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A review of cigarette smoking and pharmacological therapies (varenicline and nicotine replacement therapy) for smoking cessation in the United States

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Thesis

A REVIEW OF CIGARETTE SMOKING AND PHARMACOLOGICAL THERAPIES (VARENICLINE AND NICOTINE REPLACEMENT THERAPY) FOR SMOKING CESSATION IN THE UNITED STATES

by

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ABSTRACT

Smoking combustible cigarettes is the major cause of disease and death among adults living in the United States (U.S.). In fact, smoking combustible cigarettes causes nearly half a million premature deaths among U.S. adults every year.[1–4] It is estimated that over 14% (equating to 34 million persons) of U.S. adults smoke cigarettes currently.[2,5] This is a substantial decrease from 1965 when it was estimated that more than 42% of U.S. adults smoked cigarettes.[1] This is partly attributed to the well-established evidence that smoking cigarettes causes harm to almost every human organ system[5] and is associated with an elevated risk of developing cancer[6], cardiovascular disease [7], pulmonary disease and respiratory illnesses.[8–10] Despite the well-established health consequences of smoking cigarettes, millions of people are still smoking, which alone suggests that nicotine (the primary constituent of cigarettes) is highly addictive.[3] Thankfully, smoking cessation by means of pharmacological treatments has been shown to help smokers overcome nicotine addiction. A review of the research on the efficacy of varenicline (Chantix) and Nicotine Replacement Therapy (NRT), two of the most commonly used smoking cessation treatments, reveals that both treatments increase long-term smoking abstinence rates with odds ratios of 3.85 for varenicline and 1.74 for NRT when compared to placebo.[11–14] Even more, both drugs appear to be generally well-

tolerated, with no known life-threatening side effects when compared to placebo. Research shows that the most common side effects for varenicline are nausea, insomnia, gastrointestinal effects, headache and abnormal dreams.[11,15] The most common side effects for NRT appear to be skin irritation, insomnia, headache, nausea/vomiting and cough.[11,15] Ultimately, both varenicline and NRT appear to be strong options for achieving smoking abstinence both with respect to overall efficacy and tolerability.

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LIST OF ABBREVIATIONS

ACh ..... acetylcholine

BBB ..... blood-brain barrier

BU ..... Boston University

CDC ..... Centers for Disease Control and Prevention

COPD ..... chronic obstructive pulmonary disease

CVD ..... cardiovascular disease

DSM-IV ..... Diagnostic and Statistical Manual for Mental Disorders, 4th Edition

FTND ..... Fagerström Test for Nicotine Dependence

FTQ ..... Fagerström Tolerance Questionnaire

GED ..... general education development

IARC ..... International Agency for Research on Cancer

MAO ..... monoamine oxidase

nAChRs ..... neuronal nicotinic acetylcholine receptors

NRT ..... Nicotine Replacement Therapy

PAH ..... polycyclic aromatic hydrocarbon

TH ..... tyrosine hydroxylase

U.S. ..... United States

VTA ..... ventral tegmental area

WISDM-68 ..... Wisconsin Inventory of Smoking Dependence Motive

INTRODUCTION

Smoking combustible cigarettes, the most common method of tobacco use, is the number one cause of disease and death among adults living in the United States (U.S.), causing almost half a million premature deaths among U.S. adults each year.[1–4] There is long-standing evidence that smoking cigarettes causes harm to almost every human organ system [5] and is associated with an elevated risk of developing over 20 types of cancers [6], cardiovascular disease [7], pulmonary disease and respiratory illnesses[8–10], and pregnancy complications.[6–9,16] In fact, it is estimated that the chance of dying from a smoking-related disease or illness is nearly 50% for individuals identifying as life-long smokers.[10,17] Despite the well-established and serious health consequences of smoking cigarettes, the U.S. Surgeon General's 2020 report on smoking cessation estimates that 34.2 million adults living in the U.S. currently smoke cigarettes.[5] This estimate is equivalent to roughly 14% of the general U.S. population.[2] It should be noted that this is a substantial decrease in the prevalence of combustible cigarette use from 1965, when the Centers for Disease Control and Prevention (CDC) estimated that 42.4% of adults living in the U.S. were smoking cigarettes each year.[1] The decrease in smoking prevalence over the last fifty-seven years has been attributed to many things including: public health campaigns, medical advancements, the development of innovative smoking cessation therapies and treatments, changing social norms and social acceptance of smoking cigarettes, the implementation of smoke-free laws and policies, rising cigarette prices, and increased education surrounding the health consequences of smoking cigarettes.[1,21,5,18] Furthermore, it has been reported that of the millions of Americans that

smoke cigarettes in the U.S., over 70% would like to quit, yet only 3-5% are able to successfully quit smoking each year.[5,19] In fact, greater than 80% of smokers report a relapse within one year of quitting[17], and of the individuals who are successful, they report attempting to quit smoking an average of 8-11 times before quitting permanently.[20] The low success rates of long-term abstinence coupled with the substantial number of individuals still smoking cigarettes deserves increased attention.

This paper will begin by providing relevant background information on the history of smoking and cigarette use in the U.S., current trends in smoking and smoking cessation in the U.S., the physiology of nicotine addiction and the health impacts of smoking cigarettes. This will be followed by an in-depth look at current standard-of-care pharmacological treatments, CHANTIX® (varenicline) and nicotine replacement therapy (NRT), with a particular emphasis on the efficacy and tolerability of each treatment. Finally, this paper will end with a discussion on which treatment holds the most promise for smoking cessation and where these treatments might fall short. Of note, this thesis will focus on tobacco use in the form of smoking combustible (burning) cigarettes only.

SPECIFIC AIMS

Specific aims of the following literature thesis include:

1. Provide a brief review of the literature to characterize current trends in combustible cigarette smoking and smoking cessation in the United States (U.S.).

2. Provide a brief review of the literature with regards to the mechanisms—molecular, behavioral, and genetic—contributing to nicotine addiction.

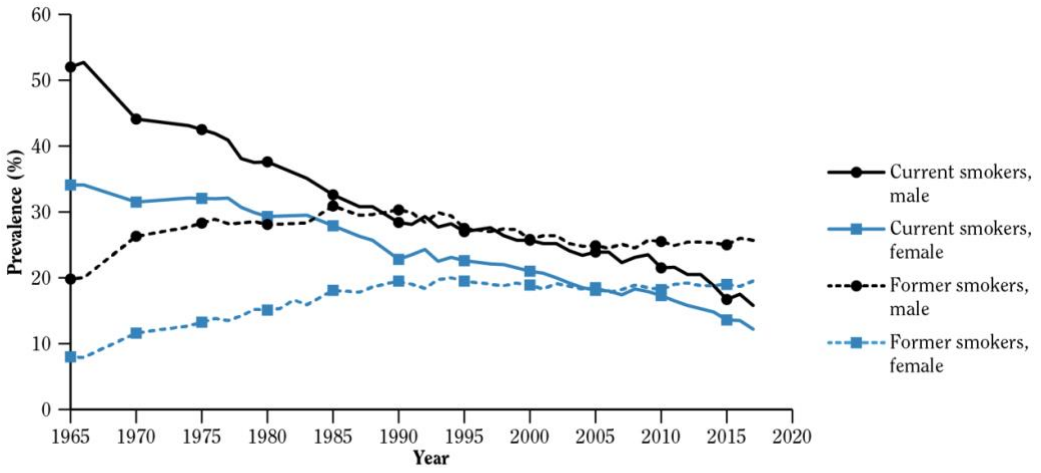
2. Provide a brief review of the literature to substantiate the health impacts of smoking and benefits of smoking cessation.

3. Compare standard-of-care smoking cessation treatments, varenicline (Chantix) and nicotine replacement therapy (NRT), with a particular emphasis on efficacy and tolerability.

BACKGROUND

Current Cigarette Smoking and Smoking Cessation Trends in the U.S.

The landscape around smoking cigarettes has shift drastically since combustible cigarettes were first introduced into the U.S. in the early 1800s. Arguably, the greatest shift in the landscape of cigarette use has occurred in the last 60 years. In fact, the rate of cigarette smoking among adults living in the U.S. has declined significantly since 1965, when the incidence of cigarette smoking was estimated to be 42.4% by the U.S. Surgeon General's Report on smoking and tobacco use. Mostly recently, smoking prevalence has been estimated to be roughly 14% percent of the U.S. adult population. Despite this drastic decrease, 14% equates to roughly 34 million U.S. adults. A graph depicting the overall decrease in smoking cigarettes over the last 60 years is provided below (Figure 1). As previously mentioned, the decrease in smoking prevalence since 1965 has been attributed to many things including public health campaigns, medical advancements, the development of innovative smoking cessation therapies and treatments, changing social norms and social acceptance of smoking cigarettes, the implementation of smoke-free laws and policies, rising cigarette prices, and increased education surrounding the health consequences of smoking cigarettes.[1,21,5,18]



Source: NHIS, National Center for Health Statistics, public use data, 1965–2017.
Note: From 1965 to 2017, data were reported for the following years: 1965, 1966, 1970, 1974, 1976–1980, 1983, 1985, 1987, 1988, 1990–1995, and 1997–2017.

Figure 1: Smoking Prevalence in the United States (1965-2017)
This figure shows the decline in smoking rates and rise in smoking cessation rates among both males and females living in the United States between the years 1965 to 2017. Of note, between the years 1965 to 2017, females consistently had lower rates of smoking when compared to men.
Source: U.S. Department of Health and Human Services (2020). *The U.S. Surgeon General's Report.*[5]
Figure downloaded from: www.hhs.gov/

In addition to the overall decrease in the prevalence of cigarette smoking, there are several other trends that characterize the current use of cigarettes among adults living in the U.S. One key trend is that women are known to have lower rates of cigarette smoking compared to men (Figure 1).[2,5] Additionally, smoking rates are highest among the ages of 24-44 (14%) and 45-64 (15%) and within populations of non-Hispanic American Indian/Alaska Native groups, where the prevalence of cigarette use is estimated to be greater than 27%. Education status and income levels also show patterns of cigarette use in that the lowest rates of smoking were found among people with higher levels of education (graduate degree smoking prevalence =

3.5%) and incomes greater than $100,000 (6.2%). Conversely, rates of smoking for persons who did not graduate high school or obtained a general education development (GED) certification were estimated to be 22% and 32%, respectfully. Finally, smoking rates are also highest within LGBTQIA+ communities (16.1%), patients who are uninsured or receiving Medicare (21.1% and 22.7%, respectfully), people living with disabilities (19.8%) or people experiencing psychiatric disorders (greater than 26.9%), when compared to their non-smoking counterparts.[1,2,5,21] Despite the substantial decrease in the incidence of smoking cigarettes over the last 60 years, 34 million Americans are still smoking. In addition to that, comprising the vast majority of people who are still smoking are individuals belonging to vulnerable communities (i.e., LGBTQIA+, uninsured, minority groups) or considered to be disadvantaged (i.e., low income). Taken together, these trends alone are strong indicators of the need for effective smoking cessation treatments.

In addition to current cigarette use trends, it is also important to consider current smoking cessation trends. It is estimated that at any one time, roughly 70% of U.S. adults want to quit smoking. Additionally, each year more than 50% of U.S. adults report making at least a single quit attempt.[5] Despite the interest in quitting and the high percentage of smokers making quit attempts each year, only 3-5% of smokers attempting to quit on their own, without the use of any treatment or assistance, are successful.[19] Even more, fewer than 33% of smokers who attempt to quit are using available pharmacological treatments. The reason for this is very complex including medication skepticism, insurance issues, affordability, access to treatment and

education barriers.[5] Trends that characterize smoking cessation rates show that men have a more difficult time maintaining smoking abstinence, in addition to younger smokers, uninsured smokers and smokers belonging to racial minority groups. Moreover, smoking cessation rates are also low in groups of people experiencing smoking related diseases and illness.[5] Finally, and most importantly, it is estimated that it takes between 8-11 times before a smoker is successfully able to achieve and maintain abstinence.[20] This last statistic is significant because it clearly indicates the addictive nature of cigarettes.

Based on the aforementioned statistics, smoking rates remain elevated despite a high percentage of smokers indicating their desire to quit. When this information is considered altogether, it is clear that the need for effective and tolerable smoking cessation treatments is high. The next section will describe some of the key mechanisms leading to nicotine addiction and long-term cigarette smoking.

Nicotine Addiction

Nicotine addiction, described as the inability to quit smoking, involves the interaction of many different variables including pharmacology, conditioned behaviors, social and environmental cues, and genetics. The following paragraphs will briefly explore a few of the key mechanisms that lead to nicotine addiction in an effort to emphasize the difficulties of quitting smoking.

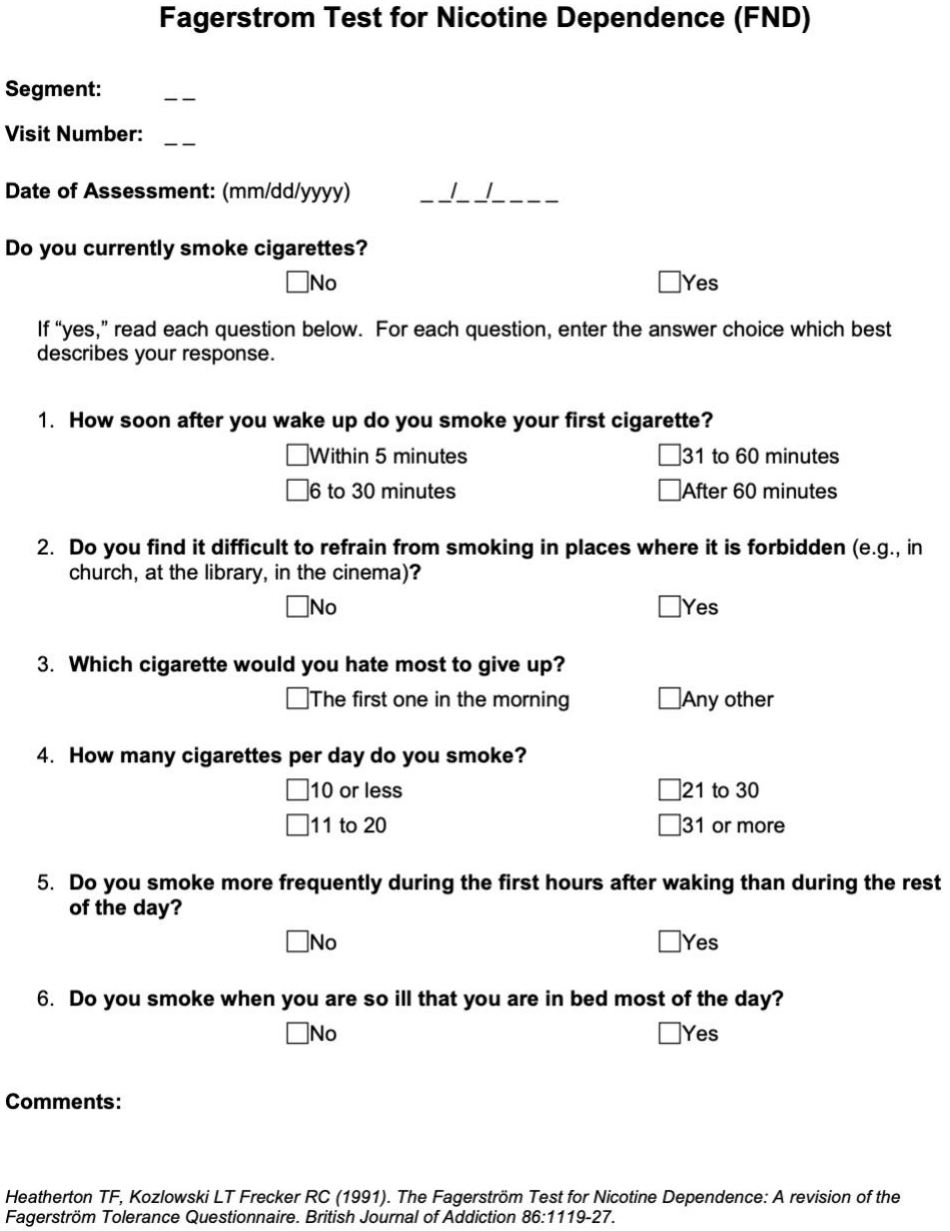
Measuring Nicotine Dependence

Prior to beginning an in-depth discussion of nicotine addiction, it is important to briefly mention how dependence on nicotine is clinically diagnosed. There are two mechanisms by which health care providers frequently diagnosis nicotine dependence. The "Diagnostic Nicotine Dependence" guidelines described in the Diagnostic and Statistical Manual for Mental Disorders 4th edition (DSM-IV) are a common tool used by health care providers to assess a patient's level of nicotine dependence.[4] Components of nicotine dependence that are assessed by these guidelines include:

> "1) tolerance, 2) withdrawal, 3) using more of the substance than intended, 4) persistent desire to quit or unsuccessful efforts to cut down, 5) great deal of time spent obtaining the substance (e.g. chain smoking), 6) important activities given up or reduced because of substance use, and 7) continued substance use despite persistent or recurrent physical or psychological problem caused or exacerbated by its use."[4]

A second commonly used tool to diagnosis nicotine addiction is the Fagerström Test for Nicotine Dependence (FTND) (Figure 2), an abbreviated version of the now outdated Fagerström Tolerance Questionnaire (FTQ).[22] Compared to the guidelines for nicotine dependence as outlined in the DSM-IV, the FTND is generally considered a more objective measure of dependence.[4] For both tools, the higher the score the higher the patient's nicotine dependence. Additionally, and despite widespread use of the FTND in both clinical and research environments, the use of

the FTND has been deemed controversial by several researchers who question its reliability and overall validity when measuring nicotine dependence.[23] Ultimately, the dependence between diagnostic nicotine dependence guidelines described by the DSM-IV and the FTND is estimated to be low to moderate, thereby suggesting that these two measures capture nicotine dependence and addiction differently.[4] Regardless of these differences, research and clinical discussions about measuring nicotine dependence are ongoing, and current efforts are focused on improving diagnostic measures and developing new diagnostic instruments. In fact, a recently developed tool called the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68), measures 13 different variables and has been shown to be significantly associated with FTND outcomes, especially with regards to tolerance.[4]



Fagerstrom Test for Nicotine Dependence (FND)

Segment: _ _

Visit Number: _ _

Date of Assessment: (mm/dd/yyyy) _ _/_ _/_ _ _ _

Do you currently smoke cigarettes?

☐No ☐Yes

If "yes," read each question below. For each question, enter the answer choice which best describes your response.

1. **How soon after you wake up do you smoke your first cigarette?**
   ☐Within 5 minutes ☐31 to 60 minutes
   ☐6 to 30 minutes ☐After 60 minutes
2. **Do you find it difficult to refrain from smoking in places where it is forbidden** (e.g., in church, at the library, in the cinema)**?**
   ☐No ☐Yes
3. **Which cigarette would you hate most to give up?**
   ☐The first one in the morning ☐Any other
4. **How many cigarettes per day do you smoke?**
   ☐10 or less ☐21 to 30
   ☐11 to 20 ☐31 or more
5. **Do you smoke more frequently during the first hours after waking than during the rest of the day?**
   ☐No ☐Yes
6. **Do you smoke when you are so ill that you are in bed most of the day?**
   ☐No ☐Yes

Comments:

Heatherton TF, Kozlowski LT Frecker RC (1991). The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. British Journal of Addiction 86:1119-27.

Figure 2: Fagerström Test for Nicotine Dependence (FTND)
This figure shows the Fagerström Test for Nicotine Dependence (FTND), a brief 7-question survey that is commonly used to assess nicotine dependence. Questions with "yes" or "no" responses are scored 0 (no) or 1 (yes), whereas questions with multiple choice answers are scored as 0, 1, 2 or 3. Scores range from a minimum of 0 to a maximum of 10. The higher the score the greater the patient's dependence is on nicotine.[22] The FTND is used both clinically and in research, however its reliability and overall validity remain controversial.[23]

Source: Heatherton, et al. (1991). *British Journal of Addiction.*[22]
Figure downloaded from https://cde.drugabuse.gov/

Neurobiology of Nicotine Addiction

Nicotine, a natural constituent of tobacco plants, is the primary active ingredient in combustible (burning) cigarettes.[17] Nicotine is also the component of cigarettes that makes them highly addictive.[10,17] Nicotine has been shown to produce the same effects, which include reward-seeking behavior and repetitive self-administration, of other well-known addictive drugs such as amphetamine and cocaine.[17] Therefore, nicotine is considered one of the main drivers of tobacco addiction and long-term cigarette smoking.[10,17]

The smoke that is produced by a burning cigarette and inhaled through the oral cavity contains tobacco particles. As the smoke is inhaled, the nicotine is pulled out of the tobacco. The nicotine particles travel to the lungs where they rapidly enter the circulatory system, first through the pulmonary veins and then through the greater arterial circulation.[10] Within seconds of entering the arterial circulation, the nicotine particles make their way to the brain. In fact, it has been estimated that once nicotine enters the lungs, it traverses the blood-brain barrier (BBB) within 10-20 seconds.[24] Upon crossing the BBB, nicotine binds to ligand-gated ion channels called neuronal nicotinic acetylcholine receptors (nAChRs) on dopamine-releasing neurons. The primary agonist for nAChRs is typically acetylcholine (ACh), however, nicotine is also an agonist. Once nicotine binds to the receptor , the receptor undergoes a conformational change, leading to an influx of sodium (Na^+) and calcium (Ca^{2+}) and a

neuronal membrane depolarization.[25] The result of this signaling cascade and eventual depolarization is the release of neurotransmitters, most importantly dopamine, into the brain's reward centers via the ventral tegmental area (VTA). The areas of the brain that are involved in nicotine addiction include to the frontal cortex, corpus striatum, nucleus accumbens, and mesolimbic region of the brain (Figure 3).[4,10,17] This is considered the primary mechanism of action by which nicotine causes addiction to smoking cigarettes.[10]

Dopamine is important when discussing nicotine addiction because it has been shown to mediate many of the behaviors characterizing nicotine addiction such as reward seeking behavior and sustained self-administration of nicotine (i.e., smoking cigarettes).[24] When nicotine binds to the receptor and dopamine is released, this signals a "pleasurable experience" causing a sensation of a momentary "high" or "buzz."[10] As the effects of dopamine fade, the pleasurable feelings associated with smoking also fade, thereby leading to reward seeking behavior of continued consumption of nicotine. To support this notion, studies have shown that the disruption of these receptor pathways in the brain via experimentally induced brain lesions or pharmacological means in nicotine-dependent rats significantly decreases self-administration of nicotine.[4,10,17]

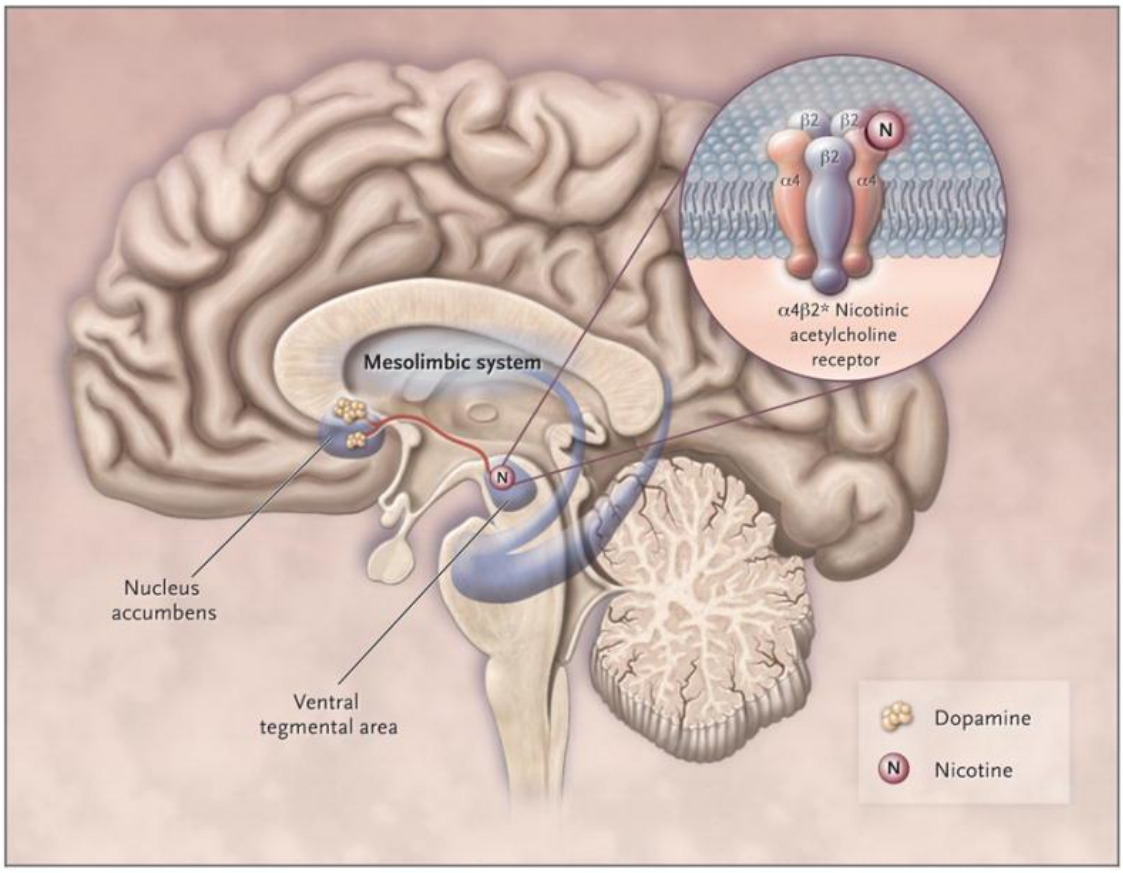


Figure 3: Nicotine's Mechanism of Action
This figure shows the mechanism by which nicotine acts as an agonist and activates the neuronal nicotinic acetylcholine receptors (nAChRs). The binding of nicotine to the receptors causes the neurons to release dopamine into the frontal cortex, corpus striatum, and mesolimbic region of the brain.
Source: Reproduced with permission from Hays, J. Taylor, and Jon O. Ebbert. "Varenicline for tobacco dependence." New England Journal of Medicine 359.19 (2008): 2018-2024.), Copyright Massachusetts Medical Society. *New England Journal of Medicine.*[10]
Figure downloaded from https://www.ncbi.nlm.nih.gov/

In addition to the direct release of dopamine, nicotine also causes the indirect release of dopamine through other mediating mechanisms. By binding to nAChRs on presynaptic glutamate neurons, nicotine induces an increase in the release of glutamate. Glutamate plays a critical role in nicotine addiction because it enables the

release of dopamine from nearby neurons.[10] At the same time, nicotine also increases the release of γ-aminobutyric acid, or GABA, by binding to nAChRs on presynaptic GABA neurons. Unlike glutamate, GABA inhibits the release of dopamine.[26] Although appearing contradictory at first glance, long-term consumption of nicotine causes desensitization of some nAChRs, causing GABA-mediated inhibition of dopamine to decrease and glutamate-mediated release of dopamine to increase. The overall net result is increased excitement of dopaminergic neurons and an overall increased responsiveness and sensitivity to nicotine.[10,24,27] Furthermore, chronic exposure to nicotine (alongside other addictive drugs such as amphetamine, opiates, alcohol and cocaine) increases levels of tyrosine hydroxylase (TH). This is important because TH is shown by research to be "the rate-limiting enzyme" involved in the creation of dopamine in the aforementioned brain regions.[27] Although there are other neurotransmitters that have been shown to contribute to the role that nicotine plays in smoking addiction, dopamine is the primary neurotransmitter causing continued self-administration of nicotine (i.e., smoking cigarettes) and reward-seeking behaviors.[10,17]

Another brain mechanism that plays an important role in nicotine addiction is neuroadaptation, also known as tolerance or desensitization. As exposure to nicotine increases, the number of nAChRs increase, specifically those with an elevated affinity for nicotine (such as, nACh receptors that contain both $\alpha 4$ and $\beta 2$ subunits). This observation is supported by several studies, involving both rats and humans, which show nAChR upregulation following periods of long-term nicotine exposure.[17,28] The reasoning for this increase is not entirely understood but is believed to be caused by

neuroadaptation or an increase in the number and frequency by which nAChRs enter a state of desenistatization.[10,28] When the receptors become desensitized (due to long-term exposure to nicotine), they are recycled into the cell at a slower rate, leading to a net increase in the number or receptors on the surface of dopaminergic neurons. Ultimately, the driving force behind this mechanism appears to be a decreased rate of turn over for desensitized receptors, followed by an overall net increase in the number of nicotinic receptors.[10] Therefore, when nicotine is removed and the nAChRs recover from a period of low tolerability, the brain enters a state of "hyperexcitability" caused by the increased number of nACh receptors on the surface of the neuron.[17,28] This results in feelings of "unrest and agigation,"[17] as well as feelings of stress, anxiety, and depressed moods[10], all classic symptoms of "nicotine withdrawal," a well-know and powerful mechanism that promotes continued smoking.[10,17] Although several studies support the aforementioned theory of long-term nicotine consumption driving nAChR upregulation, to what extent receptor desensitization plays a role in nicotine addiction is still under investigation.[28]

Finally, there is evidence that other components of cigarette smoke, in addition to nicotine, may contribute to nicotine dependence via increased dopamine levels in the reward regions of the brain. Cigarette smoke has also been shown to contain monoamine oxidase (MAO) inhibitors. MAOs are enzymes that help with the breakdown of neurotransmitters, namely dopamine.[10] Research demonstrates that cigarette smoking inhibits the brain's normal MAO activities thereby leading to elevated levels of dopamine.[10,25] Acetaldehyde and biogenic amines, as well as their

byproducts, are examples of MAO inhibitors found in cigarette smoke.[10,29] Commonly reported byproducts of acetaldehyde and biogenic amines include harman and salsolinol, both of which are known to readily cross the BBB. Harman, in particular, has been shown to have strong MAO-inhibiting abilities and serum blood levels of harman appear to be elevated in smokers vs. non-smokers, with research suggesting levels may be as much as 2-10 times higher.[29] Ultimately, MAO inhibitors inhaled through cigarette smoke are another important mechanism by which nicotine addiction develops.

In summary, the basis of nicotine addiction via biological brain mechanisms can be described as a release of dopamine that leads to positive reinforcement, reward-seeking behavior, and the avoidance of withdrawal symptoms.

Psychological & Behavioral Mechanisms of Nicotine Addiction

In addition to the biological mechanisms of nicotine addiction, research has also shown that psychological and behavioral mechanisms are involved. In fact, studies have shown that the consumption of nicotine induces feelings of pleasure, while simultaneously reducing feelings of stress and anxiety.[10] Additionally, it has been shown that when smokers are deprived of nicotine, certain cognitive functions and overall cognitive performance are impaired. Conversely, when consuming nicotine smokers report increased levels of focus, memory recall and general reasoning.[30] As such, one can imagine that feelings of stress and anxiety (known nicotine withdrawal symptoms), in addition to diminished cognitive performance might lead to reward

seeking behavior (i.e., increased nicotine consumption) following periods of nicotine deprivation.[30] This very notion is backed by several studies that show the basic of nicotine addiction involves the enhancement of mood and cognitive performance and the evasion of nicotine withdrawal.[10]

Furthermore, conditioned behavior has also been shown to contribute to nicotine addiction. For example, with frequent smoking, a smoker begins to associate certain situations, environmental stimuli, or feelings with the rewarding effects of nicotine.[10] These associations are known as "smoking-related cues" and are considered to be one of the primary drivers of habitual smoking.[10] The reason for this is because smoking-related cues are said to induce craving and trigger relapse, thereby contributing to the development of nicotine addiction. In fact, smoking-related cues are shown to "capture the attentional resources of smokers" and exploit the mechanisms that prioritize positive stimuli.[31] Animal studies support this notion in that animals experiencing continuous nicotine exposure undergo neurological changes known to underlie the process of conditioning. As a result, nicotine has been shown to enhance one's behavioral response to conditioned stimuli, such as a smoking-related cue, thus resulting in habitual smoking. [31] Common smoking-related environmental or situational cues include mealtime, a cup of coffee, driving in a car, drinking alcohol, or being around others who are smoking.[10] Eventually, after repeated circumstances by which smoking occurs at the same time as smoking-cues, a situation like meal time becomes associated with smoking a cigarette and provokes the powerful urge to smoke, even if an individual was not previously thinking of smoking.[10] In addition to

situational or environmental stimuli, feelings are shown to be another powerful smoking-related cue. For example, a smoker experiencing withdrawal symptoms such as irritability may learn that smoking a cigarette provides a sense of relief. As such, subsequent feelings of irritability, whether related to nicotine deprivation or not, are shown to elicit a strong urge to smoke.[10]

Ultimately, the link between smoking-related cues and habitual smoking is well-established, as is the driving force of withdrawal symptoms. Therefore, the desire to smoke is sustained through conditioned behaviors and the avoidance of withdrawal symptoms, in addition to the previously mentioned molecular and brain mechanisms. A figure summarizing the mechanisms of nicotine addiction discussed so far is provided below (Figure 4).

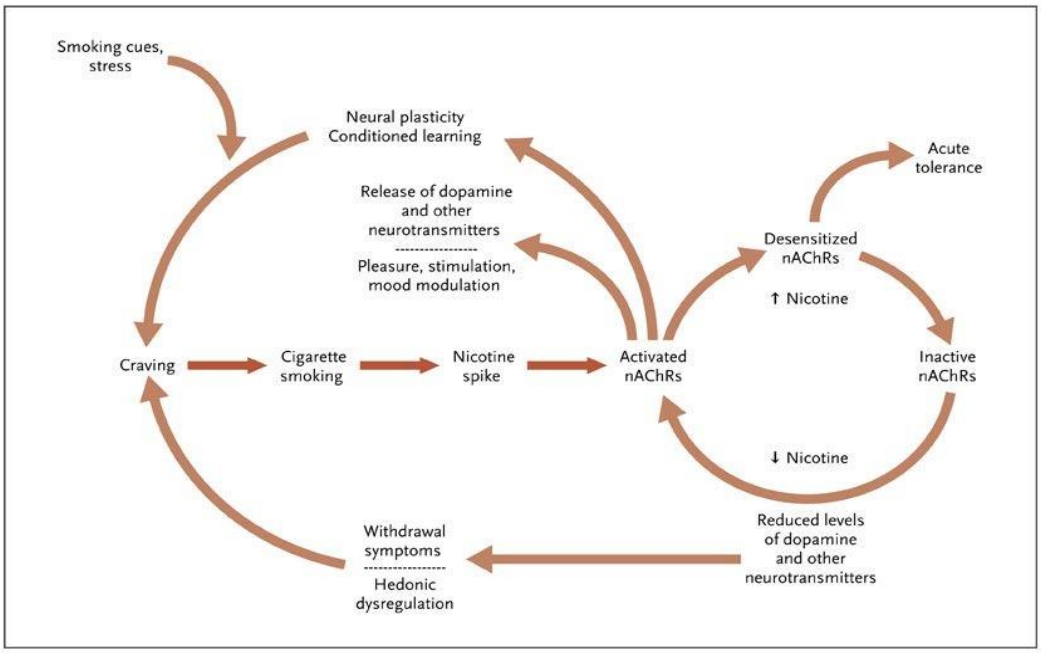


Figure 4: Nicotine Addiction: Molecular and Behavioral Factors
This figure shows the mechanisms, both molecular and behavior, by which nicotine addiction develops.
Source: Reproduced with permission from Benowitz, Neal L. "Nicotine addiction." New England Journal of Medicine 362.24 (2010): 2295-2303., Copyright Massachusetts Medical Society. *New England Journal of Medicine.*[10]
Figure downloaded from https://www.ncbi.nlm.nih.gov/

Genetics of Nicotine Addiction

Like many addictions, nicotine addiction has a fairly well-established genetic influence. [32] This next section will review the role that genetics play in nicotine addiction. For context, and as previously mentioned, the two most commonly used instruments for diagnosing nicotine dependence include the diagnostic nicotine dependence guidelines defined by DSM-IV and the FTND, a seven-question survey asking about daily cigarette use and withdrawal symptoms. For both tools, The higher the score the greater the patient's dependence is on nicotine.[22]

The majority of evidence supporting the association between genetics and nicotine addiction is derived from twin and adoptions studies.[4,32] The first twin study suggesting a genetic mechanism dates back to 1958, when it was shown that smoking rates were higher in monozygotic (one fertilized egg) vs dizygotic (two fertilized eggs) twin pairs.[32] This result was replicated across several studies over the last 60 years, and more recent reports on genetic influences suggest an even greater genetic role than ever before. In fact, each of seven previously mentioned criteria defining nicotine addiction as described by the DSM-IV, have shown a high degree of heritability, with percentages ranging from 26-73%.[4] Even more, twin studies have shown that the level of nicotine dependence (a measure of several factors including the time from waking to first cigarette) and total daily cigarette consumption show a high degree of heritability, estimated to be greater than 50%.[4] These same studies also suggest that genetic factors influence the withdrawal symptoms experienced by smokers.[4,10] That is to say, the presence of certain genetic markers may influence the type and severity of withdrawal symptoms experienced by smokers following brief and prolonged periods of smoking cessation.[4,10] As it relates to gender, studies have shown that there appears to be a higher genetic influence as it relates to a women's ability to quit compared to men, with percentages of 68% and 54%, respectively.[4]

Significant effort has been made to ascertain the specific genes underlying the mechanism of nicotine dependence over the last two decades. Early twin and family studies suggested that more than one gene is involved in the development of smoking addiction and one's risk for becoming addicted to smoking. The dramatic medical and

scientific advancements over the past few decades have allowed the research community to explore this in greater depth.[32] Most recently, research has considered genes that code for nAChRs, dopamine receptors, as well as mechanisms involved in the production, release, transportation and metabolism of several neurotransmitters relevant to nicotine dependence, such as dopamine, GABA and glutamate.[10] The complex nature of nicotine addiction, alongside the various contributing factors, makes identifying and isolating "nicotine addiction genes" difficult. Currently, there is an ongoing genome-wide association study that is attempting to pinpoint genetic determinates of nicotine dependence; the preliminary results of this research suggest that genes coding for the $\alpha_5/\alpha_3/\beta_4$ nicotinic cholinergic receptor, cell adhesion molecules and extracellular matrix molecules may be associated with nicotine addiction.[33,34] In particular, certain variants of the $\alpha_5/\alpha_3/\beta_4$ nicotinic cholinergic receptors have been shown to have a significant association with daily cigarette consumption, plasma concentrations of cotinine (the key metabolite of nicotine used to estimate amounts of nicotine consumption), and the level of tobacco smoke carcinogens found in urine. [33,34] In addition, certain variants of the $\alpha_5/\alpha_3/\beta_4$ nicotinic cholinergic receptors (nAChRs) have been shown to have an significant association with the risks of smoking-related diseases (to be discussed next).[10,35,36] Finally, the genes coding for the G-protein coupled receptors responsible for binding dopamine, DRD1-DRD5, have also been explored. For example, there is some evidence that links variations in the DRD2 gene with cigarette consumption, however, there has been conflicting results across studies.[32] With regards to the gene for DRD4,

variations in the number of tandem repeats found on exon 3 of this gene have been shown to be correlated with habitual cigarette smoking. For example, a recent study suggested that among African Americans, increased number of repeats (6-10) were associated with a shorter time period between waking and first cigarette each morning, when compared to 2-5 tandem repeats.[32] There is also some evidence that variations in the genes coding for receptors DRD1, 3 and 5 have impacts on smoking initiation and levels daily cigarette consumption. Finally, several genes involved in the metabolism of nicotine and dopamine have also shown links to smoking addiction. For example, a region of DNA near the gene for tyrosine hydroxylase (TH), "the "rate-limiting enzyme in the production of dopamine," has been linked to long-term cigarette smoking.[32]

Although not an exhaustive exploration on the role that genes play in nicotine dependence, the previously discussed studies allude to the key role that genetics may play in long-term cigarette use. Ultimately, understanding the role of genes in nicotine dependence is important because it helps inform not only our understanding of the disease but also the creation of effective treatment options.

Health Impacts of Cigarette Smoking

Smoking combustible cigarettes increases the risk of developing many different diseases, several of which can be fatal.[37] Despite these well-established health impacts, the current rate of smoking cigarettes remains high.[5] As previously mentioned, smoking cigarettes is the number one morbidity/mortality among adults living in the U.S. In fact, each year almost half a million premature deaths (estimated to be around 443,000) among

U.S. adults are attributed to smoking.[1–4] According to West (2017), premature death caused by smoking is defined as "a death from a smoking-related disease in an individual who would otherwise have died later from another cause."[37] Even more, the U.S. Department of Health and Human Services estimates that smoking cigarettes shortens a person's life by an estimated 10 years. In medical terms, this means that smoking results in 10 life years lost per smoker.[38] For the U.S. population of smokers, this equates to "5.6 million years of potential life lost" every year. It is also important to note that of the smoking-related deaths that occur each year, many of the deaths are reported to be in former smokers (i.e., persons that have quit smoking).[37] This indicates that the harm caused by smoking cigarettes is not reversible and that smoking has long-term and permanent effects on the human body. In fact, according to Beane et al. (2007), the chance of dying as a result of a smoking-related disease or illness remains increased even after a person quits smoking.[39] Finally, it should be mentioned that daily cigarette use and the chance of developing a smoking-related disease or illness are positively correlated. In other words, higher daily cigarette consumption is associated with a higher risk of developing a smoking-related disease or illness in most cases (i.e., a positive linear relationship).[37]

The following paragraphs will briefly describe several of the most common diseases and illnesses—cancer, respiratory diseases, and cardiovascular diseases—caused by smoking cigarettes. A summary of the most common smoking-related diseases shown to lead to death is provided in the table below (Table 1). Although the following paragraphs will focus on the main health impacts of smoking, it should be noted that the

harm caused by smoking is extensive.[5] In fact, and in addition to the main causes described by Table 1 and explored in the subsequent paragraphs, smoking increases the risk of rheumatoid arthritis, blindness, osteoporosis, amputation, preeclampsia, reduced fertility, gastric ulcers, decreased renal function, miscarriage, and diabetic neuropathy.[37,40,41] Even more, the U.S. Department of Health and Human Services estimates that once smokers surpass age 40 they experience higher levels of pain and increased levels of disability when compared to their non-smoking counterparts.[38]

Cause of death from smoking	Benefit of stopping smoking
Coronary heart disease and stroke	Preventable if cessation occurs in early adulthood; at least partially reversible thereafter
Cancers of the lung and upper airways	Preventable if cessation occurs in early adulthood; further increase in risk prevented thereafter
Chronic obstructive pulmonary disease	Preventable if cessation occurs in early adulthood; further decline in lung function slowed thereafter
Miscarriage and underdevelopment of foetus	Preventable if cessation occurs early in pregnancy; risk is mitigated by stopping at any time in pregnancy

Table 1: Main Causes of Smoking-Related Deaths and the Benefits of Quitting
This table provides a brief list of the main causes of death know to be attributed to smoking burning cigarettes. The main causes of death from smoking include cardiovascular disease, cancer, and respiratory disease. Smoking cigarettes has also been shown to cause miscarriage and intrauterine growth restriction of an unborn fetus. This table also provides the benefits of stopping smoking as it relates to each cause, such as decreased risk of miscarriage.[37]
Source: West, et al. (2017). Journal of *Psychology & Health*.[37]
Table taken from https://doi.org/10.1080/08870446.2017.1325890

Cancer

Cigarette smoking is the leading cause of cancer deaths in the U.S.[42], and has been shown to cause cancer in almost all parts of the body including, but not limited to, the lungs, bladder, cervix, colon, esophagus, breast, oropharynx, pancreas, stomach, oral cavity and blood.[6,37,43] Cigarette smoke contains greater than 60 carcinogens, many of

which have been found in the smoke of cigarettes in "biologically significant" amounts.[37,44] According to Hecht et al. (2006), carcinogens are best described as "any agent, chemical, physical, or viral that causes cancer or increases the incidence of cancer."[44] The carcinogens found in cigarette smoke, therefore, are said to be partially responsible for the development smoking-related cancers.[44]

The association between cancer and smoking cigarettes is arguably one of the most well-studied associations in the history of cancer according to Stephen Hecht (2006).[44] Epidemiological evidence of the link between cancer and cigarette smoking first appeared in the early 1900s.[6] It was not until 1950, however, that the first link was established. From 1950 onward, the evidence supporting the relationship between smoking cigarettes and an elevated risk of cancer has skyrocketed, with new links and disease patterns being discovered every decade.[6] Therefore, the following paragraphs will touch on a few of the cancers known to be caused by cigarette smoke.

Lung cancer has been shown to be the number one cause of all cancer-related deaths, regardless of ethnicity or gender.[43,45] Smoking has been shown to cause 90% of all lung cancer-related deaths. In other words, 9 out of 10 deaths caused by lung cancer are attributed to cigarette smoking.[43,46,47] In fact, lung cancer is the most frequent cancer among smokers, having an estimated prevalence of nearly 9-10 times greater for the average smoker and 20 times greater for heavy smokers, when compared to people who do not smoke.[45] As reported by the International Agency for Research on Cancer (2004), the greatest predictor of lung cancer among smokers is the length of time a smoker has been consuming cigarettes. Daily number of cigarettes is also a strong predictor of lung

cancer, in that higher daily cigarette consumption leads to higher risk of developing lung cancer.[48] Adenocarcinoma is the most commonly reported lung cancer caused by smoking, although all types of lung cancer carcinomas have been attributed to smoking cigarettes.[44] In addition to lung cancer, cigarette smoking has also been shown to cause bladder, ureter and renal cancers. The risk of developing the aforementioned cancers also increases with higher levels of daily cigarette consumption.[44] Gastric cancer has also been shown to be significantly associated with cigarette smoking.[49] For example, cohort studies have shown that cigarette smokers have an higher chance of being diagnosed with gastric cancer at rates that are almost two times that of non-smokers, though among smokers the risk is higher in men compared to women.[47,49] Again, a positive relationship exists between daily cigarette use and the risk of stomach cancer.[49] Cigarette smoking has also been shown to be associated with a moderate risk of breast cancer in women, the most frequent cancer affecting women across the globe.[50] In fact, several carcinogens, aromatic amines, polycyclic aromatic hydrocarbons (PAHs), and N-nitrosamines have been found to be associated with breast cancer given their ability to pass through the alveolar membrane, thereby depositing in mammary tissue.[50] Finally, and though less common than lung cancer, additional cancer types shown to be linked to cigarette smoking include cancers of the oral cavity, throat, esophagus, nasal passages, sinuses, liver, pancreas, cervix, and colon.[47] Smoking has also been shown to elevated one's risk of developing myeloid leukemia. This relationship is based off the presence of benzene, a well-established carcinogen found in cigarette smoke that has been linked to leukemia.[42,47] The risks of developing many of the previously mentioned types of cancer

is described in the following tables (Table 2 and Table 3). It should be noted that there are other types of cancer that may have links to smoking cigarettes that are not mentioned here.

Cancer diagnosis	All men			
	Proportions of cancer in smokers (%)	Proportions of cancer in non-smokers (%)	HR (95% CI)	*p*-value
Cancer total (C00-C99)	20.0	19.0	1.07 (1.04–1.11)	<0.001
Positive association				
Bronchus and lung (C34)	2.96	0.22	9.92 (8.08–12.17)	<0.001
Larynx (C32)	0.27	0.03	5.17 (3.16–8.44)	<0.001
Liver (C22)	0.40	0.13	2.83 (1.85–4.32)	<0.001
Nasal cavity, middle ear, sinuses (C30, C31)	0.15	0.05	2.61 (1.60–4.28)	<0.001
Bladder (C67)	1.26	0.59	2.32 (1.98–2.73)	<0.001
Lip, oral cavity, and pharynx (C00-14)	0.61	0.26	2.12 (1.71–2.63)	<0.001
Esophagus (C15)	0.74	0.32	1.97 (1.57–2.46)	<0.001
Pancreas (C25)	0.46	0.22	1.83 (1.34–2.49)	<0.001
Stomach (C16)	0.21	0.18	1.40 (1.02–1.94)	0.039
Kidney (C64)	0.43	0.30	1.26 (1.00–1.58)	0.048
Lymphomas (C81-88)	2.53	2.09	1.24 (1.13–1.36)	<0.001
Negative association				
Skin (C43, C44)	4.78	6.98	0.74 (0.70–0.79)	<0.001
Prostate (C61)	2.95	4.39	0.71 (0.65–0.76)	<0.001
Multiple myeloma (C90)	0.15	0.32	0.67 (0.48–0.93)	0.018
No association				
Leukemias (C91-95)	0.51	0.46	1.00 (0.82–1.22)	0.972
Colon, rectum, anus (C17-C21)	1.38	2.03	0.89 (0.79–1.00)	0.051
Bones (C40, C41)	0.05	0.09	0.84 (0.49–1.46)	0.542
Testis (C62)	0.19	0.21	0.83 (0.66–1.03)	0.092
Thyroid gland (C73)	0.04	0.07	0.83 (0.59–1.17)	0.280
Brain (C71)	0.15	0.19	0.80 (0.59–1.09)	0.155

Table 2: Men who smoke cigarettes and the risk of developing cancer
This table lists the cancers known to be associated with cigarette smoking and compares the incidence of cancer between men identifying as smokers vs. non-smokers. Lung cancer is shown to have the highest incidence among men who smoke compared to non-smokers ($p<0.001$).
Source: Jacob et al., (2018), *Oncotarget.*[51]
DOI: 10.18632/oncotarget.24724

Cancer diagnosis	All women			
	Proportions of cancer in smokers (%)	Proportions of cancer in non-smokers (%)	HR (95% CI)	*p*-value
Cancer total (C00-C99)	17.0	14.9	1.03 (1.00–1.06)	0.031
Positive association				
Bronchus and lung (C34)	2.31	0.15	14.06 (10.91–18.12)	<0.001
Larynx (C32)	0.06	0.01	4.86 (2.15–10.96)	<0.001
Bladder (C67)	0.34	0.12	2.75 (2.07–3.64)	<0.001
Esophagus (C15)	0.24	0.07	2.55 (1.73–3.77)	<0.001
Nasal cavity, middle ear, sinuses (C30, C31)	0.05	0.01	2.47 (1.09–5.62)	0.031
Vulva/vagina (C51, C52)	0.07	0.03	1.91 (1.18–3.09)	0.009
Cervix uteri (C53)	0.35	0.18	1.83 (1.43–2.33)	<0.001
Stomach (C16)	0.11	0.07	1.67 (1.08–2.57)	0.020
Pancreas (C25)	0.25	0.20	1.63 (1.17–2.28)	0.004
Lip, oral cavity, and pharynx (C00-14)	0.34	0.17	1.43 (1.12–1.83)	0.003
Negative association				
Skin (C43, C44)	3.70	5.00	0.74 (0.70–0.79)	<0.001
Breast (C50)	4.04	4.22	0.92 (0.87–0.97)	0.002
Corpus uteri (C54)	0.21	0.38	0.60 (0.48–0.76)	<0.001
No association				
Kidney (C64)	0.23	0.15	1.27 (0.94–1.73)	0.123
Brain (C71)	0.17	0.12	1.22 (0.86–1.73)	0.258
Bones (C40, C41)	0.03	0.03	1.17 (0.61–2.23)	0.639
Liver (C22)	0.17	0.09	1.12 (0.73–1.74)	0.584
Leukemias (C91-95)	0.28	0.22	1.07 (0.83–1.37)	0.613
Lymphomas (C81-88)	2.14	1.74	1.02 (0.93–1.11)	0.725
Colon, rectum, anus (C17-C21)	0.87	0.93	1.01 (0.88–1.15)	0.938
Ovary (C56)	0.36	0.41	0.88 (0.74–1.06)	0.181
Multiple myeloma (C90)	0.14	0.13	0.86 (0.57–1.31)	0.482
Thyroid gland (C73)	0.11	0.13	0.62 (0.35–1.08)	0.092

Table 3: Women who smoke cigarettes and the risk of developing cancer
This table lists the cancers known to be associated with cigarette smoking and compares the incidence of cancer between women identifying as smokers vs. non-smokers. Lung cancer is shown to have the highest incidence among women who smoke compared to non-smokers ($p<0.001$).
Source: Jacob et al., (2018), *Oncotarget.*[51]
DOI: 10.18632/oncotarget.24724

In summary, research has time and time again established a strong causal link between combustible cigarette smoking and cancer of over 20 different types, many of which have been shown to have a positive dose-dependent relationship (i.e., higher daily cigarette consumption or increased duration of smoking increases one's risk of developing cancer).[5] Thankfully, research has also shown that the benefit of smoking cessation at any age negates any further risk of developing cancer, especially in the case of lung cancer, however former smokers maintain an elevated risk of developing lung cancer for several years after quitting. Regardless, smoking cessation should be advised at any age to limit further risk of developing cancer.[37]

Respiratory Diseases and Illnesses

Similar to cancer, there is a well-established link between smoking cigarettes and the risk of developing respiratory disease and illness. This risk is based on the fact that when cigarette smoke is inhaled the smoke is absorbed and deposited into the airways and terminal branches of the lungs (alveoli) causing damage to the lung tissue and structure.[52] The consumption of toxins each time a person inhales cigarette smoke increases the risk of developing malignant (i.e., cancer) and non-malignant (i.e., not cancerous) diseases of the respiratory tract. Of note, this section will focus on non-cancer respiratory diseases caused by smoking cigarettes. In addition, and for the purposes of the following discussion, a medical description of several key respiratory diseases/illnesses caused by smoking is provided in the table below (Table 4).

Chronic obstructive pulmonary disease (COPD)	A preventable and treatable disease characterized by airflow limitation that is not fully reversible. The limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.
Emphysema	Permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis. In patients with COPD, either condition may be present. However, the relative contribution of each to the disease process is often difficult to discern.
Chronic bronchitis	Chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of productive chronic cough have been excluded.
Asthma	A chronic inflammatory disease of the airways in which many cell types play a role—in particular, mast cells, eosinophils, and T lymphocytes. In susceptible persons, the inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and/or in the early morning. These symptoms are usually associated with widespread and variable airflow obstruction that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli.

Table 4: A brief description of nonmalignant respiratory illnesses and diseases shown to be linked to combustible cigarette use
This table defines the four main respiratory illnesses and diseases shown to be linked to smoking combustible cigarettes.
Source: American Thoracic Society 2000 and American Thoracic Society/European Respiratory Society Task Force 2005. [52]
Table taken from: 7, Pulmonary Diseases

Citation: How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Centers for Disease Control and Prevention (US); National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US). Atlanta (GA): Centers for Disease Control and Prevention (US); 2010.

The first discussions of a potential link between cigarette smoking and respiratory disease dates back to the 1870s. It was not until the first Surgeon General's Report

published in 1964, however, that the original causal relationship between respiratory disease and smoking was established.[52,53] The report concluded that cigarette smoking "is the most important of the causes of chronic bronchitis in the United States…" and that "a relationship exists between pulmonary emphysema and cigarette smoking, but it has not been established that the relationship is causal."[52] Twenty years later, the 1984 Surgeon General report emphasized the role that cigarettes play in additional respiratory diseases like chronic obstructive pulmonary disease, also referred to as COPD.[52] The 1984 report concluded that smoking not only damages the lungs' structure and compromises their ability to function, but weakens the lungs' immune response and causes narrowing of the airway passages.[53] As such, smoking cigarettes was classified as one of the leading risk factors for COPD.[52] Since 1984, several other respiratory-based diseases and illnesses have joined the growing list of smoking-related diseases, including emphysema and asthma.[52]

Research has shown that cigarette smoking is the most significant risk factor when considering one's chances of developing COPD, the most common nonmalignant respiratory disease among smokers.[53] In fact, it is estimated that smoking cigarettes accounts for 80-90% of all COPD cases every year.[54] It has been estimated that as many as 50% of smokers will develop COPD in their lifetime[55], however more recent reports suggest the estimate is around 20% (most likely due to increased consideration of air pollutants as a possible cause for COPD). It is also estimated that COPD prevalence is 20-30% higher in current smokers when compared to smokers who have quit. A graph detailing these results is provided below (Figure 5). As you can see in the graph, there is

a higher incidence of COPD among current smokers vs. former smokers, both of which are higher than never smokers. Additionally, as one ages the risk of developing smoking-related COPD increases up until age 79.[56]

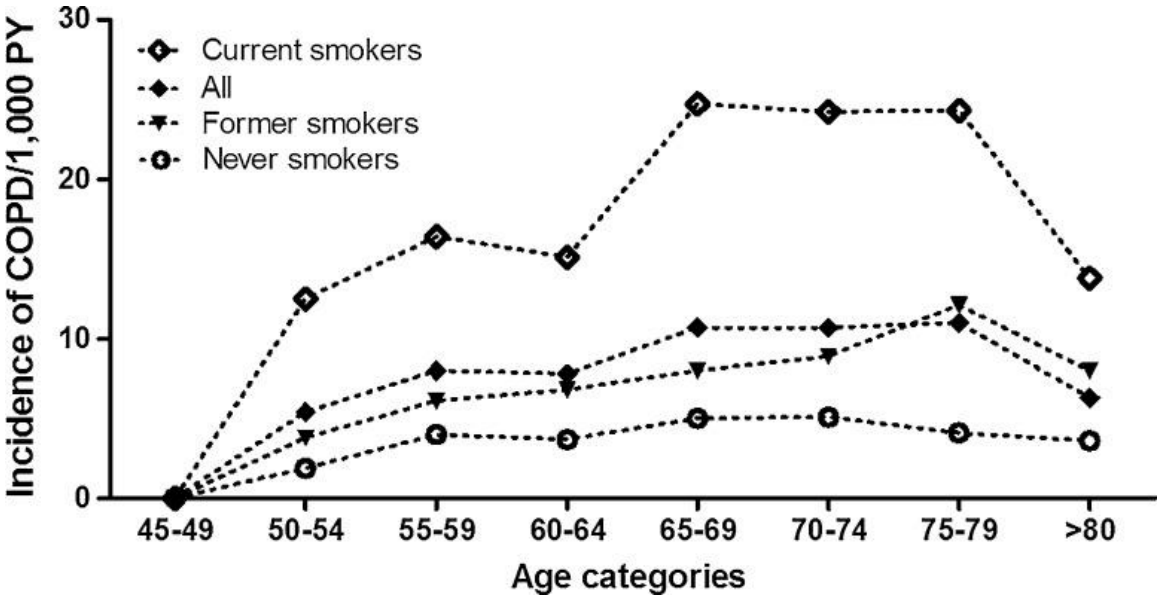


Figure 5: Incidence of COPD among current cigarette smokers, former cigarette smokers and never cigarette smokers.
This figure showcases the incidence of COPD among cigarette smokers, former cigarette smokers and never cigarette smokers across the life span. The incidence of COPD is highest of smokers, when compared to former smokers and never smokers, and is higher among former smokers than never smokers. Additionally, the incidence of COPD is higher among the elderly than in younger smokers, former smokers and never smokers.[56]
Source: Terzikhan et al., (2016). Journal of *European Journal of Epidemiology.*
Table taken from: *European Journal of Epidemiology*
DOI: https://doi.org/10.1007/s10654-016-0132-z

Once again, evidence also supports a dose-dependent risk of developing COPD, in that increased duration of smoking and higher rates of daily cigarette consumption lead

to increased risk of developing the disease.[54,57] Together, these statistics and supporting evidence raise significant concern, especially because COPD was the 6th leading cause of avoidable death in the U.S. in the year 2020.[58]

As it relates to asthma, cigarette smoking is a strong predictor of asthma severity, again in a dose-response fashion. In fact, smokers having a greater than 20 pack-year history (1 standard cigarette pack per day, for 20 years), have a risk that is estimated to be nearly 5 times greater than a smoker having a pack-year history between 1-10. Smoking was also shown to be significantly associated with an increased prevalence of poor disease control of asthma symptoms.[59] Furthermore, smoking has been shown to also be the strongest predictor of emphysema, with an estimated attribution rate of 95%.[60] In fact, research has shown that cigarette smoking causes accumulation of toxins in the lungs thereby leading to the destruction of alveoli and the development of emphysema.[60] Unfortunately, the damage caused to the lung structure and tissues is irreversible, making emphysema a particularly concerning health outcome among smokers.[61] Finally, and with regards to chronic bronchitis, research estimates that 40% of smokers will develop chronic bronchitis. Similar to the other respiratory diseases, chronic bronchitis is worrisome in that it is correlated with a rapid decrease in lung function ultimately leading to COPD and eventual mortality.[62]

In a similar fashion to smoking-related cancers, the risks of developing respiratory diseases and illnesses are well-established. In addition to COPD, asthma, emphysema and chronic bronchitis, smoking has also been linked to interstitial lung diseases, pulmonary fibrosis and acute lung infections.[63] In summary, the evidence supporting the link

between respiratory diseases/illnesses and smoking cigarettes has greatly expanded since first identified thereby contributing to the growing support for smoking cessation.

Cardiovascular Diseases

Cardiovascular disease, commonly referred to as CVD, is the number one cause of morbidity/mortality in the U.S., killing near 800,000 people a year.[2] Alongside hypertension and hypercholesteremia (elevated blood pressure and cholesterol levels), smoking is a primary contributor to the morbidity and mortality caused by CVD.[64] More specifically, smoking cigarettes is a critical risk factor in the onset of several types of CVD including, coronary heart disease, atherosclerosis (also known as coronary artery disease), stroke and aortic dissection (rupture of the aorta).[64–66] It is estimated that roughly one-third of all deaths attributed to coronary heart disease are related to smoking cigarettes. Coronary heart disease is directly related to atherosclerosis, also known to be caused by smoking. With regards to coronary heart disease, the risk of onset is directly related to the daily cigarette consumption.[37] Evidence supporting the link between smoking and atherosclerosis, a buildup of cholesterol deposits (i.e., plaque) within the wall of arteries, comes from autopsies and angiographic studies.[67] These studies show a dose-response relationship between daily cigarette consumption and the incidence of atherosclerosis.[67] The risk of developing atherosclerosis from cigarette smoking is independent of anatomical location meaning an increased incidence of atherosclerosis has been found in both the coronary arteries and in the peripheral vasculature (i.e., peripheral vascular disease) among smokers.[68] With regards to stroke, a meta-analysis estimated that

the overall relative risk of experiencing a stroke of any kind was around 1.5, with the highest relative risk indicated for stroke type subarachnoid hemorrhage (RR = 2.9).[69] Additionally, when accounting for age and sex, the relative risk of experiencing a stroke is highest for smokers under the age of 55, and slightly elevated for women when compared to men. Once again, a dose dependent relationship is supported by research for the risk for the risk of experiencing a stroke among smokers.[69] Finally, and in addition to the several CVDs previously mentioned, cigarette smoking has also been associated with decreased myocardial performance, decrease elasticity of arteries, increased heart rate, and hypertension.[68,70]

Despite these statistics research shows that among heavy smokers, smoking cessation significantly lowers the risk of cardiovascular disease within the first 5 years of smoking cessation, when compared to groups of current daily smokers. More rapid decreases in risk are seen with regards to stroke following cessation. Even more, research estimates that in smokers living with coronary heart disease who have had at least one myocardial infarction, that the risk of experiencing a subsequent myocardial infarction followed by sudden cardiac death decreases by as much as 50% following smoking cessation.[65] Finally, numerous studies have demonstrated a significant decrease in overall CVD mortality when comparing former smokers to current smokers.[65] Together, this evidence not only suggests that smoking cessation is of significant benefit for limiting the risk of developing CVD later in life[64,69], but it also support the need for strong and effective smoking cessation measures.[65]

Even given a brief review of some of the most commonly report smoking-related diseases and illnesses, it is clear that the health consequences of smoking cigarettes are substantial. Due to space limitations, a more comprehensive list of relative risks of death caused smoking-related disease is provided in table 6 for review. Ultimately, it is estimated that more than 16 million adults living in the U.S. are currently experiencing a disease or illness caused by smoking.[2] Smoking has been shown to cause cancer, respiratory diseases and cardiovascular disease, many of which lead to significant rates of death and morbidity. Given these statistics, smoking cessation measures should be investigated for efficacy and tolerability. The next section will discuss two of the most commonly used standard of care pharmacological approaches—varenicline (Chantix ©) and Nicotine Replacement Therapy (NRT)—for smoking cessation.

Table 2. Relative Risks of Death from Specific Causes among Persons 55 Years of Age or Older, According to Sex and Smoking Status.*

Cause of Death	Women				Men			
	Never Smoked		Current Smoker		Never Smoked		Current Smoker	
	no. of deaths	*relative risk*	*no. of deaths*	*relative risk (95% CI)*	*no. of deaths*	*relative risk*	*no. of deaths*	*relative risk (95% CI)*
All causes	31,786	1.0	8150	2.8 (2.7–2.9)	24,863	1.0	8325	2.8 (2.8–2.9)
Diseases established as caused by smoking†								
Lip and oral cavity cancer, C00–C14	57	1.0	42	5.6 (3.7–8.6)	82	1.0	64	5.7 (4.1–8.1)
Esophageal cancer, C15	81	1.0	50	5.1 (3.5–7.4)	178	1.0	104	3.9 (3.0–5.0)
Stomach cancer, C16	184	1.0	34	1.7 (1.2–2.5)	154	1.0	45	1.9 (1.4–2.7)
Colorectal cancer, C18–C20	1,016	1.0	174	1.6 (1.4–1.9)	753	1.0	160	1.4 (1.2–1.7)
Liver cancer, C22	228	1.0	40	1.8 (1.3–2.5)	228	1.0	74	2.3 (1.8–3.0)
Pancreatic cancer, C25	948	1.0	184	1.9 (1.6–2.2)	747	1.0	153	1.6 (1.4–1.9)
Laryngeal cancer, C32	2	1.0	27	103.8 (24.2–445.5)	23	1.0	50	13.9 (8.3–23.3)
Lung cancer, C33–C34	735	1.0	1872	22.9 (21.0–25.0)	480	1.0	1754	25.3 (22.8–28.1)
Urinary bladder cancer, C67	123	1.0	48	3.9 (2.8–5.5)	201	1.0	84	3.9 (3.0–5.1)
Kidney and renal pelvis cancer, C64–C66	256	1.0	32	1.2 (0.9–1.8)	237	1.0	62	1.8 (1.4–2.4)
Acute myeloid leukemia, C92.0	180	1.0	22	1.1 (0.7–1.7)	210	1.0	48	1.9 (1.4–2.7)
Diabetes, E10–E14	743	1.0	110	1.5 (1.3–1.9)	729	1.0	142	1.6 (1.3–1.9)
Ischemic heart disease, I20–I25	4,119	1.0	1014	3.0 (2.8–3.2)	4,947	1.0	1522	2.6 (2.4–2.7)
Other heart disease, I00–I09 and I26–I51	2,329	1.0	340	1.9 (1.7–2.1)	1,736	1.0	364	2.0 (1.8–2.2)
Total stroke, I60–I69	2,435	1.0	385	2.1 (1.8–2.3)	1,399	1.0	279	1.9 (1.7–2.2)
Atherosclerosis, I70	76	1.0	12	2.1 (1.1–4.0)	57	1.0	32	5.0 (3.2–7.9)
Aortic aneurysm, I71	99	1.0	91	10.1 (7.4–13.6)	126	1.0	116	7.5 (5.8–9.7)
Other arterial diseases, I72–I78	81	1.0	47	5.6 (3.9–8.2)	57	1.0	36	5.3 (3.4–8.2)
Pneumonia, influenza, and tuberculosis, J10–J18 and A16–A19	723	1.0	100	1.9 (1.6–2.4)	487	1.0	87	2.0 (1.6–2.6)
COPD, J40–J44	410	1.0	941	25.0 (21.2–28.1)	259	1.0	825	27.8 (24.1–32.0)
Additional diseases associated with smoking‡								
All infections, A00–B99§	598	1.0	137	2.5 (2.1–3.0)	475	1.0	125	2.2 (1.8–2.7)
Breast cancer, C50	1,748	1.0	274	1.3 (1.2–1.5)	—	—	—	—
Prostate cancer, C61	—	—	—	—	1,101	1.0	166	1.4 (1.2–1.7)
Rare cancers¶	1,233	1.0	143	1.1 (0.9–1.3)	402	1.0	84	1.6 (1.2–2.0)
Cancers of unknown site	866	1.0	237	2.7 (2.3–3.2)	665	1.0	268	3.2 (2.8–3.7)
Hypertensive heart disease, I11	244	1.0	45	1.9 (1.4–2.7)	193	1.0	75	2.9 (2.2–3.9)
Essential hypertension and hypertensive renal disease, I10 and I15	249	1.0	48	2.4 (1.7–3.4)	175	1.0	49	2.6 (1.9–3.6)
All other respiratory diseases‖	442	1.0	69	1.9 (1.5–2.5)	375	1.0	77	2.0 (1.5–2.6)
Ischemic disorders of the intestines, K55	93	1.0	48	6.1 (4.2–8.7)	46	1.0	29	5.6 (3.5–9.0)
Liver cirrhosis, K70 and K74	201	1.0	69	2.6 (2.0–3.5)	174	1.0	109	3.6 (2.8–4.6)
All other digestive diseases**	618	1.0	105	2.1 (1.7–2.5)	378	1.0	107	2.6 (2.0–3.2)
Renal failure, N17–N19	504	1.0	77	1.9 (1.5–2.5)	407	1.0	84	2.1 (1.6–2.6)
Additional rare causes combined††	1,565	1.0	290	2.0 (1.8–2.3)	624	1.0	130	1.9 (1.5–2.2)
Unknown causes	955	1.0	274	2.2 (1.9–2.5)	787	1.0	221	1.9 (1.6–2.2)

* Data are from 2000 to 2011 from a pooled contemporary cohort comprising the Cancer Prevention Study II Nutrition Cohort, the Nurses' Health Study I cohort, the Health Professionals Follow-up Study cohort, the Women's Health Initiative cohort, and National Institutes of Health–AARP Diet and Health Study cohort. Each listed cause is followed by the *International Classification of Diseases, 10th Revision* (ICD-10) code associated with that disease. Relative risks were estimated from Cox proportional-hazards models adjusted for age, race, educational level, current alcohol use, and cohort. COPD denotes chronic obstructive pulmonary disease.

† Included are the diseases that have been established by the U.S. Surgeon General as caused by smoking, with the exception of cervical cancer, which occurred only rarely in this cohort.

‡ Included are outcomes significantly associated with smoking, not including external causes or mental health disorders.

§ Tuberculosis is not included in this category.

¶ All cancer sites are included, other than the 12 established as causal by the Surgeon General and cancers of the breast, prostate, and brain; other leukemias; melanoma; and non-Hodgkin's lymphoma (individual data for which are provided in Tables S2 and S3 in the Supplementary Appendix).

‖ Included are all respiratory diseases (ICD-10 codes J00–J99) other than pneumonia and influenza, COPD, and pulmonary fibrosis (individual data for which are provided in Tables S2 and S3 in the Supplementary Appendix)

** Included are all digestive diseases (ICD-10 codes K00–K93) other than intestinal ischemia, cirrhosis, and other liver diseases (individual data for which are provided in Tables S2 and S3 in the Supplementary Appendix)

†† Included are causes that are not shown separately in Tables S2 and S3 in the Supplementary Appendix: ICD-10 codes H00–H95, L00–L99, M00–M99, O00–U89, and Z00–Z99.

Table 5: Risk of dying (reported as relative risks) according to sex and smoking history in individuals aged 55 years old or greater
This table lists the relative risk of dying from different diseases, illnesses, and disorders according to smoking status and sex. This table is specific to individuals 55 years of age or older. Of note, laryngeal cancer, lung cancer and COPD have the three highest relative risks of death in current smokers for both men and women.
Source: Carter et al., (2015). *The New England Journal of Medicine.*[71]
Table taken from: https://www.nejm.org/

SMOKING CESSATION TREATMENTS

The previous section outlined several of the key reasons that effective treatment for smoking cigarettes is important. Firstly, smoking cigarette rates among U.S. adults remains elevated, estimated to be around 34.2 million U.S. adults.[5] Secondly, nicotine is highly addictive.[10] Finally, the health consequences of cigarette smoking are substantial.[41] Therefore, effective smoking cessation treatments are essential for not only decreasing the current rates of nicotine addiction but also lowering the incidence of smoking-related morbidity and mortality. The following paragraphs will review two of the most commonly used smoking cessation pharmacological treatments—Varenicline (Chantix) and Nicotine Replacement Therapy (NRT)—with specific emphasis on efficacy and tolerability. It is important to note that Bupropion SR (Zyban) is another common treatment for smoking cessation and is often referred to as one of the "first-line" standard of care smoking cessation treatments. This thesis will not touch on Bupropion SR because its mechanism of action differs from Varenicline and NRT, both of which have very similar mechanisms of action via nAChRs.

Mechanisms of Action

Varenicline (Chantix)

Varenicline's (also known as Chantix) mechanism of action involves the previously discussed nicotinic acetylcoholic receptors (nAChR). Similar to nicotine, varenicline is an agonist for the nAChRs. As such, when taken for smoking cessation, varenicline acts by binding to the nAChRs causing a release of dopamine. This in turn

attenuates the urge to smoke thereby reducing the experience of nicotine withdrawal. Over time, varenicline reduces the reward seeking behaviors leading to increased cigarette consumption that characterize nicotine addiction.[11]

Varenicline was specifically engineered for increased affinity and selectivity for nAChRs.[11] This in part has led to the higher rates of efficacy when comparing smoking cessation rates between varenicline and NRT (to be discussed below). It is important to note that Varenicline is a partial agonist for nAChRs. According to Coe et al. (2009), partial agonists are defined as "ligands that produce a smaller than maximal response compared with the natural ligand at full receptor occupation."[72] This means that varenicline only partially binds to the receptor. As a result, only a very small amount of dopamine is released.[11,73] The amount of dopamine that is released is enough to reduce withdrawal symptoms but not enough to achieve the same level of "high" experienced during nicotine consumption.[11,74] At the same time, varenicline's increased affinity for the nAChRs allows it to outcompete nicotine. This is especially important in the early stages of smoking cessation treatment it is found a smoker may still be smoking, though usually at reduced rate, as they work towards complete cessation. In the presence of nicotine, therefore, varenicline stops the nicotine from binding thereby mitigating the reward seeking effects known to characterize nicotine addiction.[75] Finally, varenicline also works through having an increased half-life compared to nicotine. This allows the benefits of varenicline to be long-lasting.[11,73] Through these means, varenicline is able to attenuate the reward seeking behaviors, reducing smoking urges and ultimately lead to smoking cessation.

Nicotine Replacement Therapy

Nicotine Replacement Therapy, also known as NRT, is the umbrella term used to define the shared mechanism by which six different drug formulations work. NRT is the most frequently used treatment for smoking cessation that comes in six different forms—transdermal patch, gum, nasal spray, inhaler, sublingual tablet and a lozenge.[76] It should be noted that NRT does not refer to nicotine that is consumed in other ways such as through a burning cigarette, electronic cigarette, or cigar. The transdermal patch delivers nicotine in a sustained released mannerism, whereas the five other forms of NRT are acute doses of nicotine.[76] Similar to varenicline, the nicotine contained within the different forms of NRT is an agonist for the nAChRs. As such, the nicotine, delivered in a much safer, less toxic manner than through a burning cigarette, binds to the nAChRs and causes the release of dopamine. Like nicotine delivered to the brain from a burning cigarette, NRT reduces symptoms of nicotine withdrawal, one of the primary mechanisms contributing to sustained cigarette smoking. As a result, a smoker is able to "adapt to a life without smoking cigarettes." In addition to reducing withdrawal symptoms, it is also suggested that NRT allows the brain to dissociate cigarettes with feelings of pleasure, and thus decreasing one's daily cigarette consumption.[77,78] Through very similar means, varenicline and NRT work to reduce cigarette smoking.

Efficacy

Varenicline (Chantix)

Efficacy is arguably one of the most important considerations when developing a treatment plan for smoking cessation. As previously mentioned, unassisted quit attempts are estimated to result in success 3-5% of the time.[19] Thankfully, research has shown that varenicline has significantly higher rates of efficacy. In fact, research shows that varenicline has the highest smoking cessation success among all available treatments.[13]

For example, according to a study conducted by Hays et al., (2008), short-term smoking abstinence (continuous smoking abstinence lasting 4-weeks) was found to be significantly greater when using varenicline (37.3%) compared with placebo (17.1%). Varenicline was also found to have significantly higher rates of long-term abstinence for time points "12 (28.8% vs. 10.6%), 24 (20.8% vs. 7.3%), and 52 (14.4% vs. 4.9%)" weeks when compared to placebo. Even more, varenicline was reported to reduce craving scores, reduce measures of smoking satisfaction, and increase cigarette smoking aversion when compared to placebo.[11] In a similar study, investigators randomized 1,025 healthy smokers between the ages of 18-75, to receive either standard-of-care varenicline or placebo for a total of twelve weeks. The patients were followed for a total of one year post-treatment. Smoking cessation was determined by self-report and confirmed via a carbon monoxide breath test (a key clinical measurement of smoking cessation). Once again, smoking cessation rates at 52 weeks were found to significantly higher for patients randomized to receive varenicline. The study found that abstinent rates were 21.9% for patients receiving varenicline and 8.3% for patients receiving placebo.[74] Finally, more

recent randomized controlled trials (RCT) have showcased even higher rates of efficacy when compared to placebo. In fact, in one large, multicenter, double-blind RTC, efficacy rates at the 9-to-12-week marks were estimated to be 44% for varenicline and only 17.7% for placebo (Table 6 6).[11,12] In a second study of a very similar design and breadth, efficacy rates at the 9-to-12-week marks were found to be 43.9% and 17.6% for varenicline and placebo, respectfully (Table 6).[11,13] Table 6 also provides the odds ratios for both studies. Of note, these same two studies showed that longer duration of varenicline treatment is positively correlated with increased durations of smoking cessation.[11–13,74] Taken together, the research clearly depicts that varenicline has a significantly greater efficacy when compared to placebo.

	Continued Abstinence Rates (%)	
	Gonzales et al., 2006 $N_{varenicline} = 349$ $N_{placebo} = 344$	**Jorenby et al., 2006** $N_{varenicline} = 343$ $N_{placebo} = 340$
Varenicline	44.0%	43.9%
Placebo	17.7%	17.6%
Odds Ratio	3.85 ($p<0.001$)	3.85 ($p<0.001$)

Table 6: Varenicline Smoking Cessation Rates at 4-Weeks
This table showcases the continuous smoking abstinence rates at times points 9-to-12 weeks for varenicline vs. placebo. Of note, varenicline had significantly higher rates of continuous smoking abstinence when compared to placebo in both studies.
Source: Hays et al., (2008). *The American Journal of Medicine.*
This table was created using data outcomes described in the journal article titled "Efficacy and Safety of Varenicline for Smoking Cessation" by Hays et al., (2008).
https://doi.org/10.1016/j.amjmed.2008.01.017

Nicotine Replacement Therapy

Like varenicline, NRT also shows higher rates of efficacy when compared against placebo.[14] A literature review of more than 110 trials, with over 50,000 patients, looked at the average risk ratio of abstinence for all 6 types of NRT and the percent of patients reporting abstinence at 12-months post-treatment. This literature review revealed the following:

Form of NRT	Pooled Odds Ratio for Abstinence	Percent Abstinence at 12 Months Post-Treatment
Transdermal Nicotine Patch	1.74	14%
Nicotine Gum	1.66	18%
Nicotine Nasal Spray	2.27	24%
Nicotine Inhaler	2.08	17%
Subinguinal Tablet/Lozenge	2.08	20%

Table 7: NRT Pooled Odds Ratios and Percent Abstinence at 12-Months Post Treatment
This table showcases the odds ratio for abstinence and the percentage of patients using NRT and reporting smoking abstinence at 12-months post-treatment.
Source: Silagy et al., (2004). *The Cochrane Library.*[14]
This table was created using data outcomes described in the journal article titled "Nicotine Replacement Therapy for Smoking Cessation" by Silagy et al., (2004).

Citation: Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

The pooled odds ratios displayed in the table above were independent of duration of therapy or the setting in which NRT was received. When considered altogether, the overall rate of smoking cessation for NRT was estimated to be 17% vs. 10% for placebo. Even more, the overall odds ratio for smoking cessation was 1.74. This means that using NRT increases your odds of smoking abstinence 1.74-fold compared to placebo. It should

be noted that although the percent abstinence rates are different among the varying forms of NRT, the confidence intervals overlapped thereby suggesting that different forms of NRT are not significantly different from one another, despite all producing significantly higher rates of smoking abstinence than placebo[77] Finally, this large literature review suggested that using the nicotine patch in combination with any other forms of NRT resulted in significantly higher abstinence rates compared to transdermal patch alone.[14] A more recent study looking at the results of seventeen RCT comparing transdermal nicotine patch to placebo found even higher rates of abstinence for the nicotine patch. In fact, this review found that the average overall abstinence rate for the patch was significantly different when compared to placebo with abstinence rates of 27% at the end of treatment and 22% at the 6-month post-treatment timepoint. This differed from placebo nicotine patch which showed abstinence rates of 13% at the end of treatment and 9% abstinence at the 6-month post-treatment timepoint.[79] In summary, evidence suggests that all available forms of NRT are effective pharmacological therapies for smoking cessation, as they increase the odds of quitting 1.66-2.27 fold.[14]

Tolerability

Varenicline (Chantix)

Perhaps equally as important as efficacy to the overall success of a drug is tolerability. Tolerability refers to the "adverse events" or "side effects" that are known to be associated with a drug. The most frequently reported adverse event among patients in clinical trials using varenicline for smoking cessation was nausea.[11,74] In fact, according

to a study done by Hays et al. in 2008, nausea was reported at least once by 38.5% of patients undergoing smoking cessation treatment and using varenicline, compared to only 11.2% of patients randomized to receive a matched placebo. It should be noted that of the patients randomized to receive varenicline, reports of nausea were considered mild or moderate, and only 3% of patients experiencing nausea stopped varenicline treatment. [11] The percentage of patients stopping varenicline treatment due to nausea was not significantly different when compared to placebo.[80] Other commonly reported side effects include insomnia, abnormal dreams, headache, and gastrointestinal effects. Overall, this study estimates that 12% of patients stopped varenicline treatment due to side effects, which was a similar estimate to several other clinical trials studying tolerability in smokers using varenicline.[11] The percentage of subjects experiencing each side effect in a well-known randomized control trial is included in the table below (Table 8). It should also be noted that a safety warning was added to varenicline in 2008 due to reports of psychiatric symptoms, though a causal link has yet to be established. the number of patients reporting serious adverse events such as psychiatric events was 2.8% compared to placebo which was estimated to be 1% across clinical trials.[81] Regardless, health care providers are trained to monitor their patients for these symptoms. In summary, varenicline appears to be generally well-tolerated.

Table 1. Varenicline as Compared with Placebo.*

Variable	Varenicline	Placebo
	% of subjects	
Adverse effect		
Nausea	35.8	11.2
Insomnia	22.0	12.7
Abnormal dreams	14.4	5.0
Headache	16.8	14.3
Other gastrointestinal effects†	22.5	11.8
Discontinuation of study drug due to treatment-related adverse event	12.0	8.1

* Data shown are the mean percentages of subjects reporting the adverse effect in randomized trials of varenicline at a dose of 1 mg twice daily. Adverse events reported in 5% or more of subjects receiving varenicline at this dose are included.
† Other gastrointestinal effects were vomiting, constipation, diarrhea, flatulence, and dyspepsia.

Table 8: Tolerability of Varenicline compared to Placebo
This table showcases the percentage of patients experiencing side effects in clinical trials that were comparing the use of varenicline to placebo for smoking cessation.
Source: Hays et al., (2008). *The American Journal of Medicine.*[11]
Table taken from: https://www.amjmed.com/
DOI: 10.1056/NEJMct0800146
Reproduced with permission Hays, J. Taylor, and Jon O. Ebbert. "Varenicline for tobacco dependence." New England Journal of Medicine 359.19 (2008): 2018-2024.), Copyright Massachusetts Medical Society. See reference 11 for more details.

Nicotine Replacement Therapy

Evidence supporting the tolerability of NRT is well-established given it has been thoroughly tested in multiple RTCs over a duration of 30 years.[15] Several side effects are common among smokers using NRT for smoking cessation treatment. Serious adverse events, however, are considered rare. The side effects associated with each form of NRT are dependent on the mode of application and the site at which the medication is used

(i.e., oral cavity, skin, nasal cavity).-[79] The most commonly reported side effects of NRT are summarized in the following table (Table 9.

Adverse event	Number of studies	References	N of events	Pooled n	Proportion	95% CI	τ^2
Headache	17	[75,93,110,118-120,123-125,127-129,131,136,138,140,141]	1472	75764	9.7	4.6-19.5	2.97
Nausea or vomiting	14	[75,110,119,120,123,124,128,129,136-138,140,141]	1902	74449	8.5	4.6-15.3	1.39
Gastrointestinal complaints	11	[110,118,120,123,127,129,131,136,138,140,141]	593	74256	3.9	1.4-10.4	3.02
Heart palpitations	7	[75,120,122,127,131,136,141]	72	2446	3.6	1.4-9.0	1.49
Mouth and throat soreness	6	[125,129,135-137,140]	406	72533	5.4	0.9-25.6	5.00
Skin irritation	16	[75,93,118-124,126-129,131,138,141]	1337	10356	19.5	11.5-31.1	1.56
Hiccoughs	4	[129,136,137,140]	375	71948	2.5	0.3-16.5	4.63
Coughing	5	[120,125,128,135,136]	125	1672	8.1	2.1-26	2.29
Depression	6	[110,120,124,138,140,141]	69	66344	2.6	0.2-27	10.57
Anxiety	5	[118,120,129,138,141]	104	5841	2.9	0.8-9.8	1.70
Insomnia	18	[75,110,118-123,125-129,131,138,140,141]	2262	76169	11.4	4.8-24.6	4.05
Dizziness	8	[110,118,120,124,127,129,136,141]	299	7338	7.3	3.7-13.9	0.94
Self-harm	1	[110,118,120,124,127,129,136,141]	141	63265	0.2	0-8.4	NA

Table 9: Tolerability of NRT for Smoking Cessation
This table showcases the proportion of patients experiencing side effects from taking NRT. These results were obtained as a result of observational studies.
Source: Mills, Edward J., et al. (2010). *Tobacco Induced Diseases.*[82]
Table taken from: https://www.springer.com/journal/40265

The most commonly reported side effects include skin irritation (19.% of patients), insomnia (11.4% of patients), headache (9.7% of patients) and nausea or vomiting (8.5% of patients).[82] Skin irritation is particularly common among smokers using the transdermal nicotine patch for smoking cessation. However, despite elevated prevalence among smokers, most skin reactions aware considered mild and are known to resolve after stopping the nicotine patch.[73] A meta-analysis found that on average 17% of smokers using NRT and experiencing side effects will quit using NRT prematurely due to side effects.[83] Ultimately, research demonstrates that NRT is associated with side effects (none of which have been shown to be life-threatening) but appears to be well-tolerated

overall. Given the long-lasting benefits of smoking cessation, it is important to consider one's threshold for tolerating any potential side effects when using NRT.

CONCLUSION

Throughout this paper, I explored the current trends with regards to smoking cigarettes and smoking cessation in the United States, the different factors contributing to nicotine addiction and the health consequences of smoking cigarettes. A review of the literature revealed that despite significant progress over the past 60 years, smoking rates remain elevated, estimated to be greater than 34 million U.S. adults identifying as cigarette smokers. This is especially concerning given the vast number of health consequences shown to be associated with smoking cigarettes. In fact, the literature revealed that the chances of developing cancer, cardiovascular disease, and respiratory disease or illness is significantly greater than for people identifying as non-smokers. For example, combustible cigarette use is considered the primary cause of lung cancer, COPD, and coronary heart disease. Thankfully, and relative to the health consequences of smoking cigarettes, the use of smoking cessation pharmacological therapies like varenicline and NRT appear to be much safer.

A review of the research on the overall efficacy outcomes of varenicline (Chantix) and Nicotine Replacement Therapy (NRT), revealed that both treatments increase long-term smoking abstinence. In fact, the odds ratio for varenicline when compared to placebo was found to be 3.85. This means that smokers using varenicline have a 3.85-fold higher chance of achieving smoking abstinence when compared to placebo. The different types of NRT (transdermal patch, nicotine inhaler, nicotine gum, nicotine lozenge, nicotine nasal spray, and nicotine tablet) had odds ratios that ranged from 1.66-2.27 when compared to placebo. Taken together, NRT had an overall odds ratio of 1.74.

This suggests that using NRT for smoking cessation purposes increases ones odds of quitting by 1.74-fold when compared to placebo. Comparing varenicline to NRT, it appears varenicline has higher odds of leading to long-term smoking abstinence.

Even more, both drugs appear to be generally well-tolerated, with no known life-threatening side effect for either varenicline or NRT, when either were compared placebo. A review of the literature revealed that the most common side effects reported among individuals using varenicline for smoking cessation purposes include nausea, insomnia, gastrointestinal effects, headache, and abnormal dreams. However, it does not appear that these side effects cause smokers to stop the medication, thereby suggesting that these side effects are generally well-tolerated. In fact, it is estimated that only 12% of smokers using varenicline for smoking cessation purposes stop the medication prematurely due to side effects. With regards to NRT, the literature revealed that the most common side effects among smokers using NRT for smoking cessation are skin irritation, insomnia, headache, nausea/vomiting, and cough. Similar to varenicline, it was estimated that NRT is stopped prematurely in about 12% of people experiencing side effects when using NRT.

Ultimately, both varenicline and NRT appear to be strong options for achieving long-term smoking abstinence both with respect to overall efficacy and tolerability. This proves to be especially significant given both the addictiveness of nicotine and the multitude of health consequences, particularly cancer, CVD and respiratory diseases/illnesses known to be associated with the use of combustible cigarettes.

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