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Combination Treatment for Nicotine Dependence: State of the Science

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Abstract

Both nicotine replacement and sustained-release bupropion double the odds of achieving short- and moderate-term abstinence from nicotine. However, questions remain about the efficacy of combining pharmacotherapies. Our purposes were to review the evidence for (1) combined pharmacotherapy and (2) multimodal treatment combining pharmacotherapy and behavioral treatment and to recommend combinations of treatments to reduce nicotine dependence. Combining first-line pharmacotherapies with each other or with investigational drugs shows little benefit. In contrast, trials combining specific behavioral treatments with first-line pharmacotherapies show enhanced smoking cessation rates, but benefits are not seen in all populations. We recommend future directions for research, including better specification of behavioral components and further examination of the length and timing of treatment.

Keywords

nicotine dependence; smoking reduction; smoking cessation; bupropion; multimodal treatment

The strongest principle of growth lies in human choice.

George Eliot

Introduction

During the past 30 years, smoking has been identified as addictive, nicotine has been identified as the substance in tobacco smoke that produces dependency, and nicotine dependence has been accepted as an addictive disorder, with similar pharmacological and behavioral mechanisms of dependence to illicit drugs (Picciotto, 1998). The landmark U.S. Surgeon General's Report summarized the evidence supporting each of these concepts and galvanized public health scientists to address nicotine dependence with the best methods of science (DHHS, 1988). The health threats posed by smoking and by environmental tobacco smoke have been researched and enumerated. Smoking is now viewed as the number one public health threat. Nicotine dependence, sustained by smoking, causes over 430,000 unnecessary deaths annually in the United States. It is estimated that smoking directly causes 22% of all cardiovascular disease, 30% of all cancers, 70–90% of lung cancers, and 56–80% of respiratory diseases and contributes to excess morbidity and mortality in many other diseases (WHO, 2002). Nicotine dependence, when viewed as an entrenched addictive

disorder that is a profound public health threat, rather than a bad habit or weakness of the individual, became an appropriate target for treatment. In addition, the neurobiology of nicotine dependence, although not completely understood, has advanced considerably, providing impetus to medication development efforts to target different aspects of the mechanism of dependence.

Pharmacotherapies for Smoking Cessation

Quitting smoking is difficult because of the characteristic withdrawal syndrome resulting from nicotine abstinence, as well as the reinforcing properties of nicotine in the brain's reward system and the social and behavioral repertoire that accompanies nicotine administration (Picciotto, 1998; Benowitz, 1999; Gold and Herkov, 1998). One method to assist smokers to quit is to replace the nicotine derived from smoking with a safer route of administration, with planned tapering of nicotine maintenance after the smoking habit has been broken. It has been 2.5 decades since the first nicotine replacement product was developed to aid smokers to quit. Nicotine gum, providing transbuccally absorbed nicotine designed to replace cigarettes, showed early and consistent evidence of efficacy, increasing the odds of abstinence among smokers at 6 and 12 months post-treatment by 1.6–1.7 (Silagy et al., 2002). The nicotine replacement paradigm now extends to alternative dosing forms, including the nicotine transdermal patch, the nicotine nasal spray, and the nicotine inhaler. The effectiveness of all forms of NRT has been reviewed exhaustively. Recent reviews, including meta-analyses, have all concluded that NRT is safe and effective, with odds of successful quitting ranging from 1.7 to 2.2, depending on the form of NRT (Silagy et al., 2002; Fiore et al., 2000; Hughes et al., 1999; Karnath, 2002; Okuyemi et al., 2000; Peters and Morgan, 2002).

More recently, sustained-release bupropion, 150 mg. taken twice daily, has been evaluated and found to be either equivalent or slightly superior in efficacy to NRT (Jorenby, 2002; Richmond and Zwar, 2003). Sustained-release bupropion (Bupropion SR), marketed as Zyban for smoking cessation and Wellbutrin for treatment of depression, is a dopaminergic and noradrenergic agent that may increase the availability of neurotransmitters implicated in the reward system of the brain. It is posited to attenuate cravings and withdrawal symptoms, thus targeting the drive to avoid withdrawal that contributes to maintaining nicotine dependence. The specific pharmacology of bupropion has been reviewed previously (Balfour, 2001; Haustein, 2003; Hays and Ebbert, 2003; Holm and Spencer, 2000; Nardini, 2001; Steele, 2000). Bupropion provides an alternative to nicotine maintenance and is generally well tolerated with few side effects. Studies using bupropion SR for smoking cessation have found it particularly effective for subjects with prominent depressive symptoms or a history of depression. Bupropion SR has a slightly increased risk of seizures, making it inappropriate for those with diminished seizure thresholds, such as those with a history of seizure disorders, head trauma with loss of consciousness, or bulimia.

The evidence for the efficacy of NRT in all available forms and sustained-release bupropion is conclusive: these pharmacotherapies double the odds of achieving short-term and moderate-term abstinence from nicotine across the general population. These five agents (nicotine patch, nicotine inhaler, nicotine gum, nicotine nasal spray, and bupropion SR) are now considered first-line therapies and recommended for use for all dependent smokers (Fiore et al., 2000; Watts et al., 2002). Even in medically vulnerable groups including pregnant women and patients with cardiovascular disease and chronic obstructive pulmonary disease, researchers have recommended both types of first-line therapies when the alternative is continued smoking (Hays and Taylor, 2000; Koren, 2001; Oncken and Kranzler, 2003; Thomson and Rigotti, 2003; Wagena et al., 2003; Wiggers et al., 2003).

In addition, two medications are considered second-line agents with a higher rate of side effects but adequate evidence of efficacy (Fiore et al., 2000). Clonidine (brand name Catapres) is an alpha-adrenergic agonist typically used for treatment of hypertension that has also been used to reduce autonomic hyperactivity associated with abstinence syndromes in opiate and alcohol withdrawal. Clonidine has also been used to treat attention deficit hyperactivity disorder and tic disorders. It has been found particularly useful for female smokers and for those who become agitated and anxious when quitting smoking (Gourlay and Benowitz, 1995). Nortriptyline is a tricyclic antidepressant believed to reduce the dysphoria precipitated by the reduction of dopamine, norepinephrine, and serotonin during nicotine withdrawal. Studies have found it particularly useful for patients with histories of depression or who report prominent depressive symptoms during past quit attempts (Hall et al., 1998; Prochazka et al., 1998). However, like other tricyclic antidepressants, nortriptyline can induce unpleasant side effects, such as drowsiness, dizziness, orthostatic hypotension, constipation, dry mouth, weight gain, and potential for life-threatening cardiotoxicity in overdose. Because weight gain is a concern of many individuals when stopping smoking, this issue should be addressed prior to the cessation attempt.

Which Combined Treatments for Smoking Cessation are Effective?

Many questions remain about the best combinations of available pharmacotherapies. Does combining NRTs with each other or combining an NRT with bupropion result in additional benefit, and if so, how much? Can the efficacy of first-line pharmacotherapies be increased with behavioral treatment components? The purposes of this review were to (1) review the evidence for combinations of pharmacotherapy agents including investigational drugs, (2) review the evidence for multimodal treatment comprised of both combination pharmacotherapy and behavioral treatment, and (3) provide recommendations for combinations of treatments with the greatest efficacy to reduce nicotine dependence based on the state of the science.

Methods

We Searched for Articles Published in Peer-Reviewed Journals During the Decade Ending in 2003 by Using *PubMed* and *PsycInfo* Databases

Search terms included broad categories such as “*pharmacotherapy and nicotine dependence*,” “*nicotine dependence treatment*,” “*smoking cessation*,” as well as specific terms such as “*nicotine replacement*” and “*bupropion and smoking cessation*.” This initial search generated over 11,000 articles and was, therefore, narrowed to include terms such as “*randomized controlled trial*” and “*efficacy study*,” to preferentially select articles with greater experimental rigor. In addition, we reviewed over 24 previous reviews of pharmacotherapy for nicotine dependence to confirm that the basic efficacy of individual nicotine pharmacotherapies had been adequately reviewed and to verify that previous reviews did not focus primarily on combination treatments. To be included in this review, studies had to be published between 1993 and 2003 in a peer-reviewed journal in English, and report the results of a randomized controlled trial with at least a 6-month follow-up, the minimum length recommended for adequate interpretation of findings (Hughes et al., 2003; Pierce and Gilpin, 2003). Studies had to include at least one arm that was a combined treatment of, (1) a first-line pharmacotherapy paired with an investigational drug, (2) a first-line pharmacotherapy paired with a behavioral treatment, (3) two first-line pharmacotherapies paired with each other, or (4) an investigational drug with a behavioral treatment.

Results

Twenty-four studies met the inclusion criteria. Table 1 provides the authors, treatments tested, setting and samples, design and analytic methods, procedures, primary outcome measures, and main results of the 24 trials.

Combinations of First-Line Pharmacotherapies with Investigational Drugs

Five studies combined a first-line pharmacotherapy agent (either NRT or 300 mg bupropion SR) with investigational drugs. A study of the MAO-B inhibitor selegiline (brand name Eldepryl) found no significant differences among a selegiline plus patch group vs. placebo plus patch group on continuous abstinence rates (Biberman et al., 2003). Two studies of selective serotonin reuptake inhibitors (SSRIs) found no significant differences for those treated with nicotine inhaler and fluoxetine (sold under the brand name Prozac) vs. nicotine inhaler and placebo (Blondal et al., 1999), nor for those treated with nicotine patch and two different doses of paroxetine (sold under the brand name Paxil) vs. patch with oral placebo (Killen et al., 2000). One study pretreated smokers with mecamylamine (brand name Inversine), a nicotine antagonist thought to reduce the reinforcing effects of smoking, prior to smoking cessation treatment with nicotine patches. Although pretreatment with mecamylamine resulted in reduction of smoking behaviors and smoking satisfaction, there was no benefit of precessation mecamylamine detected by the 6-month follow-up (Rose et al., 1998). These studies suggest that little additional benefit is attained by adding MAO-B inhibitors, SSRIs, or nicotine antagonists to NRT. Further study should be undertaken to determine the potential benefit of mecamylamine in extinguishing reinforcement aspects of smoking.

Combinations of First-Line Therapies with Each Other

There were four studies of combinations of two first-line therapies. Bohadana and colleagues, in a study of two NRTs, compared nicotine inhalers plus nicotine patches to inhalers with placebo patches for 18–26 weeks of treatment (Bohadana et al., 2000). Although abstinence rates among the combination-treated group were consistently higher through a year, groups did not differ significantly after 3 months. Similar results were reported in a more recent study that reported superiority of the combined patch and spray at 6 weeks, with no difference between groups at 6 months (Croghan et al., 2003). Two studies examined combining bupropion-SR with nicotine patches. Treatment with bupropion alone or in combination with the nicotine patch resulted in higher 6- and 12-month cessation rates than patch or placebo conditions in a group of 467 patients who had failed to quit smoking in the first 3 weeks of treatment (Jamerson et al., 2001). In another study of smokers who did not initially respond to an 8-week course of NRT, Hurt and colleagues (2003) randomized smokers to an 8-week course of bupropion but found that only 3% who had failed NRT stopped smoking with bupropion, a rate not significantly different from placebo. It is possible that the contradictory findings of these two studies are due to differences in the definition of initial treatment failure being at 3 or 8 weeks of NRT. It is also possible that lack of cessation at 3 weeks is less predictive of eventual treatment failure, whereas persistence of smoking at 8 weeks is a better predictor. We were unable to find studies combining the use of the nicotine replacement patch and nicotine gum. In the area of combined first-line pharmacotherapies, the evidence base is too small to permit robust conclusions, but it does not yet appear promising.

Combination of First-Line Pharmacotherapies with Behavioral Treatments

Eleven studies evaluated the impact of both behavioral treatment components and first-line pharmacotherapy agents. Most of these found enhanced smoking cessation rates for the combined treatments. For example, bupropion SR combined with nicotine patch and 9

weekly counseling sessions in a media-recruited sample resulted in 48–67% cessation by 4 weeks with higher rates of cessation persisting through 12 months, favoring bupropion and combined treatment groups (Jorenby et al., 2003). Tønnesen and colleagues (2003) reported similar findings, with a doubling of abstinence at 12 months (21%) for a group receiving bupropion and 11 brief counseling sessions vs. placebo plus counseling (11%).

Several studies reported the results of combined pharmacotherapy plus counseling delivered by telephone. Macleod and colleagues (2003) found that five telephone counseling sessions enhanced 90-day abstinence at 6 months among smokers using nicotine patches to quit. Nineteen percent of the subjects who received only the nicotine patch had been abstinent for 90 days at the 6-month follow-up, whereas 28% of those receiving the patch plus telephone counseling had been abstinent for 90 days at 6 months. Similarly, Swan and colleagues (2003) reported that two doses of bupropion SR (150 mg vs. 300 mg) paired with a higher intensity telephone counseling program yielded higher cessation rates than the bupropion doses paired with low intensity telephone counseling, suggesting that response depended on dose of counseling rather than bupropion. In contrast, one study found that pharmacist-delivered counseling and health-educator telephone support yielded no additional benefit beyond NRT (Rolnick et al., 1997). These studies differed in that the telephone support in the last study was voluntary and educational, billed as a “hotline,” whereas the telephone support in the Macleod study was described as counseling and drew from empirically supported approaches to brief counseling such as solution focused therapy and motivational interviewing, and the telephone support in the Swan study included self-help materials, counseling, and follow-up by a counselor.

Molyneux and colleagues (2003) found that counseling plus nicotine replacement therapy chosen by the patient yielded higher 12-month abstinence rates for the combined group that were more than double the rates of counseling or usual care. Two studies evaluated nicotine patch treatment paired with 5 weeks of cognitive behavioral groups; both found that the patch plus counseling groups exceeded placebo patch plus counseling groups on 3- and 6-month abstinence (Richmond et al., 1994; Richmond et al., 1997). Simon and colleagues (2003) paired individual cognitive behavioral counseling with nicotine patch, and found the same pattern of results, favoring combined NRT and counseling.

Although most studies favored behavioral treatments added to pharmacotherapy, benefits are not seen in all populations. In a study of shipboard smoking cessation aided by NRT and bupropion and behavioral counseling, unusually low cessation rates were observed, which did not differ by condition (Swanson et al., 2003). In another “captive” population, Shoptaw and colleagues (2002) addressed smoking cessation among opiate-dependent smokers in methadone maintenance. They provided nicotine patch treatment alone, or with relapse prevention, contingency management, or both behavioral strategies. Only contingency management, in which smokers earned escalating monetary rewards for providing breath CO samples consistent with smoking abstinence, yielded higher abstinence during treatment, but this benefit faded once CM procedures ended. This study suggests that there was no additional benefit from two behavioral treatments beyond that provided by the nicotine replacement patches in an opioid-maintained population. It is likely that the unusual characteristics of these two samples resulted in findings that are quite divergent from the large literature using general population samples of smokers.

Taken together, these studies suggest that some forms of counseling, such as those based on principles of effective brief therapies, and using techniques of cognitive behavioral therapy can enhance the gains achieved with first-line pharmacotherapies for smoking cessation in general populations of smokers. The amount of benefit achieved by counseling alone can be estimated by examining the studies including counseling with a placebo medication. These

suggest that 6-month cessation rates of 11–17% can be achieved with multiple-session counseling, provided either in individual, group, or telephone formats. Although of some benefit, abstinence attained by counseling alone is much lower than the 22–40% 6 month abstinence rate attained by first-line pharmacotherapies. This suggests that in medically cleared patients, pharmacotherapy should always be initiated instead of counseling alone. Counseling as the sole intervention may provide some benefit for patients whose medical conditions prohibit either NRT or bupropion and provides additional benefit to these first-line pharmacotherapies in a combined treatment effort. However, further studies are needed to provide robust estimates of the maximum cessation rates attainable with current combination treatments.

Combining Pharmacotherapy with Behavioral Treatment

Four studies reported the results of trials investigating drugs for use in treating nicotine dependence in combination with behavioral treatments. Three studies tested antidepressants [two selective serotonin reuptake inhibitors (SSRIs) and one tricyclic], whereas the fourth tested clonidine and naltrexone. Results were inconsistent. A study of sertraline plus nine counseling sessions found no benefit (Covey et al., 2003). In contrast, a study of fluoxetine plus nine counseling sessions found an increased likelihood of smoking abstinence at 6 and 12 months in those who achieved higher serum fluoxetine levels (Hitsman et al., 2001), and a study of nortriptyline plus five counseling sessions found that the odds of smoking cessation increased fourfold in the nortriptyline-treated group (da Costa et al., 2002). The last study targeted Iranian male smokers with behavioral treatment combined with one of three pharmacotherapies and found that nicotine gum was superior to clonidine, which was superior to naltrexone (Ahmadi et al., 2003). The behavioral treatment in that study, “outreach counseling,” was not adequately described. The inconsistencies in these studies are expected given that they used agents that work on a wide variety of possible pathways of nicotine dependence. However, these studies also vary widely in the type of behavioral treatment used, duration of treatment, and in most, the behavioral treatment is inadequately described and fails to include a relevant description of the clinicians (training, experience, expertise, etc.) Because most of them do not provide adequate descriptions of the behavioral treatments, these studies are difficult to understand or replicate.

Summary and Discussion

Most Effective Combination Treatments

First-line pharmacotherapies, including all four forms of NRT, and bupropion SR, 150 mg. given twice daily, are effective and double the odds of smoking cessation in general samples of smokers. In combination with each other, smoking cessation rates do not appear to increase, but this literature is still underdeveloped. In combination with a variety of medications under investigation as therapeutics for treatment of nicotine dependence such as SSRIs, smoking cessation rates are not increased but may increase with mecamylamine pretreatment to reduce smoking pleasure. In combination with adequately described behavioral therapies, smoking cessation rates at 6 and 12 months are enhanced, although this benefit may not transfer to specific, more difficult populations such as opioid-maintained patients. Studies of investigational agents paired with behavioral treatments have produced mixed results, but fluoxetine shows some promise. Given the state of the science, we can recommend that combination treatment that includes both a first-line pharmacotherapy, and a well-specified behavioral treatment should be made available to every dependent smoker to provide the best chance of effective smoking cessation, with the specific combination chosen by the patient and clinician collaboratively.

How Widespread is the Use of Effective Treatment?

Although pharmacotherapy of nicotine dependence can be very effective, rates of actual use are important to estimate the possible benefit to the 16 million smokers who attempt to quit annually (Burton et al., 2000). A Centers for Disease Control and Prevention study of the use of pharmacologic treatment for nicotine dependence over a 14-year period ending in 1998 found that as each type of nicotine pharmacotherapy was introduced and made more available with over-the-counter (OTC) approval, quit attempts increased. Monthly quit attempts in the United States were estimated at 259,000 when nicotine patches were available by prescription only, increasing to 642,000 once both gum and patches were available OTC, and increasing again to 708,000 with the approval of bupropion SR (Burton et al., 2000). Unfortunately, most smokers attempting to quit still do not use pharmacotherapy (Burton et al., 2000), reducing their odds of success.

Barrier to Use of Effective Treatments

There are several barriers to treatment that reduce their universal use. A primary obstacle to treatment with NRTs or other pharmacotherapies for individuals may be cost. A monthly supply of nicotine, patches costs approximately \$55, whereas the monthly costs of nicotine inhalers, gum, or sprays can reach \$400 (DeGraff, 2002). The cost of bupropion SR under the brand name Zyban is approximately \$120 per month (DeGraff, 2002). Generic bupropion (not in sustained-release form) is available at lower costs, but its efficacy is not established, and there have been reports of lack of potency or toxicity with the generic form. Nortriptyline, a second-line agent, can be obtained for as little as \$6 per month (DeGraff, 2002). Although the cost of smoking a pack per day for a month can cost between \$70 and \$100, depending on brand and state taxes, smokers who buy cigarettes by the pack may view purchasing nicotine replacement as prohibitive because the cost is not spread over a month of days.

In addition to costs, availability, and accessibility of treatments may also play a role in their use. NRTs can be purchased over the counter, whereas bupropion, nortriptyline, and clonidine require prescriptions. With these medications the individual incurs costs associated with a doctor's visit to obtain a prescription. Furthermore, the inconvenience or anxiety of seeing a doctor and obtaining a prescription could be a deterrent to using these medications in nonresearch settings. In addition, few health plans cover the cost of pharmacotherapy and counseling, and providers may be inadequately prepared to provide state-of-the-science information to their patients (Schauffler et al., 2001).

Side effects (and perceptions of potential side effects) of various medications should be considered possible barriers to use of these agents in practice and research. Although most studies included in this review describe few severe adverse events, they describe many common minor adverse events. Side effect profiles of the various medications include skin irritation (at site of patch), dry mouth, nausea, dizziness, headaches, vivid and unusual dreams, insomnia, and sleep disturbances. Any of these side effects could serve as impetus for patients to discontinue or reduce adherence to treatment, particularly if they did not have a thorough understanding of the potential unpleasant effects before beginning the treatment.

Training Needs of Health Care Providers

To integrate pharmacotherapy of nicotine dependence effectively into the health service delivery system, health care providers, especially general practitioners, must be trained in several areas. First, providers should be trained to inquire about smoking behavior during routine visits. Some guidelines have been proposed, such as adding smoking as the fifth vital sign. This type of policy would have the effect of increasing the number of providers who routinely inquire about smoking. Once providers are asking questions on a regular basis,

patients who are smokers will be identified routinely and could be offered information or intervention. In addition to assessing smoking behaviors, providers should be educated thoroughly about the available first-line agents for smoking cessation, best practices for using these agents, and how to guide patients in making a choice. Furthermore, providers should be able to anticipate and respond to questions and concerns about the aforementioned side effects of these medications. Providers may be more comfortable holding conversations about change if they are trained in brief counseling paradigms that encourage eliciting the patient's knowledge or concerns, providing bits of evidence-based information, and eliciting the patient's reactions and plans once the information is provided (Rollnick et al., 1999).

Limitations of Current Research

There still exist a number of unanswered questions about combination nicotine replacement therapy, both with and without behavioral treatment. In part, these questions result from study design issues in existing research. Because most studies have not included a full factorial design, it is not yet possible to estimate how many more smokers would quit because of the additive effects of counseling and first-line pharmacotherapies. Further studies of combination treatments that dismantle these components would allow better estimates of the effect size of each treatment component. Additional difficulties in interpreting data from studies using single and combination NRT with and without behavioral treatment result from inconsistencies in length, timing, and dose of treatment. In studies using transdermal nicotine patches, 16- or 24-hour patches can be used (most recent research uses 24-hour patches), which can affect withdrawal symptoms and cessation rates. Furthermore, although 21-, 14-, and 7-mg nicotine patches are standard, researchers prescribe various doses in different ways depending on their specific criteria. Additional differences in duration of treatment with various agents exist, thus making comparisons difficult.

Future Directions for Research on Combination Treatments

Although existing research has begun to identify optimal combinations of pharmacotherapy and other interventions, the body of literature is small and would benefit from additional research providing more specificity. First, better specification of behavioral components is necessary. To evaluate behavioral treatments and design new treatment protocols with the necessary components, practitioners must be able to identify and understand the crucial variables. Although several studies refer to counseling interventions based on specific guidelines, others describe generic counseling treatment. Details of content, length, frequency, training of counselors, standardization of behavioral interventions, and evidence of adherence to the behavioral treatment, or intervention fidelity, should be included.

As mentioned before, inconsistencies in timing, dose, and duration of first-line therapies exist in current research. Therefore, further examination of the length, levels, and timing of treatment is necessary. Although most current treatment recommendations are for 3–6 months of treatment with the pharmacotherapy, it is possible that for some smokers, longer duration of treatment would provide additional benefits while remaining safe (Sims and Fiore, 2002). Future studies should include discussion of NRT strength, such as directly discussing the options of 16-hour nicotine replacement patches vs. 24-hour patches, as well as the optimal duration of NRT and other therapies. In addition, further investigation of pretreatment conditions is necessary to determine whether pretreatment motivation affects the results of NRT and whether prepharmacotherapy treatment introduction of behavioral treatment may be beneficial.

Few of the clinical trials reviewed discussed the level of adherence to the pharmacotherapy by their subjects. Although medications can only work if patients take them, nonadherence

to both chronic and acute regimens is common, and the same has been found for NRT (WHO, 2002). Future studies could clarify the impact of and reasons for nonadherence to first-line pharmacotherapies and behavioral treatment components by planning for their measurement in the design of research protocols.

Smoking reduction is another area to consider in future research. Although smoking cessation is the stated and ultimate goal of most studies, some researchers have included data about smoking reduction or have focused on smoking reduction as the goal (Etter et al., 2003; Etter et al., 2002; Wennike et al., 2003). Following the principles of harm reduction implemented in other areas of addiction treatment, smoking reduction may be a more viable and realistic goal for dependent smokers, and it facilitated smoking cessation despite it not being the goal in one study (Etter et al., 2002). Because smoking is such an intractable habit and the risks of smoking increase at higher levels of smoking, it may be prudent to consider reduction in the number of cigarettes as a primary, or at least intermediate, goal for some individuals.

Despite the availability of interventions that double the odds of successfully quitting, rates of smoking cessation using current methods are still low, with over 70% returning to smoking at 6- or 12-month follow-up. In addition, most smokers still do not use these effective methods during their quit attempts. Studies that identify effective methods to increase the use of available treatments by smokers are needed. Studies are needed, which provide evidence of efficacy of novel combinations of pharmacotherapies, behavior therapies, and other interventions, as well as population-specific and treatment-specific indications and contraindications for use.

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Biography

Karen S. Ingersoll is a clinical health psychologist and Associate Professor of Psychiatric Medicine at the University of Virginia. Her research and clinical interests focus on addictive behaviors in people with medical conditions.

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Glossary

Environmental
tobacco exposure

Smoke inhaled by someone other than the smoker: drugs not yet approved by the FDA being tested for efficacy or safety.

Motivational Interviewing	A counseling style using nondirective and directive techniques that seeks to enhance the individual's internal motivation for change; see Miller and Rollnick, 2002, <i>Motivational Interviewing: Preparing People to Change</i> . New York: Guilford Press.
Nicotine replacement therapies	Medications containing nicotine used to aid smokers to stop using combustible or chewed nicotine products.
Solution focused therapy	A brief therapy emphasizing a focus on actions and solutions rather than problems; see O'Connell and Palmer, 2003. <i>Handbook of Solution Focused Therapy</i> . London, Thousand Oaks Sage Publishers.
Telephone support	Counseling, advice, or feedback delivered in scheduled telephone calls from the counselor to the participant.

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Table 1

Randomized controlled trials of combination treatments for nicotine dependence with 6 month follow-up published between 1993 and 2003

Authors	Treatment tested	Setting/sample description/duration	Analytic methods	Results
Combinations of first-line pharmacotherapy plus investigational drugs				
Biberman et al., 2003	Selegiline plus nicotine patch vs. placebo plus patch	n = 109 Adult smokers who smoked at least 15 cigs/day in 3 community clinics in Tel Aviv 12-month follow-up	Chi-square and <i>t</i> -test to detect between-group baseline differences on demographic and smoking variables Fisher's exact test for continuous abstinence rates and adverse events ANOVA to analyze between-group differences in withdrawal symptoms	Continuous abstinence rates nonsignificantly higher in selegiline + patch group "Cravings" (at week 4) significantly lower in selegiline group
Blondal et al., 1999	Nicotine inhaler, fluoxetine, and supportive group therapy vs. nicotine inhaler, placebo and supportive group therapy	n = 100 Volunteers (≥10 cigs/day for preceding 3 years) in Reykjavik, Iceland 12-month follow-up	Kaplan-Meier survival analysis	No significant differences in continuous abstinence rates between fluoxetine-inhaler group and inhaler-placebo group
George et al., 2002	Compares bupropion SR with placebo combined with typical or atypical antipsychotics for smoking cessation in patients with schizophrenia	n = 32 Participants met DSM-IV criteria for schizophrenia or schizoaffective disorder and took typical or atypical antipsychotic medications 6-month follow-up	Kaplan-Meier survival analysis used to assess between-group differences in retention Chi-square analysis of smoking cessation outcomes Logistic regression to determine effects of medication Hierarchical linear modeling to assess whether rate of change varied due to medication	Trial end-point abstinence, 4-week continuous abstinence rates significantly higher in bupropion group No significant differences between groups at 6 months Abstinence rates significantly higher in group using atypical antipsychotics
Killen et al., 2000	3 doses of paroxetine (0, 20, and 40 mg) with nicotine transdermal patch on smoking abstinence	n = 224 Adults smoking ≥10 cigarettes/day 6-month follow-up	Logistic regression analysis used to test statistical significance of differences in abstinence among groups.	No statistically significant differences among groups
Rose et al., 1998	Precessation treatment with nicotine replacement patches, mecamylamine and minimal behavioral treatment	n = 80 Duke University V. A. Medical Center 4 groups of 20 participants. Ages 18–55, smoking ≥1 pack/day for at least 2 years 6-month follow-up	Kaplan-Meier nonparametric survival analysis to evaluate the effect of precessation mecamylamine and nicotine on abstinence ANOVA to compare baseline smoking history and mood variables between groups Repeated measures MANOVA to "examine potential mechanisms of action."	Nicotine + mecamylamine treatment reduced number of cigarettes most during precessation period Main effect of precessation mecamylamine highly significant ($p = .005$) Precessation nicotine patch had no significant effect on subsequent abstinence
Combination of 2 first-line pharmacotherapies				
Bohadana et al., 2000	Nicotine inhaler plus nicotine patch vs. nicotine inhaler and placebo patch	n = 400 French adults who smoked ≥10 cigs/day for ≥3 years, recruited by newspaper. 12-month follow-up	Chi-square and Fisher exact tests to analyze abstinence rates Parametric <i>t</i> -tests to compare continuous variables between groups. Mann-Whitney rank sum test for nonnormally distributed data.	Abstinence rates in group 1 consistently higher but only statistically significant up to week 12. 1-year survival analysis showed significant association between abstinence and inhaler plus patch

Authors	Treatment tested	Setting/sample description/duration	Analytic methods	Results
Croghan et al., 2003	Nicotine patch vs. nicotine spray vs. combination of patch and spray	n = 1384		Cessation rates for combination NRT (27%) at 6 weeks were superior to patch alone (21%) or spray alone (14%). Groups did not differ at 6 months.
Hurt et al., 2003	8 weeks of bupropion SR vs. placebo for smokers previously treated with 8 weeks' nicotine patch	n = 578 Adult smokers (not cancer patients) recruited through a cooperative of oncology practices	Analysis of point-prevalence cessation	31% achieved initial smoking abstinence; 28% of the bupropion SR group and 25% of the placebo group were abstinent at 6-month follow-up.
Jamerson et al., 2001	Bupropion SR, nicotine patch, combination of bupropion SR and nicotine patch, and placebo	n = 467 Patients who failed to stop smoking in the first 3 weeks of treatment 12-month follow-up	Chi-square analysis and ANOVA to test for baseline differences in demographics 2-tailed Fisher exact test for comparison of continuous cessation rates	Continued treatment with bupropion SR, alone or in combination with the nicotine patch, resulted in higher short and long term cessation rates than patch or placebo alone.
Combinations of first-line pharmacotherapy and behavioral treatment				
Swanson et al., 2003	Bupropion SR, nicotine patch, bupropion SR plus nicotine patch and counseling	n = 140 12-month follow-up	One-way ANOVA to compare groups on demographics for continuous data and onsample Chi-square for categorical variables and to compare abstinence patterns Change in smoking analyzed by general estimating equation approach to binary repeated measures data	Groups did not differ on continuous abstinence at 12 months. 6-month abstinence: 20% for patch, 5% for bupropion, 14% for patch and bupropion combined, and 16% for counseling. 12-month point prevalence abstinence rates were 20% for patch, 7% for bupropion, 27% for patch plus bupropion, and 47% for counseling
Jorenby et al., 2003	Bupropion SR, nicotine patch vs. bupropion SR and patch vs. oral placebo medications plus 9 brief weekly counseling sessions	n = 893 Adult smokers who smoked ≥ 15 cigs/day and were motivated to quit Exclusion criteria: depression; alcohol or substance abuse in past year; use of psychoactive drugs; prior use of bupropion 12-month follow-up	Chi-square and ANOVA to detect baseline differences among groups All tests two-sided and had alpha level of .05 Logistic regression to determine pairwise differences in abstinence rates. Kaplan-Meier to analyze difference in rates of continuous abstinence Composite scores for withdrawal symptoms.	Point prevalence rates at 4 weeks were significantly higher in three treatment groups than in placebo group After that point, only bupropion and combination groups had significantly higher point prevalence rates Continuous abstinence rates higher in all three treatment groups than in placebo group
Macleod et al., 2003	Telephone counseling and nicotine replacement patch vs. patch alone	n = 854 New South Wales adults smoking 10 + cigarettes per day recruited by		Telephone counseling significantly enhanced quit rates attained with

Authors	Treatment tested	Setting/sample description/duration	Analytic methods	Results
		newspaper advertisements 6-month follow-up		nicotine replacement patches.
Molyneux et al., 2002	Counseling with nicotine replacement therapy vs. usual care	n = 274 Hospitalized adult patients 12-month follow-up	Chi-square and risk ratios with 95% CI to compare abstinence and post hoc pairwise comparisons Cig. consumption compared between groups by using Kruskal-Wallis nonparametric test. Post hoc pairwise comparisons done with Mann-Whitney U-test	Rates of validated abstinence were higher in the NRT plus counseling group at all time points, whereas counseling alone and usual care did not differ.
Richmond et al., 1997	Nicotine patch and CBT group intervention	n = 305 Hospital-based outpatients in Sydney. 6-month follow-up	Chi-square and <i>t</i> -tests	Smoking cessation rates of the nicotine patch group were more than double the placebo group
Richmond et al., 1994	Nicotine patch and cognitive behavioral group treatment on smoking cessation	n = 313 Hospital-based outpatient adult smokers recruited from Sydney. Mean cig/day: 29 6-month follow-up	Chi-square and <i>t</i> -tests Predictors of outcomes analyzed by logistic regression using Wald statistic	Nicotine patch group had higher rates than placebo group of biochemically confirmed abstinence at 3 months and 6 months and higher rates of 6 months' continuous abstinence.
Rolnick et al., 1997	Combination treatment of NRT (patch) and pharmacist-delivered telephone support	n = 509 Large Midwestern HMO 18–65 year olds, ≥ 20 cigs/day who were motivated to quit. 12-month follow-up	Information not provided	No significant between-group differences: 20% of participants in all groups were smoke-free after 12-months.
Simon et al., 2003	Cognitive-behavioral intervention with nicotine patch vs. minimal counseling plus patch	n = 223 Mostly male, California Veterans' Administration patients who were long-term smokers 12-month follow-up		Self-reported quit rates were higher among intervention than comparison group. 12-month validated quit rate was 29% among intensive intervention and 20% among minimal intervention group.
Swan et al., 2003	Two doses of bupropion SR in combination with minimal and higher intensity behavioral interventions	n = 1524 Adult smokers in large health system in Seattle 12-month follow-up	Chi-square and ANOVA for overall group differences Logistic regression analysis to relate dose/ intensity of counseling intervention to smoking outcome	Nonsmoking rates at 12-months for four treatment groups highest in 300 mg bupropion + high intensity intervention and 150 mg + minimal intervention
Shoptaw et al., 2002	Nicotine replacement patch with relapse prevention (RP) vs. Patch + contingency management (CM) in methadone-maintained patients	n = 175 Methadone-maintained smokers in Los Angeles, smoking 10+ cigarettes per day 12-month follow-up	Longitudinal models, including normal mixed-effects models for continuous measures and generalized linear mixed models for categorical measures	The CM group showed higher smoking abstinence during treatment, but there were no differences between groups at follow-ups. There was no long term benefit to adding psychosocial interventions to NRT in this opiate-dependent sample.

Authors	Treatment tested	Setting/sample description/duration	Analytic methods	Results
Tønnesen et al., 2003	Bupropion SR, placebo, and	n = 707 26 centers in Norway, Sweden, Denmark, the Netherlands, France, South Africa, Australia and New Zealand 12-month follow-up	Continuous abstinence for weeks 4–7: Exact test stratified by country Point prevalence abstinence: exact test	Continuous abstinence month 12: 21% in bupropion group; 11% in placebo group Point prevalence rates at 52 weeks: 28% for bupropion group; 14% for placebo group
Combinations of behavioral treatment with a drug under investigation for treatment of nicotine dependence				
Covey et al., 2002	Sertraline and nine sessions of individual counseling vs. placebo plus counseling	n = 134 New York smokers (≥ 20 cigs/day) with a history of major depression (at least 6 months' remission) 6-month follow-up	Chi-square and <i>t</i> -tests to detect between-group differences General liner model procedure in SPSS 10.0	End of treatment and 6-month abstinence rates did not differ between groups.
Hitsman et al., 2001	Nine-session behavioral treatment plus fluoxetine vs. placebo plus counseling	n = 989 Non-depressed smokers from 16 sites 12-month follow-up	Logistic regression by means of three-step process to model outcomes of abstinence, smoking, and treatment dropout	Higher blood fluoxetine levels predicted a decreased likelihood of dropping out of behavioral therapy and increased likelihood of abstinence at 6- and 12-months,
da Costa et al., 2002	75 mg/day nortriptyline and 5-week group behavioral treatment vs. placebo plus behavioral treatment	n = 144 Adult (majority female) Brazilian smokers not currently taking antidepressants, benzodiazepines, or antipsychotics 6-month follow-up	Chi-square and <i>t</i> -tests Multiple logistic regression Significance of final model assessed using Hosmer-Lemeshow test.	At 6 months, 21% of nortriptyline abstinent vs. 5% placebo group
Ahmadi et al., 2003	Nicotine gum vs. clonidine vs. naltrexone, all with outreach counseling	n = 171 Nicotine-dependent Iranian men seeking treatment 6-month follow-up	Chi-square and two-sided <i>t</i> -tests to detect differences between groups	6-month abstinence rates: 37% for nicotine gum, 19% for clonidine, and 5% for naltrexone