pill/patch) is greater than the efficacy of amfebutamone SR alone (OR = 2.3) or the nicotine patch alone (OR = 1.1) when compared to the placebo medications.

## 4. Comment

Advances in knowledge of the neurobiology of addiction to nicotine and other substances in tobacco are likely to provide the theoretical rationale for the development of additional pharmacotherapies for smoking cessation. For instance, evidence is increasing that nicotine exerts several different types of effects on the CNS. While nicotine mimics the actions of the brain transmitter acetylcholine, it also appears to exert an action on receptors that lie outside the cholinergic system,[70] and chronic nicotine administration has been found to result in decreased activity of mesoaccumbens dopamine neurons involved in the brain reward circuit.[71] In addition, although limited information is available at the present time, increased understanding of the contribution of specific genetic factors may also help develop novel treatments that target relevant neurotransmitter systems. As suggested by the recent data from twin smokers by Kendler et al.,[72] it is conceivable that different genetic factors are differentially linked to specific neurobiological changes involved in the progression from experimentation to regular smoking, than from those involved in nicotine withdrawal and maintenance.

Pharmacological research for the treatment of smoking might also involve trials that combine the advantages of different classes of drugs. Combination nicotine and non-nicotine treatments have already begun to be tested. As noted above, findings from studies using this augmentation approach do suggest a possible enhancement of quit rates compared with monotherapy. Another approach could involve the administration of more than one non-nicotine agent, such as when nicotine substitution is contraindicated or has produced adverse effects. The selection of these agents would depend on the patient's characteristics, including the outcome of previous attempts to quit, current and past mood states, and physical status. For example, for a highly addicted smoker with an affective disorder, combined pharmacotherapy might consist of amfebutamone, for its dopaminergic activity, augmented with an SSRI such as fluoxetine. For a highly addicted smoker with hypertension and whose inability to stop smoking appears to be related to persistent depression and irritability, the clinician may decide against either the nicotine patch or amfebutamone since both medications may exacerbate the hypertension, and prescribe clonidine for its ability to

reduce craving, as well as for its antihypertensive and anxyiolytic effects, in addition to an antidepressant.

Still another mode of non-nicotine therapy which has been examined in controlled trials is the use of sensory replacement strategies. Rose and Levin[73] have suggested that since smokers have learned to associate airway sensations with the psychoactive effect(s) of nicotine, the sensory replacement strategies may work effectively by disrupting the conditioned association between the sensory aspects of smoking (conditioned stimulus) and the pharmacological effects of smoking (putative unconscious stimulus). In support of this theory, the inhalation of black pepper oil (Rose et al.[74]) and aerosolised citric acid (Westman et al.[75]) has been found to reduce craving for cigarettes, and the citric acid inhaler was found to improve 10-week smoking abstinence rates over placebo inhaler.[75]

Like the nicotine substitute therapies developed before them,[7] the medications considered in this article have generally proved beneficial for improving nicotine abstinence in the short term. This good news is tempered, however, by the long term picture where typically half of short term quitters are found to return to smoking. As table I indicates, even in those trials in which the short term abstinence rate exceeds 50%, the large majority of patients had resumed smoking 6 months to 1 year later. It remains to be seen whether increasing the duration of pharmacotherapy, combination pharmacotherapy or other new drug treatments will change that trend. Finally, an important consideration is the role of effective smoking cessation counselling.[76,77] We have not focused attention on this aspect of the treatment process in this review, in part because of the differences in counselling methods employed in the studies as well as the general lack of adequate descriptions of this aspect of treatment. Nevertheless, such therapy appears integral to a comprehensive treatment approach, especially given the longstanding clinical wisdom that psychological processes are profoundly involved in maintaining tobacco use behaviour.[78] Indeed, a role for relapse prevention therapy in promoting abstinence has been demonstrated in the treatment of other addictions.[79,80] This would suggest that the application of pharmacotherapies will need to be entwined with behavioural and psychological strategies that facilitate a tobacco-free life style.

## 5. Summary and Speculations on Future Trends

1. Substantial evidence for the efficacy of amfebutamone in broad groups of smokers has been demonstrated. Other pharmacotherapies for which some positive findings have been reported include antidepressants (nortriptyline, doxepin, moclobemide), anxiolytics (buspirone), clonidine, an opiate antagonist (naltrexone), a nicotine antagonist (mecamylamine) and oral dextrose. Available data for buspirone, clonidine and naltrexone suggest that their efficacy may be limited to certain subgroups of smokers.

2. Combining one or more of these medications with NRTs may enhance treatment outcome.

3. Although short term quit rates in clinical trials with these agents have typically ranged from 40 to 60%, these results have been short-lived as abstinence rates consistently fall once drug treatment has terminated. These transient effects highlight the importance of relapse prevention and suggests a possible role for long term maintenance pharmacotherapy.

4. The complexity of nicotine addiction, often accompanied by comorbid depression or anxiety, argues for the need to tailor pharmacotherapeutic strategies to the symptom profiles of individual patients.

5. Future pharmacotherapeutic strategies may target neurotransmitters involved in developing initial drug dependence, as well as those linked to neuroadaptive changes characteristic of maintenance and withdrawal.

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