Smoking Cessation Strategies: Health Promotion and Disease Prevention

A Thesis
submitted to the Faculty of the
Department of Human Science
School of Nursing and Health Studies
of Georgetown University
in partial fulfillment of the requirements for the
degree of
Bachelor of Science
in Health Studies

By

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Washington, D.C.
May 1, 2006
ACKNOWLEDGEMENTS

I thank my thesis advisor Dr. Charles Evans for his guidance and helpful critique of this paper. I am also grateful to Drs. Janie Heath and Stephanie Spernak for giving me the opportunity to serve as a research assistant in the Quest Clinical Study, a smoking cessation clinical study, conducted at the Lombardi Comprehensive Cancer Center, Georgetown University Medical Center.
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Abstract

In the United States, about 80% of the 45.8 million cigarette smokers smoke daily. Tobacco smoking increases a person’s risk of developing cardiovascular diseases and lung cancer. Therefore, it is important to implement effective smoking cessation strategies. Nicotine dependence is the disorder of chronic tobacco use. Nicotine Replacement Therapies (NRT) are used to aid in smoking cessation because they reduce withdrawal symptoms. The transdermal nicotine patch, gum, lozenge, inhaler, nasal spray, and sublingual tablet are current first-line nicotine replacement therapies. The transdermal patch is placed on the skin of the smoker and nicotine is released into the skin at a regular rate throughout the day. This product is an effective strategy for cessation because compliance is high and the nicotine is delivered throughout the day. However, when subjects are exposed to a smoking stimulus, they can experience bouts of craving when on the patch. The nicotine lozenge is delivered slowly into the body. It is not favored by smokers who prefer to chew. The inhaler is a prescription nicotine that is inhaled through a mouthpiece. The inhaler fulfills this behavioral action as the nicotine is absorbed into the mouth. Some smokers find this method to be tedious. Nasal spray delivers nicotine the fastest, which assists in curbing cravings. Determining the efficacy of the different nicotine replacement therapies depends on a person’s smoking habits, environment, genetics, age, and medical history. There are additional second-line tobacco use cessation treatments. In addition, a promising nicotine vaccine is the process of development. A number of factors can affect the efficacies of smoking cessation treatments. These include gender, ethnicity, and genetic factors. Lung cancer is the leading cause of smoking-related deaths. Smoking cessation strategies have been shown
to significantly reduce the risk of lung cancer in heavy smokers. Clinical management of tobacco use cessation includes a clinician’s responsibility to promote motivational clinical intervention and ensuring patient compliance.
Chapter I. Introduction

In the United States, there are approximately 45.8 million cigarette smokers and 80% of these people are habitual smokers. Tobacco smoking increases a person’s risk of developing cardiovascular and pulmonary diseases. It causes 440,000 deaths every year, which translates into 18.1% of all deaths in the United States. In addition, 40,000 people die annually from second-hand smoking. While the deteriorating health of smokers is of utmost concern, the economic impact of this behavior is also alarming. Tobacco smoking was responsible for greater than $50 billion in medical care in 1993 and $47 billion per year in disability and loss of productivity-related costs. These statistics underscore the importance of effective smoking cessation strategies for improving the well-being of Americans and the economy.

The Centers for Disease Control and Prevention have cited tobacco use as the chief preventable cause of mortality in the United States. It is encouraging to note that about 46% of the current smokers attempt to quit smoking annually. Furthermore, the health of an individual improves with cessation of smoking. For example, the risk of developing a cardiovascular disease decreases six months after cessation, while lung function returns to the level of a nonsmoker in approximately one year.

A number of tobacco products are being used by smokers. All forms of tobacco are addictive and are associated with high morbidity and mortality risks. Use of cigars has a lower risk of developing lung disease compared to cigarettes. Smokeless tobacco such as snuff and chewing tobacco has an increased risk of head and neck cancer and oral diseases. Nonetheless, cigarette smoking continues to be a major form of tobacco use in the United States. The focus of this paper is to review the current
Smoking Cessation

literature regarding the health effects and genetics of cigarette smoking and clinical strategies to treat tobacco addiction and promote smoking cessation.
Chapter II. Molecular and Behavioral Aspects of Tobacco Addiction

Addiction is the compulsive use of a drug due to increased tolerance to the drug. Cessation of the use of the drug can lead to serious withdrawal symptoms. Tobacco dependence is the term used to describe the medical disorders of nicotine dependence and withdrawal. Nicotine is the main addictive component of tobacco in cigarettes. It is an agonist of the Nicotinic acetylcholine receptors (nAChRs). These are pentameric ion channel (Na+ and Ca2+) receptors present presynaptically in the central nervous system and postsynaptically in the autonomic nervous system. These receptors regulate the release of neurotransmitters such as norepinephrine and dopamine. Dopamine is reported to reinforce the effects of nicotine and addiction to nicotine.13 Chronic exposure to nicotine leads to desensitization and inactivation of nAChRs. In this process, the numbers of receptors are increased and this is associated with development of tolerance to nicotine and increased intensity and frequency of the smoking habit.14,15 During abstinence, such as during the night, the receptors are resensitized and the need to smoke in the morning is necessary.

Nicotine is metabolized in the liver to cotinine by a group of cytochrome P450 enzymes.16a Nicotine has a half-life of 2-3 hours in the blood; however, cotinine has a longer half-life and this allows it to be a more reliable marker when measuring the amount of nicotine inhaled from cigarette smoking.17a A cigarette delivers 1.2 to 2.9 mg of nicotine depending on the type of brand. Therefore, a person smoking 20 cigarettes per day will inhale 23 to 35 ng/mL of nicotine. This amount of nicotine will cause dependence. Dependence is characterized with an increased expression of brain nAChRs, changes in regional brain glucose metabolism, and release of catecholamines.9
Cigarette smoking provides the individual with euphoria, concentration, weight control, and a decrease in tension.

Clinicians often use the Fagerstrom Test for Nicotine Dependence to measure the degree of addiction. This test includes questions that ask what is the time of the first cigarette of the day, how many cigarettes are smoked a day, and do you smoke more frequently in the morning hours compared to the afternoon and evening hours. A smoker who smokes within 30 minutes of waking in the morning is considered highly dependent. A score of 4 or above out of 10 will correlate with a dependence of nicotine. A distinction to note is the difference between a heavy and a highly dependent smoker. A heavy smoker is an individual who smokes 25 or more cigarettes a day. A very heavy smoker smokes 40 or more cigarettes a day. A highly dependent smoker is a person who scores 7 or higher out of 10 on the Fagerstrom Tolerance Questionnaire (FTQ).

Nicotine withdrawal occurs when a person experiences withdrawal symptoms due to tobacco smoking cessation. The cycle of positive reinforcement occurs when cessation leads to withdrawal, which then promotes smoking. The indicators of the level of nicotine dependence of a person include the time of the first cigarette of the day and the number of cigarettes smoked per day. For example, a person more dependent on nicotine will need to smoke earlier in the morning than a person less dependent on nicotine. To ameliorate the symptoms due to cessation, a smoker can use another form of nicotine delivery and/or to receive behavioral treatments. Smokers have varying degrees of dependence on cigarette smoking because of the differences in the genetic components that control nicotine metabolism. Nicotine Replacement Therapies (NRT) are medications that deliver a lower dose of nicotine to the smoker to avoid withdrawal.
symptoms.\textsuperscript{9} This inhibits the need to maintain nicotine levels through cigarette smoking and still provides nicotine that the smoker relies on for maintaining mood and attention. In addition to preventing the onset of withdrawal symptoms, some NRTs also mimic the behavioral patterns of smoking. Often the nicotine lozenge or gum can substitute for the behavior of putting a cigarette to the mouth. This aspect is discussed further in chapters III and IV.

Besides the pharmacological reward of the inhalation of nicotine, another reward acquired by smokers occurs as a sensory reward when a puff is able to pleasantly stimulate the airways. Each unit of puff is repeated many times a day and this represents a fundamental unit of reward for the smoker. Each puff becomes a conditioned behavior unit for reward. Naqvi and Bechara conducted a study that assessed the reward that was obtained from the sensory effects of the puff by comparing nicotinized, denicotinized, and unlit cigarettes before the nicotine was inhaled and reached the brain. To distinguish the reward received from the inhalation of the nicotine, the sensory reward was measured in the first seven seconds of inhalation. Results indicate that the airway sensory effects from the nicotinized puffs were more rewarding than the denicotinized cigarettes and unlit cigarettes.\textsuperscript{19} In a study, smoking denicotinized cigarettes provided more sensory reward than intravenous nicotine. This highlights the importance of the reward provided by the puff and not necessarily the nicotine. Furthermore, blocking the airway sensation has led to a decrease in reward as felt by the smoker.\textsuperscript{19,20} It has been shown that the sensory reward is a learned behavior since heavy smokers acquire more reward than light smokers.\textsuperscript{21,19} It is important to assess the different types of rewards smokers receive in
order to implement a proper way to compensate the decrease in reward when a clinician promotes cessation strategies.


Chapter III. First-line Tobacco Use Cessation Treatments

Originally, only self-help guides and behavioral therapy were available to smokers. Currently, a multi-modal dimension of treatment, including pharmacological and non-pharmacological treatments, is more effective than receiving only nonpharmacological treatment or only pharmacological treatment. For example, in one study a group was given nicotine patches and cessation counseling while another group was provided with just counseling. Only 13.5% of the people in the latter group abstained from smoking compared to 39% of the people in the former group. This shows the need to encourage multiple approaches to therapy.

Currently, there are several United States Food and Drug Administration (FDA)-approved NRTs on the market. These treatments work through different mechanisms of delivery and types of administration. Depending on the type NRT, nicotine can be delivered through the skin, buccal mucosa, or nose. A nicotine patch allows for passive administration since nicotine is released through the skin over the course of the day without any control by the smoker. In contrast, acute dosing is associated with NRTs that are self-administered by the person. Acute dosing can be a positive form of treatment since it allows the smoker to cure breakthrough cravings right away. These cravings occur when a smoker is exposed to smoke in the environment or when they are emotionally upset. Combining both acute and passive therapies is a promising combination. Adverse effects that are observed with many NRTs on the market include dizziness, nausea, and headaches. These adverse events can contribute to a lack of compliance. Current first-line NRTs includes the nicotine patch, the nicotine gum, the nicotine lozenge, the sublingual tablet, the inhaler, and the nasal spray (Table 1). In
addition, bupropion is a first-line non-nicotine replacement therapy. Pharmacotherapy is not directly advised for pregnant or breastfeeding women, adolescents, or people smoking less than 10 cigarettes/day.
Table 1. Smoking Cessation First-line Treatment Strategies

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<th>Cons</th>
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<td>Nicotine Gum</td>
<td>2 mg / 4 mg</td>
<td>Pleasant Taste (Flavored)</td>
<td>Jaw soreness and mild burning sensation</td>
</tr>
<tr>
<td>Nicotine Lozenge</td>
<td>2 mg / 4 mg</td>
<td>Delivers more nicotine than the gum</td>
<td>Mouth Soreness, Nausea, Hiccups</td>
</tr>
<tr>
<td>Nicotine Patch</td>
<td>7 mg / 14 mg / 21 mg</td>
<td>Good Compliance (only administered once/day)</td>
<td>Sleep disorder, skin irritation, slow delivery</td>
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<tr>
<td>Nicotine Inhaler</td>
<td>16 cartridges/day</td>
<td>Mimics hand-to-mouth behavior</td>
<td>Cumbersome to use; Less is delivered in low temperature</td>
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<tr>
<td>Nicotine Spray</td>
<td>8-40 doses/day</td>
<td>Fastest delivery</td>
<td>Nasal Irritation, watery eyes</td>
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<tr>
<td>Bupropion</td>
<td>150 mg / 300 mg</td>
<td>Reduced Irritability and Depression</td>
<td>Dry Mouth Insomnia</td>
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A. Buccal Administration

A1. Nicotine Gum

Oral acute treatments are favored among individuals that want to control the timing and dosage of nicotine administered. In 1984, the nicotine gum was the first NRT introduced. It is an effective method for cessation because it is widely available over the counter and it is flavored (mint, orange, and fruit), which eliminates the original unpleasant taste. Some adverse effects of the nicotine gum include jaw soreness and a mild burning sensation in the mouth. To alleviate jaw soreness, smokers often “park” the gum to the side of their mouth. The burning sensation can either be beneficial because it eliminates cravings or it is unpleasant and interferes with compliance. The two types of doses available are the 2 mg and 4 mg lozenge, which are recommended for use by a light and heavy smoker, respectively. Research has shown that over 60% of the heavy smokers receiving the 4 mg nicotine gum quit smoking after 6 weeks. Furthermore, only about 25% of heavy smokers receiving the 2 mg gum and 25% of the group receiving the placebo quit smoking. This indicates that lower dose of nicotine is not effective for heavy smokers. Initially, the smoker is recommended to have a piece of gum every 1-2 hours. After 6 weeks, the duration between pieces increases from every 2-4 hours to then every 4-8 hours after another two weeks. This helps slowly reduce the amount of nicotine required by the body gradually to avoid withdrawal symptoms. Even though each piece of gum contains 2 mg or 4 mg of nicotine, only 50% of it is absorbed effectively through the buccal mucosa. In addition, beverages such as soda and coffee have been shown to reduce the absorption of nicotine. In a study, 29% of the group given the 2 mg nicotine gum abstained from smoking after 6 months compared to only 19% of
the group receiving a placebo.\textsuperscript{24} A common problem regarding compliance with the gum is underdosing. Many smokers do not chew enough pieces of gum throughout the day to compensate for a similar amount of nicotine received through smoking. Self-administration of the nicotine gum is beneficial in treating cravings.\textsuperscript{9} The behavioral act of chewing immediately weakens cravings; however, the administration of the nicotine gum will inhibit the craving even longer. The nicotine gum is an effective treatment for many smokers since it can treat acute cravings.

Smoking cessation requires a lot of planning and dedication on the part of the smoker. Therefore, smokers often need to slowly reduce the number of cigarettes smoked per day through harm reduction. In a double-blind, randomized, placebo-controlled study, researchers suggest that the 4 mg nicotine gum may be effective in at least reducing the amount of smoking from the original intensity.\textsuperscript{25} The goal of the 364 heavy smokers, smoking at least 20 cigarettes/day, in Germany and Switzerland was to reduce the amount of cigarettes they smoked over the course of a year by supplementing using the Nicorette (Pfizer Consumer Healthcare) 4 mg nicotine gum. The subjects were monitored at baseline, 6 weeks, 4 months, and 12 months. Carbon monoxide levels, blood samples, and self-reports were used to determine the success of study. In comparison to the 6 week follow up, the 4 month assessment demonstrated a 15.8% reduction for nicotine gum users in contrast to a 6.7% reduction for the individuals in the placebo group. After 13 months, it was reported that 12% of the participants in the nicotine group were able to reduce smoking in contrast to only 4.5% of the placebo group. Even though not all participants were able to reduce their smoking rate by 50% at month 13, 64% of the smokers in the treatment group were able to reduce the number of
cigarettes smoked.\textsuperscript{25} Harm reduction, i.e. reduced intake of nicotine, is important for an addiction that is influenced by many behavioral and psychological factors.

A2. Nicotine Lozenge

Compared to the nicotine gum, the nicotine lozenge delivers more nicotine even though both are absorbed by the buccal mucosa. About 25\% less nicotine is delivered using the nicotine gum because some remains in the gum.\textsuperscript{26} It is important to provide the correct dosage of nicotine in these replacement therapies. In a double-blind, placebo-controlled, randomized study, the safety and efficacy of the nicotine lozenge in maintaining cessation among smokers was assessed. Since the time of the first cigarette of the day is an indicator of the level of nicotine dependence (part of the Fagerstrom Tolerance Questionnaire), a 4 mg lozenge was assigned to the heavy smoker; whereas, a light smoker was given a 2 mg lozenge. There were 4 groups in this study. Within the low and high dependent smokers, there was an “active” and “placebo” group. The light smokers received either the 2 mg nicotine lozenge or a placebo. The highly dependent smokers either received a placebo or a 4 mg nicotine lozenge. The participants used 7-8 lozenges per day in the beginning. After one year, 17.9\% and 9.6\% of the light smokers in the active and placebo group, respectively, were abstinent. About 14.9\% and 6.2\% of the heavy smokers in the active and placebo group, respectively, remained abstinent after one year.\textsuperscript{26} With respect to weight gain at week 6, the participants receiving the 4 mg lozenge had a decrease in the amount of weight gain; whereas, the 2 mg lozenge cohort did not have any effect on their weight. However, after 6 months all groups exhibited similar weight change. The participants given the lozenge reported more adverse effects such as gastrointestinal and respiratory problems. Despite the symptoms, Shiffman and
colleagues report, “The odds of being abstinent after 6 weeks of treatment were 2.1 to 3.7 times greater among those receiving the active lozenge (2- and 4-mg doses, respectively) than among those receiving the placebo”. Interestingly, this study did not provide a large amount of behavioral therapy except a support guide. They attribute their high cessation rate in the active groups to assigning the participants with the correct dosage. Overall, the nicotine lozenge is a safe and effective treatment.

A3. Sublingual Tablet

The sublingual tablet is another form of NRT and this is administered under the tongue and it is pharmokinetically similar to the nicotine gum. A 2 mg or a 4 mg tablet is recommended every hour for a person who smokes less than a pack a day or more than a pack a day, respectively. In one study, the Nicorette® Microtab nicotine sublingual tablet was used. After 12 weeks, the frequency of administration of the tablet was decrease by 25%. The most common adverse effects reported were sore mouth and throat. The results indicate after six months of treatment, the sublingual tablet was more successful at promoting cessation in nicotine-dependent people than the placebo. It was reported that 33% of the group given the tablet were smoke-free compared to 18% given the placebo at six months. After six months, the participants were not given any more tablets. After 1 year, 23% of the groups given the tablet were smoke-free compared to 15% in the placebo group. Many of the heavy smokers were unable to maintain abstinence in the period when no tablet was administered. It is recommended that heavy smokers should remain on the sublingual tablet for longer than 6 months or use the 4 mg sublingual tablet. The tablet is an effective treatment for those who want to receive more nicotine and want to avoid chewing.
B. Transdermal Administration

Nicotine Patch

Transdermal nicotine patches are placed on the skin and the delivery of nicotine is continuous through the day. 28,19,9 Within the several brands of patches, the dose strengths vary. Light smokers, people smoking less than 10 cigarettes per day, are advised to use the 14 mg NicoDerm CQ patch. In contrast, the heavy smokers, people smoking more than 10 cigarettes per day, are instructed to use the 21 mg nicotine patch. This particular brand of patch is manufactured by GlaxoSmithKline Consumer Health Care and will deliver nicotine for either 16 or 24 hours. To gradually decrease the amount of nicotine over time, a smoker is advised to use a 21 mg/day patch for 6 weeks subsequently followed by 2 weeks on the 14 mg/day and then another 2 weeks of the 7 mg/day patch. Other brands of patches include the Nicotrol and Habitrol patch and these are marketed by Pfizer and Novartis, respectively. These manufacturers recommend a similar time-course for treatment. The NicoDerm CQ and Habitrol patches can be worn for 24 hours, whereas a Nicotrol patch is to be used for 16 hours. While the 24-hour patch prevents morning cravings, it is known to disrupt sleep. Smokers with prior sleeping disturbances are advised to remove the patch at night. In a study, the 24-hour patch had been shown to reduce the cravings throughout the day and people self-administering this patch were more likely abstain longer than people on the 16-hour patch.30 Smokers did experience cravings when exposed to smoke in the environment. In general, nicotine patches are an effective NRT because it results in high compliance due to only providing nicotine replacement once a day.
In 2003, the New York City Department of Health and Mental Hygiene, the New York State Department of Health, and the Roswell Park Institute participated in a project that provided nicotine replacement therapy to a large population of New York residents. Over 34,000 people called the New York State Smokers’ Quitline toll-free number to receive their nicotine replacement therapy.\(^{31}\) They were given a 6 week course of treatment which included 2 weeks each of 21 mg, 14 mg, and 7 mg doses. Over 2,100 people were randomly selected from the 34,000 people to contact after 6 months. Approximately, 1,300 of the people receiving the treatment were successfully contacted after 6 months. This follow-up survey contained questions on the current smoking status and demographic information. The control group for this study was the people who were not able to receive the nicotine replacement therapy due to mailing errors. The study represented about 5% of the smokers in New York City who smoked 10 or more cigarettes a day. The population consisted of a majority of people who were non-white, foreign-born, or resided in low-income housing areas. The results after six months indicated that 33% of individuals who received the 6 week treatment successfully abstained from smoking compared to only 6% of the control group. Interestingly, people who were older then 65 years, foreign-born, and smoked less then 20 cigarettes per day was the group that was able to quit smoking most successfully. In addition, counseling over the telephone seemed to add to successful quit rates. These findings suggest that large-scale population-based initiatives are important in prevention of numerous deaths (greater than 1,000) caused by smoking.
C. Inhaler and Spray

The inhaler is an important type of NRT because it compensates for the behavioral aspect of placing an object to the mouth. The hand-to-mouth behavior with the inhaler is helpful in providing the smoker with a familiar action associated with smoking. The inhaler is made up of a mouthpiece and a cartridge containing the nicotine. Out of the 10 mg of nicotine in each cartridge, 6 mg is received.\textsuperscript{32,33} Approximately, 6-16 cartridges should be used per day. The nicotine is sprayed into the mouth from where it is distributed to the oral cavity, esophagus, stomach, and slightly to the lungs. The mechanism of action can be quite cumbersome since 80 puffs will be required to provide 4 mg of nicotine.\textsuperscript{9} In addition, it has been reported that less nicotine will be delivered in lower temperature compared to a higher temperature. Smokers who puffed continuously for 20 minutes achieved the most success. However, this is an impractical method to receive adequate nicotine for many smokers as it is time-consuming to achieve satisfaction of a sufficient amount of nicotine.

The nasal spray is the NRT with the fastest delivery and absorption so it is ideal to treat acute cravings quickly.\textsuperscript{34,22} One dose is administered when 0.5 mg of nicotine is delivered by squirting the bottle into each nostril. It is advised that smokers should have 1-2 doses per hour and the concentration of peak nicotine occurs in 10 minutes. The nicotine blood levels rise quickly to 5-12 ng/mL. Adverse effects with this type of administration are nasal irritation and watery eyes. However, these symptoms decrease over time with more use.
D. Non-Nicotine Replacement Therapy: Bupropion

Bupropion, an antidepressant, is approved as a first line treatment of smoking cessation. Bupropion functions to “be related to reduced reuptake of dopamine in the mesolimbic system and reduced re-uptake of noradrenaline in the locus coeruleus.” Bupropion is metabolized to its primary metabolite, hydroxybupropion, by cytochrome P450 isozyme, CYP2B6. It is advised that the 300 mg/day is effective in nicotine dependence. One study showed two 150 mg tablets of bupropion ameliorated irritability and depression that can be associated with cessation. Side effects that were reported after using bupropion include dry mouth and insomnia. Bupropion in conjunction with a NRT is a better therapy in promoting cessation. It was also shown that Bupropion alone could be just as effective as the combination therapy of a nicotine patch and bupropion. In one trial comparing bupropion versus a placebo, 39% and 44% of the people given 150 mg and 300 mg of bupropion, respectively, quit smoking compared to the 17% of the placebo group after 7 weeks. Furthermore, after one year, 23% remained nonsmokers in the 300 mg bupropion group in comparison to the 12% in the placebo group. In another study, the combination of psychological intervention and bupropion was not found to be more effective than the drug alone in the management of smoking cessation.

E. High Dose Therapy

Heavy and highly dependent smokers need to receive a higher dose of nicotine replacement therapy in order to achieve an effective response. A 2 mg dose and a
placebo exhibit the same effect on a heavy smoker.\textsuperscript{38} About 8% of smokers are heavy smokers.

Two studies were conducted to assess the effect of the 4 mg lozenge and the 21 mg nicotine patch in heavy smokers. A multicenter, double-blind, and placebo-controlled study was conducted using the nicotine patch. In the first six weeks of treatment, smokers were given either a placebo patch or a 21 mg/day nicotine patch. After 6 weeks, the dose was decreased. There was some behavioral support. In this study, moderately heavy smokers were defined as smoking 20-39 cigarettes/day; whereas, heavy smokers were classified as individuals who smoked 40 or more cigarettes/day. Highly dependent smokers had a FTQ score greater or equal to 7. In the second study, the nicotine lozenge was given to highly-dependent smokers, as defined as participants that smoked within 30 minutes of waking, a 4 mg nicotine lozenge. The results indicate that 4 mg nicotine lozenge and 21 mg nicotine patch are effective treatments for heavy and heavily dependent smokers.\textsuperscript{16b} Even though heavy smokers do not represent a majority of the smoking population, it is important to identify more effective treatments for this group because they have the most difficulty abstaining and are prone to developing serious health conditions.

F. Combination Therapies

NRTs might be more efficacious in heavy smokers if the dose increases beyond the 4 mg in the gum or lozenge. Conflicting results have been reported on whether increasing the dose of nicotine will increase compliance. It is important to administer
products with faster release to prevent relapse due to acute cravings. A transmucosal route of gum that delivers nicotine faster may curb cravings.

To improve the efficacy of the NRT, combining the transdermal patch with a form of acute therapy (gum or lozenge) will allow for continuous nicotine delivery with the ability to cure breakthrough cravings when needed. Combination therapies overall are useful. However, it is can be dangerous to combine therapies without consulting a healthcare provider. Combination therapy has proven very effective in some studies. A study showed that the use of a patch and bupropion was more effective than the patch alone or a placebo. In this study, the efficacies of sustained-release bupropion were compared with nicotine patch, both bupropion and sustained-release bupropion, and a placebo. For the group assigned to bupropion, they were given 150 mg of bupropion twice a day. The smokers receiving the nicotine patch were given a nicotine patch contained 21 mg of nicotine at the beginning. The dose of nicotine was decreased over time to 7 mg. This double-blind, randomized study showed the combination therapy of bupropion and the nicotine patch was most effective with over 35.5% of the subjects in this group abstained from smoking after one year compared to about 30.3%, 16.4%, and 15.6% of the individuals in the bupropion, nicotine patch, and placebo group, respectively. All groups experienced withdrawal symptoms in the beginning. The adverse effects that were reported included insomnia and headache. Another concern for smokers that are trying to quit is the impending weight gain. The results indicate that 2.1 kg, 1.6 kg, 1.7 kg, and 1.1 kg were gained on average in the placebo, nicotine-patch, bupropion, and the combination therapy groups, respectively. It is important to note that the cessation rate for the individuals in the bupropion and in the combination therapy
group was similar at the one year follow up. Combination therapy of bupropion and the nicotine patch might be best for smokers who have psychiatric problems. It is the clinician’s responsibility to assess the needs of the patient and to study the different NRTs to find a combination that is most effective and would result in the highest compliance.
Chapter IV. Second-line Tobacco Use Cessation Treatments

A. Nortriptyline

Often second-line treatments are recommended only if the first-line therapies are unsuccessful or if there is a contraindication. While the most common antidepressant approved with smoking cessation is sustained-release bupropion, nortriptyline is an antidepressant that is approved to be used as a second-line treatment for smoking cessation. Nortriptyline, a generic drug, has been shown to be similarly effective as bupropion. Nortriptyline works to block the reuptake of norepinephrine. The adverse effects associated with nortriptyline are tachycardia, blurred vision, constipation, dry mouth, sedation, and urinary retention. The presence of these adverse effects indicates the transdermal nicotine is more beneficial in reducing symptoms. The psychological support offered in this study did not seem to have a long term effect on promotion of cessation.37

Nortriptyline in conjunction with a transdermal patch has proven effective in promoting cessation and diminishing withdrawal symptoms. In a double-blind, randomized, and controlled study, subjects participated at the Denver Veterans Affairs Medical Center.39 Twenty-one days into the study was the assigned quit date. Two weeks prior to the quit day, they took either a placebo or nortriptyline and the dose of nortriptyline was increased closer to the quit date. After quit date, they still took their assigned treatment, but slowly reduced the dose. All participants received a 21 mg transdermal nicotine to be taken daily for two weeks. The dose of the transdermal nicotine was subsequently reduced after two weeks following quit date (from 21 mg to 14
mg to 7 mg). The participants received regular counseling from a nurse. Assessments that were performed included measurement of carbon monoxide levels and urine cotinine levels as well as assessing for depression using the Beck Depression Inventory. This study enrolled 158 eligible participants and the results indicated that after six months the cessation rate for the nortriptyline group was 23% compared to a 10% of the placebo group. The treatment group experienced side effects such as dry mouth and sedation. Although the long-term cessation rate in the treatment group was improved, the adverse effects were not reduced. Therefore, this combination therapy is recommended as a second-line treatment.

A study conducted by Haggstram and colleagues assessed the efficacies of nortriptyline (75 mg/day), sustained-release bupropion (300 mg/day), and a placebo for 9 weeks. These smokers were also provided counseling. The quit day was day 10. Abstinence was determined was the subject was not smoking since the quit day and had an expired carbon monoxide concentration of 10 ppm or less. At six months, 21.6% people showed abstinence in the placebo group, 30.8% remained abstinent in the nortriptyline group, and 41.5% were smoke-free in the bupropion group. The common adverse effects reported were dry mouth and drowsiness due to nortriptyline and dry mouth and insomnia as a result of bupropion treatment. It was concluded that the nortriptyline response was not statistically significant.

B. Clonidine

Clonidine, an alpha-2-noradrenergic agonist, is a drug that primarily is used for hypertension. It can also reduce withdrawal symptoms due to opiate and alcohol.
Against a placebo, clonidine was an effective treatment for cessation of smoking.41,9

There are many adverse symptoms such as dizziness, drowsiness, allergic reaction, or even bradycardia.
Chapter V. Counseling

Counseling is a very important component of smoking cessation because of the discomforts such as the withdrawal symptoms experienced by the smoker. It is important for a healthcare provider to give motivation and support to the smoker as they are coping with withdrawal symptoms. Quitlines are important in that there is a potential to reach a large number of smokers. A randomized trial in California assessed the importance of the telephone quitline, California Smokers’ Helpline.\(^42\) Seven counseling sessions were given to the treatment group. The control group was given information and would receive counseling if they called on their own. Cessation rates were measured at 1, 3, 6, and 12 months. For the participants in the treatment group, the cessation rates were reported as 20.7%, 15.9%, 11.7%, and 7.5% at the incremental months. For the individuals in the control group, they were reported as 9.6%, 6.7%, 5.2%, and 4.1%.

Population-based programs are important and smokers are more likely to use a quitline than go to a clinic.\(^43\) The FREE & CLEAR program provided by the Group Health Cooperative (GHC) of Puget Sound was tested in a randomized clinical trial. Two groups were provided behavior modification support system. One group received proactive telephone calls and the second cohort met in groups. The telephone specialists assessed the smoker’s nicotine needs and motivation to quit. A quitting plan was developed that included reduction of nicotine by switching the brands. Follow-up phone calls were scheduled over one year. In the meeting group, eight classes were held in a six-week period and the patients received letters and feedback regarding their progress. Patients were assessed for withdrawal symptoms and given behavioral support during the
first week of quitting. A decrease from 25% to 15.5% in smoking was observed over ten years among more than 550,000 adult participants.
Chapter VI. New Developments in Treatment: Vaccine

Antinicotine vaccines are currently in development. The basis for the vaccine is the production of antibodies against nicotine. These antibodies inhibit nicotine from attaching to nicotinic acetylcholine receptors in the brain, which prevents nicotine from reaching the brain so the body is not dependent on nicotine.\(^4\) The antibodies are too large to pass through the blood-brain barrier. In one study, rats received 204 injections in the course of 4-8 weeks. Then, the rats are given the amount of nicotine that is equal to the amount a person would receive after smoking two cigarettes. It was found that after 1-3 minutes, the amount of nicotine in the brain was reduced by 60%.\(^5\)

The Cytos vaccine was developed by Nabi Biopharmaceuticals and has completed the Phase II Clinical Trial.\(^4\) Over 300 subjects were given either a placebo or the Cytos vaccine. The results indicate that people with the highest nicotine-specific antibodies could achieve a greater rate of cessation compared to the group receiving a placebo. Unfortunately, the vaccine can not treat acute breakthrough cravings; therefore, this vaccine in conjunction with a NRT would prove more effective. In addition, it might be more effective if this vaccine is only administered to individuals who have already quit because current smokers would require high levels of antibodies stimulated by the vaccine to counteract the high level of nicotine present in the blood. The use of the vaccine by pregnant women is still being studied; however, early results do show this vaccine would not increase nicotine uptake by the placenta to reach the fetus.

A clinical trial was performed on the NicVAX, a conjugate nicotine vaccine. This is formally named AMNic-rEPA. This vaccine is made up of hapten 3’-aminomethylnicotine conjugated to recombinant \textit{Pseudomonas aeruginosa} exoprotein A
The study is described as a multicenter, randomized, double-blinded, and placebo-controlled study. A total of sixty-eight subjects were recruited to the University of Minnesota, University of Nebraska, or University of Wisconsin. The objective of the vaccine is to produce antibodies against nicotine that will bind to the nicotine. This will also reduce the amount of nicotine that reaches the brain. Sixty-eight subjects received a 50, 100, or 200 microgram dose of the NicVAX vaccine on day 0, 28, 56, and 182. Based on the results, this vaccine appears safe since the only adverse effects noted were headache, malaise, and myalgia. In addition, the vaccine was considered immunogenetic especially for the 200 microgram dose exhibiting the highest serum antibody concentrations. A nicotine vaccine is a novel approach to promoting cessation and with more research this may become a leading treatment in the future.
Chapter VII. Factors Affecting Efficacy of Treatments

A. Gender

It has been shown that women adhere to first time quitting smoking better than men when a health care provider provides the quit date. In a smoking cessation study, Borrelli and colleagues reported, “Among those who did not adhere to the quit date, women were more than 2.5 times as likely to relapse than men, whereas among those who did adhere to the quit date, women were only 1.3 times as likely as men to relapse. Thus, although women were more likely to relapse than men regardless of adherence to the prescribed quit date, adherence to the study protocol was strongly protective against relapse for women”. It has been suggested that women suffer more from depression. In addition, women are concerned about the potential for weight gain. It is important to note that women have a difficult time successfully quitting if a previous attempt failed. Research has shown that some NRTs are not as successful in women compared to men because women are more likely to become depressed or are concerned about their changes in weight.

B. Ethnicity

In addition to differences in gender, ethnic groups also experience different success rates with NRTs. For example, studies have shown African Americans found the nicotine patch, counseling, self-help guide, and telephone counseling are all effective tools in promoting smoking cessation. Similarly, Hispanics benefited from those methods as well as mood management. It is important to assess the needs or lifestyle of
certain groups in order to provide the most effective treatment. Individualized treatment is important to ensure cessation.

C. Biomarkers

The biomarkers are assays used to provide the level of a tobacco metabolite or DNA damage in a human tissue or in sputum, saliva, blood, urine, or exhaled air.\textsuperscript{48} To measure exposure to tobacco carcinogen, the assay is used to determine carcinogen levels such as that of a metabolite in urine or in a target organ. In addition, the amount of exhaled carbon monoxide can be measured. Similarly, polycyclic aromatic hydrocarbons can be measured in lung and in urine. Biomarkers are also used to measure the biologically effective dose of the tobacco. These assays measure the level of the carcinogen and DNA-adducts, carcinogen-DNA hemoglobin adducts, chromosomal aberrations, and lipid peroxidation in target tissues. Biomarkers can also measure harm at the level of RNA or protein expression and loss of heterozygosity of certain genes as well as methylation status of genes. There is no single biomarker that can predict the risk from cigarette smoking.

The genetic polymorphisms in genes such as N-acetyltransferase-2, glutathione S-transferase M1 and CYP1A1, glutathione S-transferase Pi, and mutations in p53 gene and DNA repair enzymes can affect biomarker levels such as DNA-adducts in different individuals exposed to tobacco.

It is also important to identify potential exposure reduction products (PERPs) that could lead to reduced risk due to smoking.\textsuperscript{48} According to a recent Institute of Medicine (IOM) Report, carcinogen risk can be significantly reduced by reducing the exposure in
smokers. Additional biomarkers are critically needed to evaluate the effectiveness of new tobacco cessation strategies and differences in susceptibility to carcinogens in different individuals. These biomarkers will also be used in the assessment of harm reduction and genetic susceptibility for smoking behavior.
Chapter VIII. Smoking and Lung Cancer

Approximately, 150,000 deaths related to smoking (about 35%) are caused by cancer in smokers. According to the Centers for Disease Control and Prevention, cancer of trachea, lung, and broncus are the leading cause of cigarette smoking (CDC, 2002) (Table 2).

Tobacco smoke contains more than 100 mutagens and carcinogens. Specific chemicals in tobacco smoke are polycyclic aromatic hydrocarbons (PAH), tobacco specific N-nitrosamines (TSNs), aromatic amines, and ethylene oxide. PAHs and TSNs are the more common type of human cancer risk. These compounds are carcinogenic in animals and have been detected in human lung tissue. PAHs are metabolically activated in humans through cytochrome P450 (CYP family of enzymes). TSNs can transform lung cells in culture and their metabolites have been found in urine and their adducts have been found in blood. There are three different types of DNA-adducts formed by TSNs: Methylation of DNA nucleotides, bulky adducts, and oxidative DNA damage. In addition, chromosomal damage has been measured in target tissues and mutations in p53 have been measured in target tissues.
Table 2. Cancer-Related Deaths Attributable to Smoking in the United States*

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Total Number of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trachea, Lung, and Bronchus</td>
<td>124,813</td>
</tr>
<tr>
<td>Esophagus</td>
<td>7,893</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6,480</td>
</tr>
<tr>
<td>Oral Cavity, Pharynx, and Lip</td>
<td>5,137</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>4,752</td>
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<tr>
<td>Larynx</td>
<td>3,127</td>
</tr>
<tr>
<td>Kidney and Other Urinary</td>
<td>3,035</td>
</tr>
<tr>
<td>Cervix and Uterus</td>
<td>552</td>
</tr>
</tbody>
</table>

*Adapted from Henningfield et al., 2005
A. Ethnic and Racial Differences in the Incidence of Lung Cancer

In addition to the differences observed in the efficacy of nicotine replacement therapies among ethnic populations, the incidence of smoking-related lung cancer among these groups varies. African American and Native American smokers have been reported to have a higher incidence of lung cancer compared to other ethnic groups. From 1993-2001, researchers assessed the incidence of lung cancer in a Multiethnic Cohort Study. The population consisted of African-Americans, Japanese-Americans, Latinos, Native Hawaiians, and White smokers. The study comprised of 215,000 adults ages 45-75 years old residing in Hawaii and California. Among men and women, the rate of smoking was the highest in the African American and Native Hawaiian population. The data is self-reported through comprehensive questionnaires. One can conclude that African Americans and Native Hawaiian Americans are more likely to develop lung cancer.

B. Smoking Cessation and Reduction of Lung Cancer Risk

Limited studies have been performed that show that heavy smokers (more than 15 cigarettes/day) who take 50% less intake of cigarettes do not decrease their risk of cardiovascular disease and pulmonary disease. Compensatory smoking, increasing the puff volume per cigarette, has been associated with lack of benefit in smoking reduction and health outcome in these studies. In one population-based study, 31 years of follow-up was conducted on 11,151 men and 8,563 women. These participants were divided into six groups according to their smoking habits: heavy smokers (more than 15 cigarettes/day), reduced smokers (people who reduced from more than 15 cigarettes per day to 50% less without quitting), continued light smokers (1-14 cigarettes/day), quitters (stopped smoking after first and second examination), stable ex-smokers, and never
smokers. There were 864 incidence of lung cancer during the follow-up. This study demonstrated that heavy smokers who reduced smoking by 50% had significant in reduction in the risk of lung cancer. This study demonstrates that smoking cessation decreases the risk of lung and other cancers.\textsuperscript{51} In addition to a reduction in lung cancer risk, smoking cessation is directly correlated with a decreased risk of renal cell carcinoma.\textsuperscript{52}
Chapter IX. Clinician’s Role in Smoking Cessation

The clinicians must be trained in effective intervention treatments for smokers. The training should include clinician’s education and knowledge of the guidelines for tobacco dependence treatment. The recognition of tobacco dependence as a chronic disorder should imply to a health care provider that comprehensive treatment is warranted. Clinicians are expected to become proactive in implementing cessation programs for their patients. Patients need counseling and advice in addition to prescribing the best-suited prescription. In 1995, only 21% of smokers who visited their physician received smoking cessation counseling. Folstrom and colleagues conducted a study with 285 individuals in which they had a control group and an intervention group. Only 2% more people quit in the intervention group that was advised by their physician to abstain from smoking. This implies that the physician community needs to improve the way their message is delivered to their patients because their advice can be a strong influence in their patient’s lives.

The following steps are recommended by the Public Health Service in their Clinical Practice Guideline on Treating Tobacco Use and Dependence: 1) ask the patient if he or she uses a tobacco product, 2) advise the patient to quit, 3) assess the patients’ desire to quit, 4) assist the patient in quitting, and 5) arrange for future contact to assess the situation (Figure 1). Since many smokers unsuccessfully attempt to quit every year, clinicians should guide smokers to strategies that are individualized to the patient’s needs in order to ensure compliance. The physician should evaluate the tobacco use status for every patient at every visit. In a personalized manner, physicians should
approach the patient to quit the use of tobacco. In addition, they should determine the willingness of the patient to make this effort. If a patient is willing to quit, physicians should provide them with adequate counseling and pharmacotherapy. Physicians should schedule frequent follow-up visits within the first week after the quit date.

If the patient is reluctant to quit smoking, the physician should emphasize the importance of health and the risk factors associated with smoking. They should consider motivational strategies such as social factors, family health, and children in their communication with the patient. They should identify acute risks, long-term risks, and environmental risks associated with smoking (Table 3). Acute risks include shortness of breath, asthma, harm to pregnancy, impotence, infertility, and increase in serum carbon monoxide. Long-term risks include heart attack, stroke, lung cancer, cancers of the larynx, oral cavity, esophagus, chronic bronchitis, emphysema, and long-term disability. Environmental risks include lung cancer and heart disease in spouses, increased risk for low-birth weight, and respiratory infection in children. Clinicians should also provide information to their patients about the rewards of quitting smoking. The rewards include improved health, tastier food, better sense of smell, and serving as a good role model for the family. Furthermore, the physician should explain the amount of money that will be saved by not purchasing tobacco products.

The physician should also explain the challenges associated with quitting such as withdrawal symptoms, weight gain, and depression. The motivation should be a key component of the clinical intervention especially during the early stages of smoking cessation.
Patients who show relapse should be encouraged to return to their goal. If it is a heavily dependent patient, it might be necessary to achieve the goal of harm reduction before a plan for cessation is implemented. Significant counseling and routine follow-up visits and telephone calls should be continued.
Figure 1. Clinical Treatment Plan for Tobacco Users. 
Adapted from Fiore et. al, 2000.
## Table 3. Risks Associated with Smoking

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Long-Term</th>
<th>Environmental</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shortness</strong></td>
<td><strong>of Breath</strong></td>
<td><strong>Heart Attack</strong></td>
<td><strong>Increased Risk of Cancer in</strong></td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td></td>
<td><strong>Shortness of Breath</strong></td>
<td><strong>Family</strong></td>
</tr>
<tr>
<td><strong>Impotence</strong></td>
<td></td>
<td><strong>Lung and other cancers</strong></td>
<td><strong>Increased Rate of Smoking in</strong></td>
</tr>
<tr>
<td><strong>Infertility</strong></td>
<td></td>
<td><strong>Long-term disability</strong></td>
<td><strong>Family</strong></td>
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<td></td>
<td></td>
<td><strong>Low-birth weight</strong></td>
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<td></td>
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<td></td>
<td><strong>Respiratory Infections</strong></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Middle ear disease</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Increased Serum Carbon Monoxide</strong></td>
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</tbody>
</table>
Chapter X. Conclusion

Chronic cigarette smoking leads to serious medical conditions and even death. Since the prevalence of smoking is on the rise, it is important for clinicians to be proactive when meeting with their patients. By asking the patient about smoking history and providing a means for cessation against this chronic disease, smoking-related deaths can decline. Many smokers have attempted to abstain, but are unsuccessful. Therefore, it is important to provide an effective treatment strategy that is individualized to each patient’s needs. There are several nicotine replacement therapies (NRT) with different mechanisms of action. The variety of therapies available allows smokers to choose the method that would fit their needs. Multimodal treatment strategies are highly recommended. Behavior counseling in conjunction with a NRT is a promising combination. Smoking cessation has been shown to reduce the risk of lung cancer in heavy smokers. Harm reduction is an important goal for some heavily dependent smokers to achieve before reaching the goal of smoking cessation. Clinicians play an important role in the successful management of tobacco control by implementing motivational intervention strategies, following-up with the patient’s progress, and ensuring patient compliance. Smoking cessation is important disease prevention strategy that is necessary to improve well-being of the population.
Chapter XI. References


