Nicotine Addiction: Challenges and Recommendations

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Defense Date: April 9, 2024

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Abstract

This review is a synthesis of current knowledge based on tobacco and nicotine research. Special emphasis is placed on adolescents, who are highly sensitive to addiction, as targets of nicotine companies. Types of nicotine use are described briefly, as well as the broad impact of cigarettes and E-cigarettes on American society. Then, the history of tobacco companies, their advertising campaigns specifically geared towards youth, and their increasingly addictive and problematic products are summarized. Next, biological impacts of smoking nicotine products on the lungs, the brain, and the microbiome and immune system are described with attention to common nicotine-associated pathways and mechanisms. A brief summary is given of the complex effects of pure nicotine (rather than smoking). Moreover, treatments that aid in smoking cessation are described, along with their limitations and barriers that prevent nicotine addicts from quitting. This insight is used to formulate recommendations for future research, specifically into smoking by adolescents as well as into empathetic and holistic approaches that can also inform public attitudes and policy making as well as early prevention. Concerning preventive approaches, I recommend an approach to education of youth that focuses on building emotion-regulation skills for improved coping mechanisms and life skills as opposed to scare tactics to discourage drug use. In summary, a comprehensive approach, integrating multiple perspectives and factors, has the potential to have positive impacts on the life and health of individuals, their communities, and society at large.

Background and Approach

Background on key systems

Nicotine can be consumed in many forms, such as cigarettes, chewing-tobacco, E-cigarettes, cigars, dissolvable tobacco, and pipes or hookah (waterpipes for smoking). Cigarettes (also termed combusted cigarettes) are typically wrapped in paper and represent a type of tobacco consumption where tobacco is burned, or combusted, and the smoke is inhaled (PMI Science, 2010). Cigarette alternatives, popularized in the 21st century due to an increasingly negative public attitude towards cigarettes, include nicotine in any form other than a cigarette. Usually, the term cigarette alternative is used to describe vapes (nicotine vaping or E-cigarettes as interchangeably used terms), which is generally assumed to be less harmful than smoking of regular cigarettes (Bartoń et al., 2014). However, there may be no safe form of tobacco use because all forms of such use appear to pose serious risks due to the addictive nature of nicotine and the chemicals associated with tobacco-product consumption (Castaldelli-Maia et al., 2015). This thesis delves into literature on a range of topics associated with smoking. In order to limit the complexity of pathways examined, this thesis focuses on cigarettes and E-cigarettes.

Approach

This thesis is a literature synthesis that provides a comprehensive overview on effects of nicotine, factors impacting nicotine use, and current research perspectives. Table 1 provides a summary of my approach to this literature synthesis, including disciplines and subdisciplines considered as well as major keywords used in the search for sources (Table 1).

Table 1: Overview of keywords used for research in various disciplines.

Discipline/ Sub-Discipline	*Major Keywords Used*
Nicotine Company Advertising	"History of Nicotine Ads" "Tobacco Campaigns" "History of Tobacco Companies" "Tobacco Company Lawsuits" "Juul Lawsuits" "Evolution of Nicotine Advertising"
Nicotine Impact on Lung Disease	"Lung function of smokers" "smoking impact on the lungs" "E-cigarettes impact on the lungs" "respiratory disease in smokers" "carcinogens and the lungs"
Nicotine Impact on Immune System and Microbiome	"nicotine long term effect on immune system" "microbiome and nicotine" "microbiome impact on immune system"
Neurotransmitters and Receptors	"nAChRs" "Dopamine pathways" "nicotine impact on dopamine" "nicotine impact on serotonin"
Addict Perspective	"Nicotine cessation statistics" "Smoking-related death"
Treatment Options	"Nicotine addiction treatment plan" "Nicotine therapies" "smoking cessation medications"
Teen Smoking	"nAChRs in the adolescent brain" "Adolescent nicotine tolerance" "Adolescent nicotine trends" "Dopaminergic pathway development in adolescents" "Effect of nicotine on youth"
Mental Health and Nicotine	"Nicotine in schizophrenic patients" "Nicotine and anxiety" "Mental illness rates" "Nicotine as a stress relief" "nicotine and emotion regulation" "nicotine and intervention"
Personalized Medicine and Nicotine	"Genomics of Smoking" "Genomics of nicotine addiction" "therapies for nicotine addiction" "personalized medicine research" "gene variants and nicotine" "gene variants and smoking"

Literature Synthesis

Focus of this Literature Synthesis

Most research on nicotine-related issues to date is heavily focused on (regular, combusted) cigarettes, and literature on cessation of tobacco use via other products is still sparse. This presents an important gap in the research, which is becoming increasingly evident as cigarette alternatives rapidly gain popularity. Despite public and policy attention to youth nicotine

addiction, interventions to treat E-cigarette use in adolescents (and their evaluation) are lacking (Prochaska and Benowitz, 2019). Future research is also needed to focus on new nicotine-consumption trends. My literature review and synthesis focus on cigarette and E-cigarette research and provide a summary of the key factors for understanding nicotine addiction based on research available to date. I integrate several perspectives as detailed in **Figure 1**. Addiction is a complex issue with multiple biological (physical and mental/psychological) and social dimensions, as well as a strong commercial aspect, and these complexities must be considered in relation to each other. My synthesis considers three overarching categories: corporate issues, biological impacts of smoking, and barriers for quitting nicotine. Together, these perspectives elucidate why smoking is impacting so many Americans every day, what that impact is, and why so many addicts find themselves unable to quit. Conversely, this understanding can illuminate pathways for how this crisis can be addressed comprehensively via effective, evidence-based smoking-cessation aids.

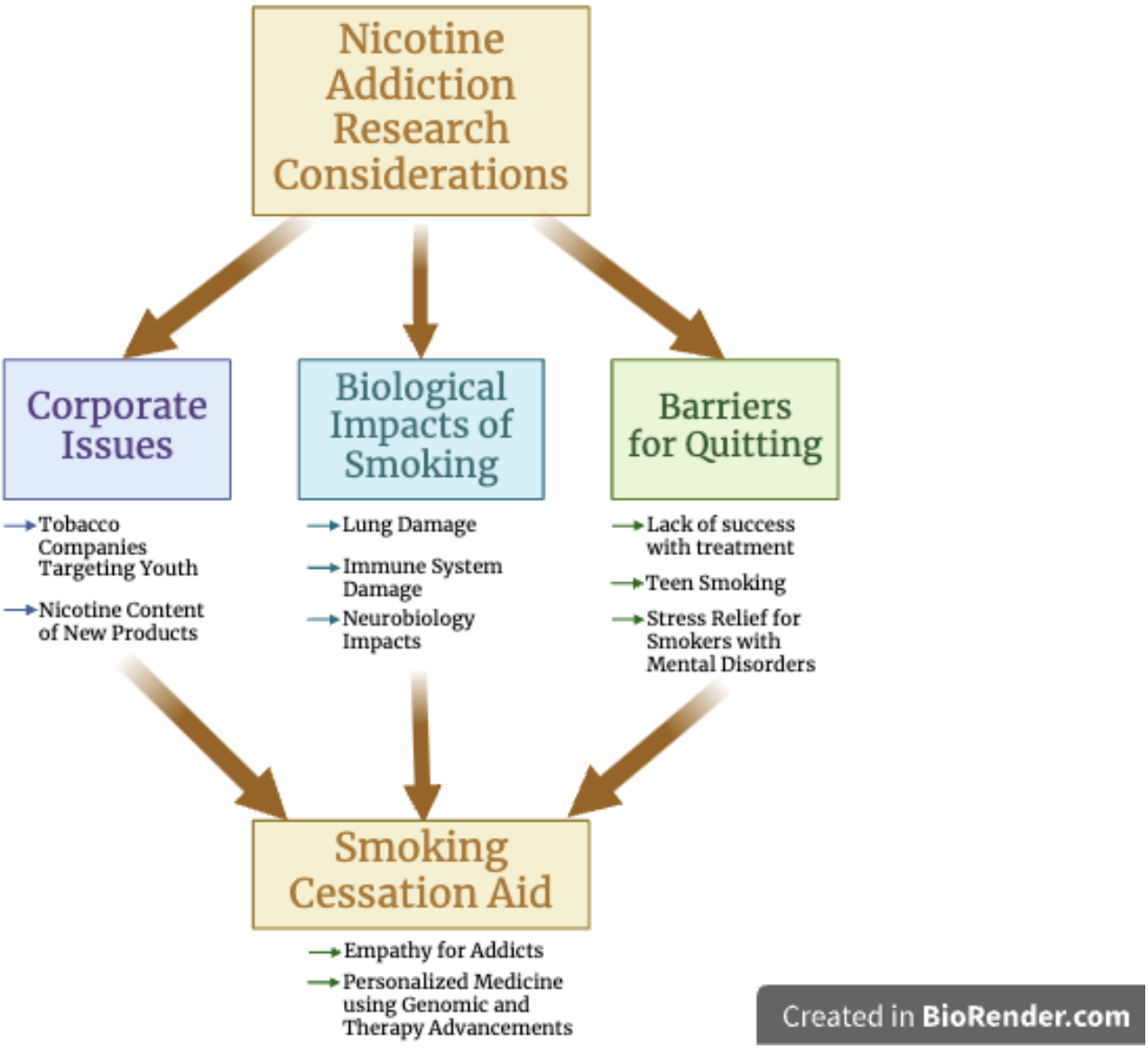

Figure 1: Relevant dimensions of nicotine research. Relevant concepts surrounding nicotine addiction research can be grouped into three categories: corporate issues, biological impacts of smoking, and barriers to quitting. These will be discussed in further detail throughout this thesis. All of the above have vast impacts on the life of an individual addicted to nicotine. When each of these perspectives are applied, they shed light on the methods of smoking cessation aid that need more attention in future research, and can be applied in smoking cessation aid, which will be discussed further in this paper. (Figure generated in Biorender.)

Corporate Issues

Nicotine Consumption: Cigarettes and Beyond

Whereas most nicotine research to date focuses on combustible cigarettes, cigarette alternatives are on the rise, with E-cigarette (also known as vape, juul, and Ecig) use, in particular, rapidly gaining popularity. It is widely assumed that there are both fewer toxicants and less nicotine in E-cigarettes than in combustible cigarettes. Concerning toxicants, recent reviews suggest that despite somewhat reduced levels of toxicants, serious health problems are nevertheless associated with E-cigarettes, including but not limited to increased cardiovascular risk (Sheth et al. 2024) and immune-system dysfunction and microbiome disruption (Sharma et al. 2021; Park et al. 2023). Concerning nicotine level, available evidence suggests that these can be even higher in E-cigarettes compared to cigarettes, and that labels are not accurate. One research study (Raymond et al., 2018) sampled 70 E-cigarettes manufactured in the United States and tested the accuracy of the labeled nicotine content. A product labeled as containing 18 mg/mL of nicotine was found to contain between 11.6 to 27.4 mg/mL, which is up to 52% more nicotine than stated. Moreover, in 91.4% of "nicotine-free" E-cigarettes from two main American manufacturers (who were anonymized), as much as 23.9 mg/mL of nicotine was detected (Raymond et al., 2018). This failure of labeling accuracy is due to a lack of regulations placed on production companies and/or lack of effective enforcement of regulations, which puts users at risk. Several E-cigarettes from various companies (Logic Technology Development LLC, NJOY LLC, and RJ Reynolds Vapor) were authorized by the FDA (FDA, 2024). However, other large vape distributors such as JUUL have not been subjected to review and are not authorized, with the FDA stating that JUUL lacked evidence for safety of their products (FDA,

2024). Moreover, where in place, current regulations fall short and leave room for loopholes through which companies can continue to take advantage of the youth. An example of such loopholes exists in the sale of flavored pod-based ENDS (electronic nicotine-delivery systems), devices with removable cartridges, or pods, of pre-filled liquid that users connect to their devices (Riggs and Church, 2024). Flavored, pod-based ENDS are banned in the United States due to their popularity among minors (Riggs and Church, 2024). However, flavored disposable ENDS are not explicitly prohibited (Riggs and Church, 2024). This loophole allows for flavored nicotine products, which specifically entice young consumers, to remain on the market.

E-cigarettes were popularized as a smoking-cessation tool (Al-Hamdani and Manly, 2021). However, they are easily abused due to their convenience, low cost, and high nicotine content, causing them to be used as a more convenient alternative to smoking rather than a tool to quit (Al-Hamdani and Manly, 2021). Additionally, the nicotine content of E-cigarettes in the United States is unusually high in comparison with other countries. The European Union's (EU) version of Juul contains 20 mg/mL per pod, while US Juuls contain an astonishing 59 mg/mL, comparable to a whole pack of cigarettes. Furthermore, US Juuls deliver more nicotine to the smoker than either EU Juul or combustible cigarettes, with an AUC (area under the curve, i.e., total drug exposure integrated over time) of 355.9, compared to 77.3 (EU Juul) and 324.8 (cigarettes) (Phillips-Waller et al., 2020).

Cigarette smoke contains at least 10 of the 36 compounds identified by the International Agency for Research on Cancer as cancer-causing (Fowles and Bates, 2000). Additionally, cigarettes contain many mutagenic chemicals in the "probably carcinogenic" and "possibly carcinogenic" categories (Fowles and Bates, 2000). Furthermore, for every cigarette, the smoker

inhales 1.04 mg of the 10-12 mg nicotine present in the cigarette overall (Benowitz and Jacob, 1984).

Addiction on the Rise: Tobacco Companies Target Youths

Teenagers and young adults have long been targeted by tobacco companies that rely on this demographic for their continued economic success (Washington Post, 1998). Since the prohibition of cigarette advertising to children (known as the Tobacco Master Settlement Agreement), tobacco companies have brazenly violated this ban and rather paid billions of dollars in fines for this violation ("Cigarette Ads Target Youth Violating 250 Billion 1998 Settlement", 2002). It is increasingly understood that the marketing of tobacco actively works to mislead consumers on the health risks involved in smoking, and to use celebrity endorsements to create an illusion of popularity and attraction surrounding nicotine (Lynch and Bonnie, 2013). Due to the success of such campaigns, 89% of current smokers tried their first cigarette by age 18, and 77% of current smokers were already smoking daily by age 20 (Lynch and Bonnie, 2013). Companies known to invest the most in advertising are the most preferred brands by high schoolers, which is a predictor of future success of the company (Washington Post, 1998). Youths remain the most likely source of new smokers (Lynch, 2013).

Tobacco companies see targeting youths in advertising as critical to their ability to continue to make profits. For example, Senior Researcher Claude Teague from RJ Reynolds Tobacco noted in a 1973 memo that "if our company is to survive and prosper, over the long term we must get our share of the youth market. In my opinion, this will require new brands tailored to the youth market" (Washington Post, 1998). It would appear that things have not changed substantially since this 1973 memo. As the second largest tobacco company in the United States, RJR Tobacco set the precedent for whom tobacco companies target. In 2020, a

lawsuit against Juul Labs was launched in response to their purchase of ad space on youth platforms such as Nickelodeon, Cartoon Network, Seventeen Magazine, and several educational sites for middle and high school students (Kaplan, 2020). It would appear that such ad campaigns are indeed effective. Teenage E-cigarette use increased 900% from 2011 to 2015, and continues to rise, with US data for 2019 suggesting that E-cigarette use climbed, with 27.5% of high school students reporting daily nicotine use (CDC, 2023). These trends are highly concerning because smoking remains a leading cause of premature disability and death, responsible for 87% of lung cancer deaths, 61% of pulmonary disease deaths, and 30% of overall cancer deaths (Prochaska and Benowitz, 2019). In addition, a host of other dysfunctions and diseases are linked to the impacts of smoking on vital systems, such as the immune system and the microbiome (see *Immune System, Gut Microbiome, and Disease Risk in the Smoker* below) and this is an area where public education is sorely needed. Considering the rise in popularity of nicotine-based products, together with the prevalence of tobacco-related dysfunction, disease, and death, smoking in youth, and the associated long-term addiction, is a crisis that needs to be addressed.

Biological Impacts of Smoking Nicotine

Smoking and Lung Disease

The most obvious direct impact on the smoker is in the lungs. The bronchioles and alveoli that line the lungs, allowing oxygen to reach the bloodstream, are sensitive tissues; when irritated over time by toxins in tobacco smoke, these tissues become inflamed and scarred (CDC, 2011). Smoke contains very large amounts of oxidants (reactive oxygen species, ROS) that cause (i) direct damage to cellular constituents, such as DNA, proteins, and membranes (Fowles and Bates, 2000) and (ii) dysfunction of the immune system (see below). For example, smoking

causes irreversible damage to the protein elastin that is essential to elasticity and ventilatory function of the lung (Starcher, 2019). This damage significantly harms the lung's ability to efficiently exchange air. Smoking also causes DNA damage and a host of genetic mutations (CDC, 2011). These mutations include changes that tip the protease-antiprotease balance in the lung towards protease, resulting in excessive protein degradation and tissue damage (CDC, 2011). Many of the chemicals in cigarettes have dangerous effects; for example, benzo[a]pyrene damages the tumor suppressor gene p53 that normally protects cells from cancer by committing cells with mutated genes to programmed cell death (Pichandi et al., 2011). Other carcinogens in tobacco smoke cause mutagenesis and damage of genes that regulate the cell cycle and cell growth, which can lead to cancer via abnormal and rapid cell division and growth (Pichandi et al., 2011). Some of the chemicals in smoke interfere with enzymes that convert toxins in the lungs into more harmless forms (Pichandi, 2011). The effects of benzo[a]pyrene and similar chemicals are further exacerbated by other compounds in cigarettes, such as chromium that increases the risk of DNA damage and arsenic, cadmium, and nickel that interfere with DNA-damage repair (Pichandi et al., 2011). Together, all of this increases the probability that damaged cells become cancerous in the smoker (Pichandi, 2011).

Immune System, Gut Microbiome, and Disease Risk in the Smoker

The health issues caused by smoking go far beyond the lungs, and cause deeper and more system-wide, both short-term and long-term issues than commonly realized. The gut microbiome is recognized to have a large impact on overall immune function, and its composition is a key indicator of health overall (Sublette et al. 2020). In COVID19-diseased models, chronic, non-resolving inflammation (leading to massive organ attack), gut microbiome disruption (dysbiosis) and impaired viral defenses were observed (Enichen et al., 2022). These responses

are similar to trends seen in the body of a smoker, with immune dysfunction and elevated risk for a host of diseases (Sublette et al., 2020). Similarly, the microbiome of nicotine users exhibited an altered composition. For example, research found profound changes linked to chronic inflammation and increased disease risk were found in the oral microbiome of smokers using E-cigarettes (Park et al. 2023). Furthermore, the gut microbiome of nicotine users exhibited a high relative abundance of microbial clades that are considered immunostimulatory (Kaakoush 2015; Chivero et al., 2020). These effects were associated with altered levels of metabolites such as the neurotransmitters gamma-aminobutyric acid (GABA) and glutamate that are produced by the gut microbiome and transferred to the brain, where they alter brain function (Chivero et al., 2020). Thus, nicotine has significant impacts on the microbiome and associated immune-system and brain function. Although much emphasis has been placed on detrimental effects of nicotine addiction and smoking for health later in life, new research is making it clear that the effects of nicotine use are also much more immediate and include triggering of psychiatric disorders such as depression, anxiety, and psychosis (Chivero et al., 2020). These effects on the brain are likely caused by a combination of immune-system imbalances and neurotransmitter imbalances (Chivero et al., 2020). It is noteworthy that pure nicotine is associated with some beneficial as well as some harmful pharmacological effects depending on contexts (Zhang et al., 2022). While tobacco smoke consistently increases the risk of multiple diseases, the pure nicotine monomer has mixed effects; these include anti-inflammatory effects that could be beneficial as well as pro-inflammatory effects that could be harmful (Zhang, 2022). The potential benefits of pure nicotine are thus an area in need of further research. Clear identification of any instances where ingestion of pure nicotine without inhaling the carcinogens in tobacco may be safe could allow for some de-stigmatization of nicotine as well as for nicotine addicts to receive the desired

effects without the serious health risks. The following section delves deeper into additional connections among nicotine, neurotransmitters, and brain function.

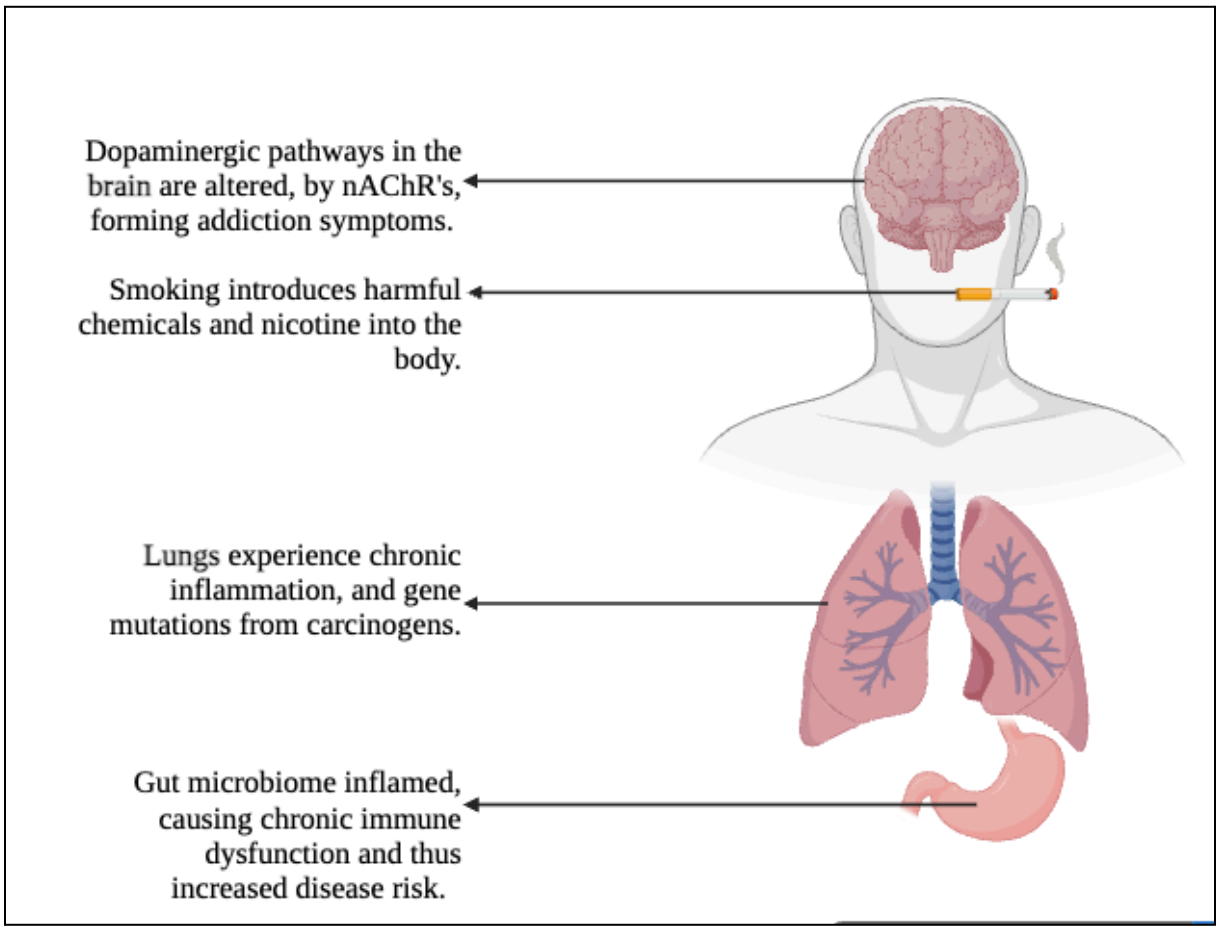

Figure Two: The physiological impacts of smoking cause increased risk for mental dysfunction as well as mental disorders and multiple diseases. Some of the impacts discussed are represented in the graphic above. Created in Biorender.

Nicotine Receptors and Neurotransmitters

Nicotine was first studied in depth in 1905 by John Langley to test his proposal that pharmacological agents work through receptors, with his research making great progress on the understanding of ligand initiation of physiological pathways. Nicotine works as a ligand for Nicotinic Acetylcholine Receptors (nAChR) that are neurotransmitter-gated ion channels located

in the neuromuscular junction (Unwin, 2013), a synaptic connection that communicates signals between nerve and muscle cells. The nAChR is an important receptor in this junction because it transduces chemical signals to electrical signals with particularly high efficiency (Rose, 2007). This contributes to the addictive nature of nicotine because of how rapidly effects take place, allowing for instant gratification for the smoker. These receptors' subunits exhibit a high degree of evolutionary conservation and play a central role in functions essential to life (i.e., reward pathways, motivation, learning, etc.), which makes them a target for toxins like nicotine produced in nature as a plant defense against predation (Albuquerque et al., 2009). Nicotine, a highly effective plant-defense metabolite, is toxic to all heterotrophs with neuromuscular junctions through poisoning of acetylcholine receptors (Baldwin, 2001). Nicotine kills insects via convulsions and paralysis by preventing binding of the neurotransmitter acetylcholine to acetylcholine receptors at nerve synapses and causing uncontrolled nerve firing (Steppuhn et al., 2004). nAChRs exhibit upregulation when chronically exposed to nicotine prompting them to increase their expression (Rose, 2007), although the mechanism by which this takes place is poorly defined. Such upregulation in the smoker's brain increases high-affinity nicotine binding by nearly fourfold when compared to age- and gender-matched controls (Rose, 2007). Nicotine acts on brainstem, thalamic, striatal and cortical sites in the brain to enhance the release of several neurotransmitters, including dopamine, norepinephrine, acetylcholine, GABA, glutamate, and serotonin (Rose, 2007). These neurotransmitters are highly evolutionarily conserved and responsible for reward pathways in the brain (Rose, 2007). They facilitate pleasure, satisfaction, motivation, memory, focus, stress reduction, and positive moods in the brain (Purves et al., 2001). Activation of the dopamine reward pathway is common in many addictive drugs, such as cocaine opiates and alcohol (Rose, 2007). These rewarding feelings are part of why nicotine is so

addictive. These responses are also related to the fact that nicotine is particularly addictive, and leads to severe problems with smoking cessation, for individuals with a low capacity for emotion regulation under distress (as is detailed further in several sections below). Overall, nicotine can be thought of as hijacking nAChRs and disrupting the "normal" physiological functions of the cholinergic system that, as part of the autonomic nervous system, plays important roles in memory, digestion, heart function, movement, and many other functions (Dani, 2015).

Treatment and Barriers

Nicotine Addiction: Addict's Perspective

Nationwide campaigns such as Drug Abuse Resistance Education (DARE), Just Say No, The Truth Initiative, and Tips from Former Smokers, have had success in raising awareness that smoking has serious harms on health (Centers for Disease Control and Prevention, 2024), despite the misinformation that nicotine companies have spread (see above). Today, the adverse health impacts of smoking are well known, and 68% of smokers want to quit (Prochaska and Benowitz, 2019). Individuals who smoke are motivated to rationalize their behaviors, and will even return to such rationalizations when relapsing, consistent cognitive dissonance theory, suggesting that many smokers both fully understand the harms of smoking and still justify their lack of drive to quit (Fotuhi et al., 2019). Of those who attempt to quit nicotine, only 55% are able to make it a full 24 hours (Prochaska and Benowitz, 2019). 60% of those who are able to quit for a day do not make it a full week, of which only 7% stay clean for 6 months (Prochaska and Benowitz, 2019). 45% of those who sustain for 6 months end in relapse (Prochaska and Benowitz, 2019). Smoking cessation is known to result in withdrawal syndrome, symptoms of which including bradycardia (slowed heart rate), gastrointestinal discomfort (stomach pain, nausea), and increased appetite, as

well as affective symptoms such as craving, depressed moods, dysphoria, anxiety, irritability, and difficulty concentrating (Kenny and Markou, 2020). These symptoms manifest starting around 4 hours after smoking cessation and may last up to 10 weeks after cessation (Kenny and Markou, 2020). The unpleasant side effects of smoking cessation are a common barrier for addicts who wish to quit, particularly when experienced without support systems in place (Britton, 2009). Quitting nicotine is extremely difficult and the statistics show that the desire and the ability to quit are different battles entirely. The resources available to smokers who hope to quit include support groups and counseling, which has a 13-17% success rate, Bupropion, which has a 24% success rate, Varenicline, which has a 33% success rate, and nicotine replacement therapy, (such as the patch) which has a 19-26% success rate (Britton, 2009). These resources target the chemical foundations of nicotine addiction and the behavioral aspect of addiction. Unfortunately, these treatment and education resources are not sufficient and long-term cessation rates remain around 20%, while half a million people die every year from tobacco-related health issues (Prochaska and Benowitz, 2019). This number is a lowball of the actual figure, however, and more research needs to be done to properly quantify the true impact of tobacco, as it is connected to more diseases and dysfunction than is widely recognized. For example, there is a consistent correlation between nicotine use and suicide, though the causal relationship has not been clarified.

Established Treatments

There are two aspects of nicotine addiction that must be treated in order for nicotine users to quit: behavioral and chemical. Behavioral aspects refer to the habit of smoking, which may manifest in oral fixation, and visual cues that elicit cravings (Merillen Silveira et al., 2021). These are generally treated through counseling, which may help build new, replacement habits

(Cognitive Behavioral Therapy Los Angeles, 2020). Counselors/therapists usually engage with patients using cognitive behavioral therapy, which works to identify smoking triggers, which can be any type of situation, emotion, or activity, and developing alternative behaviors to replace smoking (Cognitive Behavioral Therapy Los Angeles, 2020). Addicts will generally work with a counselor to set realistic goals and reframe thoughts and behavioral patterns, such that they can be more productive and healthier (Cognitive Behavioral Therapy Los Angeles, 2020). Counseling works best when used in combination with a medicinal treatment to alleviate symptoms of withdrawal (Cognitive Behavioral Therapy Los Angeles, 2020). One common medicine for smoking cessation is Bupropion, an aminoketone antidepressant prescribed to many addicts, as it is useful to help with withdrawal symptoms by lightly inhibiting norepinephrine and dopamine reuptake (Huecker et al., 2022). The drug also works on nicotine and serotonin receptors, although to a lesser degree (Huecker et al., 2022). Bupropion increases some of the neurotransmitters that are increased in the brain of smokers, thus alleviating withdrawal symptoms (Huecker et al., 2022). Varenicline, another smoking-cessation drug, works as a highly selective partial nicotine receptor agonist– able to bind to nicotinic acetylcholine receptors and prevent the binding of nicotine molecules as well as decrease cravings in the patient (Singh and Saadabadi, 2023).

Teen Smokers

Brain maturation in adolescence is a sensitive period of development, where essential reorganization of brain regions takes place responsible for mature cognitive and executive function, working memory, reward processing, emotional regulation, and motivated behavior (Yuan et al., 2015). Nicotinic Acetylcholine Receptors play a large role in regulating brain maturation during this time (Yuan et al., 2015), which is why nicotine has unique consequences

for adolescent brain development (Yuan et al., 2015). Due to hypersensitivity of certain receptors in the dopaminergic pathways in young adults, namely the nAChRs, adolescents are more sensitive to nicotine-induced long-term potentiation associated with plasticity of glutamate receptor function (essential for long-term memory and learning), compared to adults (Yuan et al., 2015). This implies that, when an adolescent smokes nicotine, the reward pathways are hypersensitive to dependence on nicotine, as their brain is highly plastic at this stage (Yuan et al., 2015). Furthermore, acute nicotine has been shown to increase extracellular serotonin overflow in the nucleus accumbens shell (involved in many reward-related behaviors), while decreasing both dopamine and serotonin levels more strongly in adolescent medial prefrontal cortex (essential for cognitive processing, emotional regulation, motivation, and sociability) as compared to adults (Yuan et al., 2015). This also leads to a greater rewarding effect from nicotine use in adolescents compared to adults.

The addictive nature of nicotine is thus acutely impactful in the young brain due to the hypersensitivity of the developing brain (Yuan et al., 2015). In studies on rodents, adolescent rodents exhibited an increase in locomotor activity in response to nicotine, which is the opposite effect nicotine has on the adult brain (Yuan et al., 2015). Furthermore, adolescent rodents were more susceptible to the rewarding aspects of nicotine, while the adult brain was more susceptible to the adverse impacts of nicotine (Yuan et al., 2015). Nicotine also increased self-administration of psychostimulant drugs and alcohol in adolescent rodents, a trend not present in adults (Yuan et al., 2015).

It is quite clear that current anti-drug campaigns in schools are not effective at preventing smoking in teens, as indicated by 27.5% of teens using nicotine daily (CDC, 2023; see also above). The DARE (Drug Abuse Resistance Education) program is currently taught in all 50

states and involves police officers visiting classrooms in grades K-12 to speak about the harm of drugs, encouraging students to resist peer pressure and report drug use. However, the available evidence indicates that such anti-drug campaigns delivered by force of authority are ineffective in keeping students off drugs, and that effective drug-prevention programs instead focus on interactive development of life skills and emotional awareness (Aliye et al., 2020). As discussed further in the following section, high anxiety and poor emotional-regulation skills are two variables that substantially increase the risk of drug addiction (see Wilkinson et al., 2022) . Providing students with practice in these important life skills is a promising way to decrease drug and nicotine addiction in youth. I advise that these skills should be a focus of how schools provide students with the tools they need to build coping mechanisms long before encountering drugs, thus decreasing the likelihood that nicotine becomes their coping mechanism of choice (see also Wilkinson et al., 2022).

The Appeal of Nicotine: The Role of Mental Disorders

In order to understand the progression from trying a cigarette to a life of addiction, one must consider why the smoker continues. Pure nicotine can improve cognitive function, including learning, memory and attention, by stimulating and desensitizing nicotinic receptors (Castaldelli-Maia et al. 2015). Such cognitive effects are responsible for some of the appeal of nicotine (Castaldelli-Maia et al., 2015). On the other hand, nicotine withdrawal is associated with deficits in cognitive function, including sustained attention, working memory and inhibition of the response, which creates the opposite cognitive effects as what the addict was originally searching for, which creates barriers to smoking cessation (Castaldelli-Maia et al., 2015). Research on the positive cognitive effects of pure nicotine is underway (Rusted et al., 2008) with the goal of exploring the potential of future pharmaceutical use of pure nicotine in a professional

medical environment. However, this is an issue separate from unsupervised use of nicotine in the context of smoking, which has been proven again and again to be unsafe –and with vapor products showing evidence of being hardly better than combustible cigarettes.

Based on the cognitive effects of nicotine described above, a useful way to understand the motives of a smoker is through the perspective of attempted self-medication. Individuals suffering from mental illness are significantly more likely than those without such an illness to have a nicotine addiction (Dalak et al., 1998). In particular, rates of smoking are highest among patients with schizophrenia, of which around 88% identify as smokers, followed by those with mania/bipolar disease (70% smokers), major depressive disorder (49%), anxiety or personality disorders (45%), and the control population (30%) (Dalack et al., 1998). There is thus a clear trend that poor mental health causes an increased pressure to use, and thereby become addicted to, nicotine (Dalack et al., 1998). Anxiety reduction is the number one cited reason for nicotine use (Dalack et al., 1998). Schizophrenics appear to use nicotine for many of the same reasons as those without psychiatric illness, i.e., mainly relaxation (Dalack et al., 1998). The difference comes after the first use, as association studies found more positive symptoms in schizophrenic smokers than nonsmokers (Dalack et al., 1998). Positive symptoms are used in psychology to describe delusions, and many prefer these symptoms over depressive episodes (known as negative symptoms) (NHS, 2021). Heavy smokers (25+ cigarettes per day) had the highest number of such positive symptoms and the lowest number of negative symptoms in comparison with light smokers with schizophrenia (Dalack et al., 1998). Nicotine has also been shown to improve memory and attention in individuals experiencing psychosis (Chivero et al., 2022). Additionally, individuals trying to quit reported an increase in their psychiatric symptoms during withdrawal from tobacco (Dalack et al., 1998).

However, these observations have to be considered in the context of neurotransmitter imbalances caused by (i) the effect of nicotine on the cholinergic system (Nees, 2015) and (ii) by nicotine-associated triggering of neuroinflammation (Heldt et al., 2022). It is clear that mental disorders already involve elevated levels of both neurotransmitter imbalances and neuroinflammation (Calcia et al., 2016). Nicotine use would thus appear to make both worse and thus create a dual effect of alleviating some negative symptoms, while simultaneously exacerbating underlying problems. There is also direct preclinical evidence for electronic nicotine delivery system–associated neurovascular impairment, causing neurological as well as mental health decline (Heldt et al., 2022).

This scenario can be described as poor mental health creating a feedback loop that not only aggravates the condition but also prevents smokers from quitting. Due to its impact on dopamine pathways, smoking seems to provide greater incentive for individuals suffering from increased anxiety due to mental disorders (Dalack et al., 1998). This is alarming in view of a 34.6% increase in teenage mental illness prevalence from 2012 to 2018 (Tkacz and Brady, 2021). Concerningly, there was a 95% increase in anxiety disorders during this time, further suggesting a significantly higher vulnerability to nicotine and drug dependency in the younger generation (Tkacz and Brady, 2021).

Smoking Cessation and Personalized Medicine

Research on effective smoking cessation needs more attention and unbiased funding in order to combat the growing number of people impacted by nicotine addiction. The established treatments described above are not effective enough, as reflected by the death toll: 447,751 Americans died of tobacco-related causes in 2023 alone (Le et al., 2023). Smoking cessation is complex, with multiple environmental and individual factors (Bitar et al., 2024) of which the

latter author described 39 distinct factors. Such factors influencing cessation include tobacco policies, smoking norms, smoking cessation services, friends and family, psychological characteristics, smoking behavior pre-quitting, nicotine dependance symptoms, and use of other substances. There is also a lot of embarrassment and self-consciousness when it comes to seeking aid in smoking cessation, which needs to be addressed in smoking-cessation programs (Bitar et al., 2024). A particular barrier to quitting nicotine is a lack of emotion regulation, particularly when dealing with distress, which makes individuals vulnerable to relapse (Tran and Morell, 2023). Moreover, a preexisting low capacity for emotion regulation increases use of tobacco products in the first place (here, specifically investigated for E-cigarettes) in addition to interfering with smoking cessation (Tran and Morell, 2023). Recent research is, therefore, targeting resources that ameliorate anxiety and improve emotion-regulation capacity in order to reduce or eliminate nicotine use (McLeish et al., 2021). Some of this research includes a focus on Acceptance and Commitment Therapy, (which uses mindfulness and behavior change commitment strategies to aid smokers in their cessation journey; Kwan et al., 2024) and cognitive reappraisal (which works to reframe stimuli and down regulate emotional reactions) to aid smoking cessation (Faulkner et al., 2022). These are both promising approaches and examples of how empathy-based research and aid can help nicotine addicts quit. Empathetic approaches, combined with traditional therapy, societal assistance, normalization of smoking cessation, and medicinal tools can help combat the pressing societal issue of nicotine addiction and smoking. Considering all aspects, both societal and personal, of the life of a smoker is the most promising way to combat the nicotine crisis in America.

Personalized medicine is gaining traction as technology develops and we grow to understand the complexities of any individual's condition. With advances in therapy, genomics,

and pharmacology, personalized medicine is more promising than ever before, especially when it comes to combating addiction. “Personalized medicine tailors therapies, disease prevention, and health maintenance to the individual, with pharmacogenomics serving as a key tool to improve outcomes and prevent adverse effects” (Wolfgang et al., 2023). Genomics has progressed immensely in the nicotine-addiction field, with recent research finding gene variants associated with altered (accelerated) nicotine metabolism (Li et al., 2022), different operation of nAChR (Jones et al., 2022), altered GABA release in the dopaminergic pathways (Mouro Ferraz Lima et al., 2023), and a different form of a serotonin transporter that exacerbates problems with emotion regulation (Wilkinson et al., 2022), all of which have immense effects on the likelihood of smoking cessation, as well as implications as to what tools work best for the individual. With such research, as well as developments in the field of smoking cessation therapy, personalized medicine may be able to provide many more individuals with the tools they need to quit smoking. This is why investment of research efforts and funding is so essential at this time to ensure personalized medicine continues to advance and improve in order to aid nicotine addicts with cessation.

Conclusions and Recommendations

Based on the trends identified in this synthesis, it appears that the current spikes in smoking-related health problems cannot be combatted effectively solely with education for smokers and youth. More research is needed on the impact of practices and products of nicotine companies on smoking-related behaviors and health effects. A better understanding of nicotine and other toxicants in new technologies such as vapes is needed to protect the health of a new wave of nicotine addicts who have never even touched an actual cigarette. A new, transformative

and comprehensive approach to smoking cessation efforts is needed to improve the current low success rates for individuals who seek to quit their nicotine addiction. The high, and continuously increasing, numbers of young adults who develop nicotine addiction, combined with the number of people unable to follow through with goals of smoking cessation, provide alarming projections for the future health of millions of Americans. Action must be taken now by society to invest in new and innovative solutions to end nicotine addiction. My literature synthesis suggests that a multi-pronged approach is needed to simultaneously address all key factors that impact nicotine use and addiction. This should include policy making and public resolve to hold tobacco, vape, and related nicotine companies accountable. Because it appears that the targets of current pharmacological tools are insufficient to help the majority of nicotine addicts, future research should explore additional molecular targets, especially keeping in mind that most addiction starts in the youth. Though research involving minors is not easy, it is essential that the changes in the brain of a smoker who started before 25 be better understood, to understand the long-term impacts as well as develop possible tools for cessation in the new generation of nicotine users.

Overall, the focus should be shifted from placing responsibility on the individual to a more empathetic view centered on causative factors beyond the individual's control and combined with a commitment to improved policy making and a compassion-centered environment. A compassion-based approach should also be the centerpiece of psychological counseling and intervention and should be applied as personalized medicine advances and even becomes the norm. Personalized medicine, with the help of unbiased research funding for nicotine cessation resources, can make an immense contribution to decreasing nicotine addiction.

Acknowledgements

I would like to show appreciation for Dr. Barbara Demmig-Adams, who believed in me when others did not, and reminded me that I love science. She is an inspiration to me and many others. I would also like to thank Dr. Pamela Harvey for her endless encouragement. I also thank Dr. Kenneth Krauter for his support on my committee. I am grateful to the EBIO faculty and staff at the University of Colorado Boulder for their teachings and tremendous support. I also want to thank my parents for raising a little scientist and then cheering her on ever since. Lastly, I wish to thank my friends for allowing me to talk about my research every day for many months. No science is possible without immense support.

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