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Combination Pharmacotherapy for Stopping Smoking: What Advantages Does it Offer?

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Abstract

Globally, tobacco kills almost 5 million people around the world annually. Seven first-line pharmacotherapies are currently available and recommended by the USPHS Clinical Practice Guideline for treating tobacco dependence, all of which have been proven to be effective for increasing tobacco abstinence rates when used as monotherapy. However, not all smokers are able to quit with single-drug therapy. Some smokers may benefit from combination therapy which includes the simultaneous use of different nicotine replacement therapies (NRTs) or medications with different mechanisms of action (e.g., NRT and bupropion). Combination therapy with different types of NRT may provide a therapeutic advantage by increasing serum nicotine concentrations, and combination therapy with different drugs may capitalize on synergy obtained from two different mechanisms of action. However, controversy exists regarding this approach. Available data suggests that combination therapy may increase abstinence rates compared to monotherapy. However, the cost-effectiveness of this approach **has not clearly been demonstrated**.

1. Introduction

The tobacco epidemic claims 4.9 million lives globally each year with an expected 10 million annual deaths by 2020.[1] Around the globe, 1.3 billion people are tobacco smokers over one-half of whom will die prematurely from a tobacco-related illness.

Nicotine is the addictive substance in tobacco and is the driver for compulsive tobacco use.[2] Drug addictiveness is, in part, related to how rapidly it reaches the central nervous system, and the inhalation of smoke from combusted tobacco is the quickest way to deliver nicotine to the brain. Nicotine interacts with neural networks involved in producing "reward." Specifically, nicotine is associated with the release of the neurotransmitter dopamine in the mesolimbic system of the brain which is involved in the positive reinforcement of addictive drugs.[3]

Stopping smoking is associated with significant health benefits. Compared with continuing smokers, former smokers have longer survival and smokers who quit before 50 years of age have one-half the risk of dying in the next 15 years.[4] The risk of death from any cause returns to that of a person who never smoked after 10 to 15 years of smoking abstinence.[4]

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2. Tobacco Dependence Treatment Model

Approximately 70% to 80% of smokers want to stop smoking and about **44%** attempt to quit each year, most often on their own.[5] However, 95% of self-initiated efforts are unsuccessful at producing smoking abstinence rates at one year.[5] Many smokers seek and require treatment to achieve long-term tobacco abstinence.

The United States Public Health Service (USPHS) Clinical Practice Guideline *Treating Tobacco Use and Dependence* concluded that strong evidence supported the use of both behavioral and pharmacologic interventions for increasing tobacco abstinence rates. The USPHS recommended the use of two types of behavioral counseling which have been consistently shown to increase smoking abstinence rates: (1) providing practical counseling such as problem-solving, and skills training; and (2) providing support during a tobacco users' direct contact with a clinician.[5] In addition to behavioral counseling, every patient should be offered pharmacotherapy unless a contraindication exists.

Pharmacotherapy is a cornerstone of tobacco dependence treatment. Seven "first-line" pharmacotherapies are currently available and recommended by the USPHS Clinical Practice Guideline for treating tobacco dependence: five nicotine replacement therapies (i.e., patch, gum, lozenge, inhaler and nasal spray), and two non nicotine medications: bupropion sustained-release (SR) and varenicline. "Second-line" medications include clonidine and nortriptyline **which are not FDA-approved for smoking cessation**. First-line medications should be selected initially because of their well-reported efficacy and favorable side effect profiles.

Among the currently available pharmacotherapies, varenicline appears to be associated with the highest long-term smoking abstinence rates. Large clinical trials have demonstrated the superiority of varenicline over bupropion SR for increasing tobacco abstinence rates among cigarette smokers.[6, 7] Varenicline also appears to be superior to NRT.[8-10]

3. Limitations of Monotherapy

Each of the first- and second-line medications have evidence of efficacy for treating tobacco dependence when given as monotherapy.[5] However, with all first line-therapies one-half or more of smokers are smoking at three months and more than two-thirds are smoking by one year. Furthermore, many tobacco smokers, especially heavy users, experience significant withdrawal symptoms while on the maximum recommended doses of these medications. Opportunity exists to increase smoking abstinence rates and decrease withdrawal symptoms by using combinations of pharmacotherapies that have been proven to be effective as monotherapies.

4. General Principles of Combination Pharmacotherapy

Two principal types of combination pharmacotherapy have been used and evaluated for increasing smoking abstinence rates among cigarette smokers: 1) therapy with different forms of nicotine replacement therapy (NRT) and different pharmacokinetic profiles [e.g., nicotine patch + nicotine gum]; or 2) therapy with two drugs that have different therapeutic targets such as non nicotine medications (e.g., bupropion SR) and NRT.

Combination therapy with two different drugs provides the opportunity to gain therapeutic synergism by using medications with distinct mechanisms of action or therapeutic properties. For example, the combination of varenicline and bupropion SR combines the efficacy of varenicline with the ability of bupropion SR to reduce post-cessation weight gain.[11, 12] Combining different forms of NRT provides a stable baseline nicotine level

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from the sustained release NRT (i.e., nicotine patch) with the opportunity for intermittent increases in the nicotine level from immediate-release NRT (nicotine gum, lozenge, inhaler or nasal spray) in response to withdrawal symptoms.

Combination pharmacotherapy remains controversial and underutilized because only the combination of bupropion SR + nicotine patch has been approved by the FDA for smoking cessation.

5. Combination Nicotine Replacement Therapy (NRT)

NRT does not deliver nicotine as rapidly as a cigarette, and nicotine blood concentrations obtained from other tobacco products (i.e., smokeless tobacco, cigars or pipes) is higher than can be achieved from NRT at standard doses. Initial smoking abstinence is often not achieved with NRT due to, in part, to inadequate nicotine "replacement" (i.e., achievement of venous nicotine concentrations with NRT comparable to those achieved when using tobacco *ad lib*).[13] As a consequence, tobacco users who achieve initial tobacco abstinence with NRT have an increased risk for relapse due to cravings and withdrawal that are inadequately treated as a consequence of nicotine under-replacement. However, the effect may not all be related to the higher serum nicotine concentrations achieved. For example, studies of higher dose nicotine patch therapy have not consistently demonstrated increased tobacco abstinence rates compared to standard dose patch therapy.[14] Instead, efficacy may be related to the timing or form in which the NRT is delivered

The two types of combination NRT that have been described are sequential and concurrent. Sequential therapy can theoretically provide initial stable nicotine dosing to achieve abstinence (i.e., nicotine patch) and then intermittent *ad lib* dosing to prevent relapse.[15] However, little data exists to support sequential therapy.

Relatively more data exists regarding the simultaneous use of multiple NRTs (i.e., concurrent therapy). Concurrent NRT therapy allows for the delivery of nicotine passively with long-acting NRT (i.e., nicotine patch) and for the active *ad lib* administration of short-acting NRT (i.e., gum, lozenge, inhaler, and nasal spray). This combination provides the advantages of higher treatment adherence with the nicotine patch[16] and the empowering of smokers to deal with acute cravings and withdrawal symptoms through self-administration of short-acting NRT. Combination NRT also provides the opportunity to achieve higher serum nicotine concentrations which **may** translate into improved treatment efficacy and withdrawal symptom relief and, ultimately, improved treatment efficacy. Despite the inclusion of combination pharmacotherapy in the 2008 USPHS Guidelines, many clinicians and pharmacists are reluctant to recommend or prescribe doses that are not recommended on product labels.

5.1. Efficacy

Studies evaluating the combination of the nicotine patch + nicotine gum have demonstrated that the combination is superior to monotherapy for increasing smoking abstinence rates **at** 12[17, 18] and 24 weeks.[18] Combination therapy is also associated with higher salivary cotinine concentrations and lower withdrawal scores.[19]

Combination therapy with the nicotine patch + nasal spray has been investigated. In an open-label trial of 1384 smokers randomized to nicotine patch therapy + nasal spray or either therapy alone, combination therapy was associated with significantly higher smoking abstinence rates at 6 weeks compared with either monotherapy.[20] In a placebo-controlled clinical trial, 237 subjects were randomized to the 15 mg nicotine patch with tapering for 5 months + nasal spray for up to 1 year or the nicotine patch + placebo. The nicotine patch +

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nicotine nasal spray was superior to nicotine patch + placebo nasal spray at both short (6 weeks & 3 months) and long-term (12 months) follow-up.[21]

Combination therapy with the nicotine patch + inhaler has also been investigated. In a placebo-controlled randomized trial, 400 subjects were randomized to the 15 mg/16 hour nicotine patch + nicotine inhaler (group 1) or placebo patch + nicotine inhaler (group 2).[22] Significantly higher smoking abstinence rates were observed with the nicotine patch + inhaler at 6 and 12 weeks compared to the inhaler alone. Combination therapy was also associated with higher levels of nicotine replacement and with less tobacco withdrawal.

In a large effectiveness study in the primary care setting, 1346 patients were randomized to bupropion SR, lozenge, patch, patch + lozenge, or bupropion SR + lozenge.[23] The nicotine patch + lozenge was observed to be superior to patch monotherapy.

In a systematic review of NRT for stopping smoking, seven studies including over 3200 subjects evaluating combination NRT were identified. Combination NRT significantly increased long-term (≥ 6 months) smoking abstinence rates compared to single NRT or no NRT (Risk ratio 1.35; 95% CI: 1.11-1.63).[14] The strength of this effect was similar when removing the study with the no-NRT control condition.

5.2. Safety & Tolerability

In general, combination NRT is well-tolerated and side effects are consistent with the anticipated side effects of each agent alone. Specifically, studies have not observed an increase risk of nicotine toxicity with combination therapy.

6. Combination Therapy with Non Nicotine Pharmacotherapy & NRT

Studies investigating the efficacy of combination therapy with non nicotine drugs have evaluated bupropion SR and nortriptyline in combination with NRT.

6.1. Bupropion SR + NRT

In a trial of 1504 smokers, subjects were randomized to 1 of 6 conditions: 1) nicotine lozenge (2 or 4 mg); 2) nicotine patch (21 mg/d with taper); 3) bupropion SR (300 mg/d); 4) nicotine patch + nicotine lozenge; 5) bupropion SR + nicotine lozenge; or 6) placebo.[24] At 6-months, only the nicotine patch + nicotine lozenge arm was associated with significantly higher smoking abstinence rates than placebo.

In a multicenter, double-blind, placebo-controlled study, 893 cigarette smokers were randomized to four groups: 1) bupropion SR (titrated over one week to 300 mg/d); 2) nicotine patch (21 mg/d with taper); 3) bupropion SR + nicotine patch; or 4) placebo.[12] Treatment consisted of 9 weeks of bupropion SR therapy and 8 weeks of nicotine patch therapy. Continuous smoking abstinence rates over 12 months were higher in all three active-treatment groups than in the placebo group. Although bupropion + nicotine patch was not observed to be associated with significantly higher smoking abstinence rates than bupropion alone, smoking abstinence rates were higher in the bupropion SR + patch group compared to the nicotine patch group. However, in a study enrolling 1700 smokers, combination therapy with bupropion SR + nicotine inhaler was observed to be superior to either agent alone.[25] In the large effectiveness trial in primary care, bupropion SR + lozenge was observed to be superior to all monotherapies (i.e., lozenge, patch, bupropion SR).[23]

Combination therapy with bupropion + NRT has been evaluated in cigarette smokers with co-morbid schizophrenia. In a placebo-controlled trial randomizing 58 patients to 10 weeks

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of bupropion SR (300 mg/d) + nicotine patch (21 mg/d) or placebo + nicotine patch, combination therapy increased continuous smoking abstinence rates for days 43 to 70 compared to monotherapy.[26] Combination therapy was not noted to increase positive or negative symptoms of schizophrenia in either study.

In a study among alcoholics enrolled in a treatment program, the addition of bupropion SR (300 mg/d) to the nicotine patch (21 mg/d with taper) did not increase smoking abstinence rates compared to the patch alone.[27] However, alcoholic smokers may be more severely tobacco dependent than their non-alcoholic counterparts and may have more difficulty achieving long-term smoking abstinence.[28]

Two randomized trials have evaluated the efficacy of three pharmacotherapeutic agents compared to either one or two NRTs. In a placebo-controlled study evaluating the addition of bupropion SR (300 mg/d) to the nicotine patch (21 mg/d with taper), nicotine gum (2 mg), and cognitive behavioral therapy among 51 patients, the addition of bupropion SR increased the primary outcome of smoking reduction (≥ 50%) at weeks 12 and 24 and continuous smoking abstinence at week 8.[29] In a study evaluating the effect of triple therapy, 127 smokers were randomized to the nicotine patch (10-week tapering course) or the combination of the nicotine patch, nicotine inhaler, and bupropion SR *ad lib*.[30] Combination therapy significantly increased smoking abstinence rates at 26 weeks and increased the median time to smoking relapse. However, blinding was not used which may have led to an overestimation of the treatment effect in the combination therapy group.

In general, the published literature suggests that combination therapy with bupropion SR and NRT increases short-term smoking abstinence rates. The USPSH Guideline meta-analysis suggests that a non significant trend exists for bupropion SR + nicotine patch to increase long term (≥ 6 months) smoking abstinence rates compared with nicotine patch alone [odds ratio (OR) 1.3; 95% CI: 1.0-1.8].[5]

6.2. Nortriptyline + NRT

Data regarding increased efficacy with combination therapy using nortriptyline and NRT compared to monotherapy has been conflicting. In a study of 901 patients randomized to active or placebo nortriptyline (up to 75 mg per day) and allowed to pick their own NRT, the effect of the combination was less than either pharmacotherapy alone with no enhanced effect on withdrawal symptoms.[31] However, in a randomized, placebo-controlled study of 158 smokers randomized to nortriptyline (up to 75 mg per day) + nicotine patch (21 mg/d), combination therapy significantly increased smoking abstinence rates at 6 months compared to monotherapy at 6 months.[32] A meta-analysis of studies evaluating nortriptyline + NRT compared to NRT suggests that there is a non significant trend toward increased smoking abstinence with combination therapy (OR 1.29; 95% CI: 0.97-1.72).[33]

6.3. Varenicline + Bupropion SR

We have conducted a single-arm, open-label pilot study of the combination of varenicline (titrated to 1 mg twice daily) and bupropion SR (titrated to 150 mg/d twice daily).[34] Thirty-eight smokers with a mean age of 49.1 ± 12.4 years who smoked an average of 19.9 ± 7.8 cigarettes per day for 30 ± 12.3 years were enrolled. Subjects received varenicline and bupropion SR for a total of 12 weeks along with behavioral therapy. Seven-day biochemically-confirmed point prevalence smoking abstinence rates were 71% (95% CI: 54-85%) at 3 months and 58% (95% CI: 41-74%) at 6 months. Mean ± SD weight change during the medication phase among smoking abstinent subjects was 1.6 ± 2.4 kg. For both medications, 74% of subjects took ≥ 90% of the prescribed doses. No safety concerns were identified in subjects taking the combination treatment. We concluded that combination

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therapy with varenicline and bupropion SR may be effective for increasing smoking abstinence rates above that observed with monotherapy. Larger, randomized trials to investigate this hypothesis are currently underway (clinicaltrials.gov NCT00935818)

6.4. Varenicline + NRT

Varenicline is a partial agonist that binds with high affinity and selectivity at the α4β2 neuronal nicotinic acetylcholine receptors.[35] **Data from a pharmacokinetic study** has documented that among smokers not instructed to quit who continued to smoke while taking varenicline, varenicline was associated with a 60-80% (N = 44) reduction in the mean number of cigarettes smoked within 2 to 4 days of initiation accompanied by a reduction in the mean plasma nicotine and cotinine concentrations.[36] This has led us to the hypotheses that: 1) varenicline does not completely saturate nicotinic acetylcholine receptors leading to incomplete “reward” response and incomplete blockade of continuing smoking reinforcement; and/or 2) varenicline incompletely replaces the dopaminergic effect of smoking leading to a continued craving to smoke. We considered, therefore, that some smokers may need NRT in addition to varenicline to reduce withdrawal and urges to smoke and allow smokers to achieve complete abstinence. Furthermore, since varenicline is an oral medication taken twice daily, it does not allow for moment-to-moment treatment of urges to smoke associated with internal and external triggers which can be addressed with an *ad lib* nicotine product.

Furthermore, in certain clinical circumstances, such as hospitalization or inpatient treatment programs, forced smoking abstinence may occur. The use of varenicline as monotherapy may be associated with significant patient discomfort from withdrawal since steady-state plasma concentrations of varenicline are achieved after four days.[37] In these situations, the use of NRT during the first several days makes sense clinically to relieve nicotine withdrawal and tobacco craving. We have extensive experience with combination therapy using varenicline + NRT in our 8-day residential (inpatient) treatment program at the Nicotine Dependence Center (NDC) at Mayo Clinic.[37] We use NRT to provide withdrawal symptom relief as smokers are being titrated up on varenicline. We have observed no increase in adverse effects compared to smokers who were treated in the same program prior to the release of varenicline. However, the subjects in this study were medically screened and resided in a closely monitored environment. Also, adverse events reports were derived from the clinical notes and not systematically collected. Therefore, results from this study may not be generalizable to other patient patient populations and should be interpreted with caution.

6.5. Safety & Tolerability

Although capitalizing on different mechanisms of action to increase therapeutic efficacy, combination therapy imparts the adverse effect liability of both medications. However, the evidence does not suggest that this effect is more than additive. In the study investigating five different therapies including the combination of bupropion SR + NRT, 32 serious adverse events were observed during the 6-month period following the target quit date.[24] However, only a hospitalization for seizures was adjudicated as possibly related to study medication. Seizures are a potential adverse effect of bupropion which the participant was taking at the time of the seizure. For patients receiving bupropion, the seizure rate is 0.1% (1/1000) in smokers with no seizure history nor past serious head trauma or structural central nervous system abnormality. In our varenicline + bupropion SR combination pilot, the most common side effects were sleep disturbance (26%) and nausea (24%).[37] Importantly, we did not observe an increase in depressive symptoms and no subjects reported suicidal ideation. With nortriptyline, an increased incidence of dry mouth and constipation but reduced anxiety and depression are observed.[31] In our study of

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combination therapy with varenicline + NRT, we observed that combination therapy was generally well-tolerated, and the observed adverse events of medication therapy in our clinical sample did not exceed that observed in the cohort of residential patients not receiving varenicline.[37]

7. Cost-Effectiveness

Cost is an important consideration when prescribing any therapy for the treatment of tobacco dependence. The cost-effectiveness of counseling and monotherapy has been demonstrated in Canada, France, Spain, Switzerland, the United States, and the United Kingdom.[38]

In order to determine incremental costs per quit with combination therapy, we analyzed data from the USPHS guideline.[5] Incremental costs per quit can be calculated by dividing the difference in treatment costs between comparison groups by the difference in the point-prevalence long-term quit rates.[39] For long-term patch therapy (> 14 weeks) + *ad lib* nicotine gum or nicotine nasal spray, the additional cost per quit compared to the nicotine patch alone is the price of 14 weeks of the nicotine nasal spray (~$5/day for 12 doses × 14 weeks = $490) divided by the difference in long-term abstinence rates (36.5%-23.7% = 12.8%) which equals approximately $3828. The incremental cost per quit for nicotine gum is similar. For bupropion SR (10 weeks) + nicotine patch, the incremental cost per quit is approximately $3054 compared to the nicotine patch alone. For the nicotine inhaler (assume average of 6 cartridges per day for 6 weeks) + the nicotine patch compared to the nicotine patch alone, the incremental costs per quit is $10500. The incremental costs for the nicotine nasal spray and bupropion SR compare favorably with the incremental costs of adding the nicotine patch to counseling ($8271/quit) or adding nicotine gum to advice ($6735/quit).[40]

8. Expert Opinion

Combination therapy offers the advantages of increased abstinence rates, enhanced relief of withdrawal symptoms and is well-tolerated. Combination therapy may be most useful for those smokers at highest risk of relapse, e.g., heavy smokers, smokers who have relapsed multiple times, or smokers with psychiatric co-morbidities. However, cost is an important consideration. In our clinical practice, we have experienced that insurers do not cover combination therapy. Additional research is needed to justify to private and governmental insurers that combination therapy is a cost-effective approach to the treatment of tobacco dependence.

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