# A 5-Factor Framework for Assessing Tobacco Use Disorder

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**ABSTRACT:** Cigarette use is the leading cause of preventable death in the United States. Despite the well documented dangers of smoking, nearly 20% of adults report regular use of tobacco. A majority desire to discontinue but the long-term cessation success rate remains near 4%. One challenge to reducing the prevalence of tobacco use is an incomplete understanding of the individual correlates that reinforce continued use. Evidence from research on nicotine and tobacco suggests that Tobacco Use Disorder is a complex, and multifactorial condition. Personality traits, comorbidities, habits and lifestyle, genetics, socioeconomic status, and mental and physical health all contribute to the risk for dependence and to the likelihood of quitting. This perspective review provides an overview of some common factors that contribute to liability risk for Tobacco Use Disorder and a framework for assessing individual tobacco users. The framework includes 5 areas that research suggests contribute to continued tobacco use: nicotine addiction, psychological influences, behavioral dependencies, neurobiological factors, and social reinforcement. Nicotine addiction includes drug-seeking behavior and the role of withdrawal avoidance. Psychological and emotional states contribute to a perceived reliance on tobacco. Behavioral dependence is reinforced by associative and non-associative learning mechanisms. Neurobiological factors include genetic variables, variations in neurotransmitters and receptors, pharmacogenetics, and interaction between psychiatric illnesses and nicotine use and dependence. Finally, social reinforcement of smoking behavior is explained by a network phenomenon and consistent visual cues to smoke. A comprehensive assessment of individual tobacco users will help better determine appropriate treatment options to achieve improved efficacy and outcomes.

**KEYWORDS:** Nicotine, tobacco, cigarettes, smoking, dependence, assessment, addiction, quitting, relapse, anxiety, tobacco use disorder, nicotine addiction, smoking cessation, tobacco use cessation, cigarette smoking, addiction medicine

## Implications

This perspective review synthesizes the extensive research into nicotine and tobacco cessation that is siloed by discipline, into a comprehensive, cross-disciplinary, assessment framework for Tobacco Use Disorder. The paper highlights areas of research in nicotine addiction, psychological influences, behavioral dependence, neurobiological factors, and social reinforcements, that all contribute to continued tobacco use. The research derives a 5-factor assessment framework to help improve the efficacy of treatment. Evidence suggests that an accurate assessment of an individual's contributing factors to continued tobacco use, and personalized, multifaceted treatment modalities, with currently available, often non-pharmacological, therapeutic options can improve treatment outcomes.

## Introduction

Cigarettes are the leading cause of preventable death in the US. Despite the apparent dangers, tobacco use remains prevalent, with nearly 20% of adults reporting daily or near-daily use of tobacco.[1] More than 90% of people who smoke have tried or want to quit,[2] but only 7% of quit attempts are sustained at 6 months,[3] and less than 4% of people can maintain long-term abstinence.[2]

Barring an outright ban on tobacco, public health officials have exhausted the tools at their disposal to bring smoking rates down to a minimum, namely raising tobacco taxes, education initiatives, and public smoking bans. Therapeutic options for people who want to quit smoking have primarily been limited to nicotine replacement therapy (NRT), including nicotine patches and gum. However, these strategies are not uniformly successful,[4,5] demonstrating that individuals respond differently to treatments. Behavioral therapies show similarly variable results.[6,7]

Factors that contribute to the development of Tobacco Use Disorder (TUD) are complex and multifactorial, and their relative contributions vary between individuals.[2,8] Several studies have categorized people who smoke based on the frequency of use, level of dependence, number of quit attempts, and other factors that pertain to cigarette use.[9-11] While these studies have provided valuable information about the broad demographics of people who use tobacco, they have yet to comprehensively identify unique traits that affect nicotine dependence and withdrawal and many of the known contributing factors to dependence and addiction. Therefore, the studies cannot lead to a predictive model of treatment strategies that will improve treatment efficacy-based identification and characterization of phenotypes that support the personalization of smoking cessation therapy.[12]

The purpose of this paper is to aggregate the extensive research already done in the many disciplines of tobacco and addiction into a cohesive framework to help healthcare

providers evaluate and treat people with TUD. An effective 5-factor framework for assessing TUD, which offers a holistic assessment of the individual, should take into account the combination and varying degrees of each contributing factor. Evidence suggests a comprehensive assessment framework includes nicotine addiction and should consider both drug-seeking behavioral and withdrawal avoidance, psychological factors that contribute to tobacco's continued use, behavioral influences, neurobiology such as pharmacogenomics, and an undiagnosed mental disorder, and finally, social influences.

Precision medicine is the new ideal across medical specialties, including in the field of addiction.[13] Pre-clinical models have identified several differentially regulated pharmacological targets for a personalized approach to treating nicotine dependence.[14-16] However, people who smoke have unique profiles that are influenced by their habits, personality, lifestyle, and sociocultural exposure in addition to their genetics, metabolism, and physical and mental health status.[2] Expanding the scope of treatment to include psychological, behavioral, neurobiological, and social contributions to the development and maintenance of TUD will improve treatment precision and clinical outcomes.

As a note, this paper refers to nicotine dependence when discussing the addiction to nicotine and neurobiological components, and TUD when discussing non-nicotine contributing factors that influence the continued use of tobacco cigarettes.

## Nicotine Dependence and Addiction

Nicotine is a highly addictive drug, but the liability risk is not the same for everyone.[8] Biological factors like sex[17] and ethnicity[2] affect the development and maintenance of nicotine dependence. Likewise, psychological factors like mental health,[9] emotional state,[18] and behavioral factors like habit patterns[19] and cue-reactivity[20] also play a role in nicotine dependence. Dependence development, reinforcement, and cue salience are regulated by different mechanisms.[21] This means someone who becomes dependent on nicotine quickly may not become as dependent as someone who did not become dependent quickly and will have different smoking-cue-related craving intensities.

These observations support a framework where nicotine dependence is not only influenced by intrinsic and extrinsic factors, but that the effects of these influences on subsequent health and behaviors vary from person-to-person. In addition, nicotine-induced behavioral changes will reinforce dependence differently between people. In other words, a predisposition toward dependence, effects of dependence, and how strongly the effects reinforce smoking behavior each vary between individuals.

Not everyone progresses from dependence to addiction. Dependence is characterized by tolerance and physical and/or psychological withdrawal symptoms that can be managed. Addiction is characterized by compulsive drug-seeking behavior despite a high risk for negative consequences.[22] People with similar smoking behaviors will fall on different points on the dependence-addiction spectrum, which should inform NRT dosage and duration in a treatment protocol.

Several tests can help determine the level of dependence or addiction, including the Fagerström Test for Nicotine Dependence,[23] the Cigarette Dependence Scale, and the Heaviness of Smoking Index.[24] These tests provide different insights into dependence and should not be substituted for one another.[25]

### Nicotine withdrawal avoidance

Nicotine withdrawal is associated with cravings, anxiety, and irritability, which are barriers to cessation. The tendency to continue to smoke and the probability of relapse are correlated with the desire to avoid experiencing withdrawal symptoms. Experiential avoidance is learned through negative reinforcement:[26] Quitting is associated with distress, which can be avoided by smoking. There is interindividual variability in predisposition to withdrawal avoidance, making it a promising opportunity for tailoring a cessation strategy.

Within hours after the last cigarette, people dependent on nicotine will begin to experience withdrawal symptoms. As nicotine, which non-specifically antagonizes nicotinic acetylcholine receptor (nAChR) isoforms, is metabolized, nAChR occupancy falls, and dopamine-mediated activity in the reward system is diminished. This physiological alteration has physical, psychological, and behavioral consequences, and each of these can be specifically targeted to improve treatment for nicotine withdrawal.

A promising pharmacological target is the habenulo-interpeduncular (Hb-IPN) circuit,[27] which modulates reward-seeking, punishment aversion, mood, and higher-order thinking.[28,29] Animal studies have identified sex differences in how nicotine use and withdrawal affect activity in the HB-IPN,[30] and nAChR subunit expression in the medial Hb-IPN is differentially regulated in male and female mice during nicotine exposure and withdrawal. In humans, a receptor imaging study showed significantly higher availability of β2-nAChR in male smokers in multiple brain regions as compared to male non-smokers, whereas female smokers showed no difference in β2-nAChR availability in comparison with female non-smokers.[17] These findings provide a preliminary framework where sex-specific pharmacotherapies could improve treatment efficacy.

Behavioral therapies can also be tailored to address unique factors that contribute to withdrawal. For example, anxiety sensitivity is a transdiagnostic risk factor for cigarette use and PTSD (ie, it increases the risk for either and contributes to both). Bakhshaie et al demonstrated that cognitive inflexibility and experiential avoidance link anxiety sensitivity and smoking in people with PTSD.[31] Thus, therapy for people who smoke and have PTSD should incorporate cognitive-behavioral skills that address avoidance and inflexibility.

## Psychological Dependence

Psychological TUD is a state where unpleasant emotional-motivational symptoms (eg, cravings, anxiety, dysphoria) coincide with abstinence and are alleviated with use. Even people with similar smoking patterns can have dramatically different psychological dependencies. Understanding the relationship between dependence, addiction, and psychological states will lead to improved treatment strategies for different people.

Two psychological measurements have proven to be significantly predictive of quitting success: affect and distress tolerance, both of which often respond well to behavioral therapy.

Affectivity describes mood states and emotional responses; someone who has a "glass half full" outlook has positive affectivity, while a "glass half empty" outlook identifies negative affectivity. Negative affectivity is linked to higher anxiety and stress, which are known smoking triggers. Someone with negative affect is also more likely to succumb to cravings to reduce negative emotions, perpetuating negative reinforcement.

Distress tolerance (DT) describes how well someone manages emotional responses to stressful events. Two metrics can be used: "the *perceived* capacity to withstand negative emotional and/or other aversive states" and "the behavioral act of withstanding distressing internal states elicited by some type of stressor."[32] Low DT increases the risk that someone will rely on nicotine to manage emotional responses to stressors, and, through negative reinforcement, habitual smoking can reduce DT. Self-reported low DT is associated with increased nicotine dependence and withdrawal severity.[33]

False safety behaviors (FSB) are behaviors that are intended to decrease anxiety, but that maintain or even increase anxiety long-term.[34] FSB is nearly ubiquitous among people who use nicotine products, especially in the context of avoiding stressful or anxiety-inducing situations. Many people who smoke develop a false belief that they require cigarettes to get through stressful situations, social interactions, and even complete a day's work. Reliance on FSB prevents someone from learning that their anxiety is maladaptive. Simply by identifying the FSB and making the person who smokes aware of their behavior may improve treatment outcomes.

It has been shown that the number of previous quit attempts is inversely correlated with the likeliness of successfully quitting smoking, suggesting that people who have previously attempted to quit create defeating self-talk and negative psychology.[35] Interestingly, no correlation between quitting success and demographics or level of dependence has been found, further supporting the hypothesis that different people have unique psychological contributions to smoking behaviors.

Psychotherapy tools can be tailored to address affect[36] and/or DT,[18] improving treatment efficacy and clinical outcomes for individuals. Several therapies have been shown to strengthen quitting success, including Cognitive Behavioral Therapy, Dialectical Behavior Therapy, Acceptance and Commitment Therapy, and Mindfulness-Based Cognitive Therapy.

## Behavioral Dependence

Behavioral dependence describes a compulsion to engage in rewarding habits and patterns, irrespective of substance use. However, habits and cues are potent reinforcers of continued tobacco use, and people who smoke due to a behavioral dependency are at risk for developing physical and psychological dependencies as well.

Behavioral dependence is established through both non-associative and associative learning mechanisms.[37] Non-associative learning occurs through habituation (attenuation) and/or sensitization (augmentation) of a behavioral response to a stimulus. In this case, nicotine is a primary reinforcer that sensitizes nAChRs and changes dopaminergic signaling, which is sufficient to elicit cravings in the absence of cues and drives subsequent nicotine administration.[37] Nicotine dependence development is related to dopaminergic projections on the nucleus accumbens (NAc), and, accordingly, synaptic plasticity plays an important early role. Nicotine also acts as a reinforcement enhancer; that is, nicotine use enhances the reinforcing properties of nicotine use. This is known as the dual-reinforcement model.[38]

After years of smoking, structural modifications in the nervous system become persistent and strongly reinforce dependence. Nicotine causes lasting changes in critical learning-related and habit-forming structures in the brain, including the ventral tegmental area (VTA), NAc, hippocampus, prefrontal cortex (PFC), and basal ganglia.[39] Before dependence is established, nicotine use causes aberrant dopamine release in these regions and, because these regions are fully sensitive to dopamine, the consequence is a rush of positive sensations. However, over time, the brain becomes habituated to the elevated dopamine levels, and increased nicotine is required to elicit the initial level of response.[40] When people respond by increasing their tobacco use, long-lasting structural changes occur in these brain regions. The result is a shift away from nicotine use as a source of pleasure and toward a stimuli-response behavioral model that aims to minimize the unpleasant consequences of not smoking.[37]

The environmental stimuli and sensory experiences associated with smoking episodes gain salience; in other words, when people who currently smoke (or who used to smoke) are exposed to stimuli that they associate with smoking, they will experience cravings. These cravings are a physical manifestation of increased activity in diverse neural networks, including the reward system, which links a smoking-related salient cue to reduced anxiety, increased alertness, and improved attention. When someone who has cue-induced cravings doesn't smoke, the cravings become more intense because the network activity is never "rewarded."[40]

Associative learning is the process of learning that a stimulus (eg, a coffee break) predicts an event (smoking). Over time, neutral stimuli associated with smoking become conditioned stimuli that will elicit cravings whenever they are encountered.[37] Conditioned responses drive smoking behavior, and

they can persist for many years after someone quits. Conditioned stimuli can also act as conditioning reinforcers that maintain the behavior in the absence of nicotine.

Reward responsiveness and cue-reactivity vary between people, and high reward responsiveness and high cue-reactivity tend to occur together.[20] This has implications for individualized treatment strategies: People who are more cue-reactive are likely to be more responsive to non-nicotine rewards, and they may respond particularly favorably to a treatment strategy with behavioral reward contingencies. Ray et al proposed a model of "behavioral habitualness," which posits that an overreliance on habit is a common trait among people with addiction.[19] Self-reported habit measures were found to correlate with the degree of dependence, with higher habit scores predicting increased dependence. This could be used to differentiate habit and dependence, which is an important distinction. Treatment options to consider are aversion therapy and habit substitution for those prone to reward responsiveness.

Bupropion is a dopamine and norepinephrine reuptake inhibitor approved for smoking cessation that works to attenuate the stimulant effects of nicotine on the nAChR. However, pharmacogenetics data suggest that they could make a difference in specific segments of the population with genetic variations for slower nicotine and bupropion metabolism activation.[41] Additionally, the response of β2*-nAChRs to nicotine seems to vary between the sexes. Men respond better to NRTs while women often experience relief from denicotinized tobacco inhalers, that is, an alternative to the conditioned response.[42] This indicates variations in the non-nicotine-conditioned stimuli associated with cigarette smoking between the sexes with likely individual variations.

As further evidence for behavioral dependence, clinical studies show that smoking is most often maintained on a variable-interval schedule, even while nicotine is metabolized at a constant rate.[43] This indicates an important aspect of smoking: Diminished satiation levels of nicotine in the β2*-nAChRs are not the sole reinforcing factor for continued tobacco use; other possible contributing factors could come from exogenous stimuli. Similarly, smokers often continue to smoke, despite full β2*-nAChRs occupancy, further illustrating the idea that smoking is less directly linked to nicotine addiction in many tobacco users, and there are likely other contributing factors.

## Neurobiology

The neurobiological underpinnings of nicotine dependence are complex, and several neurotransmitters, receptors, and pathways are implicated.[2,8,44] Chronic exposure to nicotine is associated with structural and functional neuroadaptations that drive dependence and promote continued use,[45] as well as pharmacogenetics, and untreated mental health disorders. The age at which someone starts smoking affects the extent of change, with people who started smoking in their teenage or young adult years being the most severely affected.[46] The extensive variability of genetics and concurrent mental health issues emphasizes the need for individual evaluation and treatment.

### Nicotinic acetylcholine receptors

Nicotinic acetylcholine receptors are pentameric ligand-gated ion channels that can have a homologous or heterologous composition.[47] NAChRs are widely distributed and are present in every organ system. In the brain, they are present in addiction-relevant regions, including the ventral tegmental area (VTA), nucleus accumbens (NAc), hippocampus, prefrontal cortex (PFC), and amygdala.[48] The nAChR subtype-specific localization, density, and functional properties determine the influence of nicotine on the brain.

NAChRs' endogenous agonist, acetylcholine, has a pivotal role in functions as varied as cognition,[49] movement,[50] pain,[51] and immunity.[52] Nicotine is an exogenous nAChR agonist that indiscriminately activates nAChRs, leading to widespread, unregulated cholinergic signaling and increases glutamate and dopamine levels in the VTA, NAc, and other regions.[2,47] Desensitization to nicotine occurs rapidly, with some subunit compositions desensitizing more rapidly than others.[48] Chronic nicotine exposure upregulates nAChR expression and trafficking in neurons.[53]

In the human nervous system, there are 12 varieties of nAChR subunits, named α (α2-α10) and β (β2-β4), that are arranged into homogenous or heterogenous pentamers. α4β2* (*indicates the possibility of other subunits) subunits are required for establishing and reinforcing nicotine dependence. Increased α4β2* availability is linked to increased attentional control,[54] which likely contributes to the transient cognitive enhancement that nicotine can deliver. Although α4β2* is the most well-understood in terms of nicotine dependence, several other subunits have recently been implicated in modulating nicotine aversion, liability risk, cigarette consumption, and ability to quit.[15,47] Studies indicate that activation of α7 nAChRs by ACh counters the behavioral effects of nicotine and suggests using a full or partial agonist to desensitize the α7 nAChRs in the NAc shell or anterior cingulate cortex would help reduce the desire to smoke cigarettes.[55]

There are 11 nAChR subunit-encoding genes, many of which have at least one single-nucleotide polymorphism (SNPs) that can affect nicotine functionality and metabolism.[47] In addition, the sensitivity of α4β2 to nicotine is affected by the composition of the remaining nAChR subunits.[48] Preclinical and clinical evidence suggests that targeted nAChR–based ligands (eg, the smoking cessation aid varenicline) are promising therapeutic agents for nicotine dependence.[56]

### Dopamine

The dopamine system has diverse brain functions, including mediating addiction via the mesolimbic dopaminergic system's

reward pathway, which includes dopaminergic projections from VTA and NAc neurons.[48] NAChR activity causes dopaminergic neurons to transition from tonic firing to phasic bursts, which increases dopamine release and signals reward and salience.[57]

Increasing or decreasing activity at 2 types of dopamine receptors, D1 and D2, changes the neurons' firing patterns and sets up an interesting double dissociation. In an animal model, changing D1 activity blocked acute nicotine aversion but did not affect withdrawal. Changing activity at D2 blocked withdrawal aversion after chronic nicotine exposure. These observations suggest that D2 may be a unique target for treating withdrawal.[57]

The frequency of the dopamine transporter (DAT) also affects how rewarding nicotine is by controlling how quickly dopamine is removed from the synaptic cleft. Someone with high DAT levels will have a weaker response to nicotine than someone with low DAT levels.[15,58] As well, nicotine indirectly affects DAT functionality in a dose- and exposure duration-dependent manner.[59]

*Pharmacogenetics*

Recent advances in the field of pharmacogenetics have led researchers to seek candidate genes that are affected by smoking.[60,61] One large scale meta-analysis indicates 566 genetic variants shown to influence substance use, with ranging mechanisms implicated from neurotransmission, reward-related learning, and stress response.[62] Several genes and non-coding regions have been implicated in both nicotine pharmacodynamics (responses in the brain), pharmacokinetics (metabolism),[15,63] and the quality of response to NRT[5] and behavioral therapies.[64]

The best way to prevent TUD and smoking related diseases is to prevent smoking initiation. There are 259 genetic loci associated with smoking initiation, including risk seeking propensity and nicotine metabolism rates, indicating a strong genetic component to developing TUD.[65] One gene specifically, the REV3L protein coding gene, displays a high level of correlation with smoking initiation. Decreasing the expression of the REV3L gene reduces the probability of initiation, identifying it as a potential gene to target with drugs for cessation and prevention.[66]

All drugs activate the mesolimbic dopamine system reward pathway and dopamine-related genes have long been popular candidate genes because of the high level of association and variability in stages of smoking. The variations in the D2 dopamine receptor have been linked to continued nicotine use. While initiation of smoking is associated with a signal transduction gene, the protein phosphatase 1 regulatory subunit 1B (PPP1R1B) affects reward-based learning by variations in synaptic plasticity.[62]

The most well studied polymorphic gene that affects nicotine liability is the cytochrome P-450 isoform CYP2A6, which determines how fast nicotine is metabolized in the liver.[15] Fast CYP2A6 metabolizers have a lower risk for initial dependence, but as they continue to smoke, their risk for dependence increases relative to slow CYP2A6 metabolizers, and they experience more severe withdrawal symptoms.[67] In addition, slow CYP2A6 metabolizers have a higher quit success rate using a nicotine patch, while normal metabolizers responded more favorably to the drug varenicline.[5,68]

Polymorphisms in dopamine-related genes can have substantial effects on dependence and withdrawal.[69] The D3 dopamine receptor drives drug-seeking behavior and reinstatement,[70] and the D3 rs6280 Ser9Gly variant has been shown to reduce cravings in response to a smoking cue.[21] The D3 rs6280 C/T polymorphism has been linked to success rates in addiction recovery.[71] Polymorphisms in the dopamine transporter *DAT1/SLC6A3* gene affect nicotine liability and reinforcement,[72] cue response,[73] cessation,[74] and pharmacotherapy efficiencies (particularly bupropion).[75,76] The D4 receptor genotype also moderates the efficacy of the smoking cessation drug bupropion.[41]

NAChR gene diversity is another significant source of variability among people who smoke regularly. The *CHRNA5/A3/B4* gene cluster encodes the α5, α3, and β4 nAChR subunits, and variants are known to affect reinforcement,[77] cravings,[78] and quitting success.[79] *CHRNB4* loci affect nicotine initiation,[80] and *CHRNB2* loci affect pharmacotherapy efficacy.[81] Many other nAChR variations could potentially be leveraged for personalized approaches to smoking cessation.[15]

Epigenetic modifications, particularly genome-wide DNA methylation, have also been linked to nicotine use, with more variability in DNA methylation being observed in people who smoke chronically.[82,83] Since DNA methylation states rapidly return to normal levels after quitting, this may prove to be a useful measurement of treatment efficacy.[84]

Understanding genetic contributions that lead to smoking related behaviors, nicotine dependence, and TUD, may better inform treatment strategies. Studying the genetics of nicotine dependence and other smoking related traits is important to help to predict the likelihood of initiation, quitting smoking, and guide treatment response.

*Self-medication*

The self-medication hypothesis of nicotine use stems from the observation that cigarette smoking often co-occurs with mental health disorders, including major depression, bipolar disorder, schizophrenia, ADHD, and PTSD.[2] Epidemiologists estimate that as many as 80% of people diagnosed with schizophrenia smoke cigarettes, and they tend to smoke heavily.[55] This hypothesis posits that nicotine's effects include improved cognitive function and reduced psychiatric symptoms, so people with mental illnesses smoke to manage their symptoms better.

In specific instances, nicotine does provide cognitive enhancement.[85] For example, acute nicotine administration can improve focus and attention in ADHD. Similarly, nicotine reduces negative affect, relieving depression symptoms. These observations are qualified by substantial literature on the detrimental effect of nicotine on mental health, and lifetime smoking (>40 years) is associated with a 2-fold higher odds of suicide.[86]

Researchers have long theorized, and more recently shown, that quitting smoking is more difficult for smokers with preexisting clinical depression.[87] Depressed smokers tend to experience more severe withdrawal symptoms, including low mood and reduced cognition, which lead to lower cessation and higher relapse rates. Additionally, nicotine can help mitigate some of the symptoms of depression, which is why depressed people tend to smoke at higher rates initially. It is possible that treating depression with medication in this targeted population could lead to better outcomes. That said, a meta-analysis of 26 longitudinal studies evaluated mental health before a quit attempt and at least 6 weeks after cessation and found reduced depression, anxiety, and stress, elevated mood, and improved quality of life when compared to people who continued to smoke.[88] Therefore, it appears that smoking and depression may be self-perpetuating and reinforcing of the initial cause of dependency.

Although the self-medication hypothesis's validity is not universally acknowledged,[89] it is a model that can offer substantial insight into developing personalized treatment approaches for TUD. For example, if someone initiated smoking to improve their focus, they may have an underlying attention deficit disorder that could be managed with a safer and more effective prescription drug. Addressing underlying mental health conditions in a clinical setting can substantially reduce TUD and improve the odds of quitting successfully.

## Social Factors

The contribution of social factors to TUD is substantial, and psychosocial influences begin very early in life.[90] Social experiences during childhood and adolescence (eg, parents who smoke, peer influence) can establish an early tobacco use pattern that persists throughout adulthood. A history of childhood neglect or harmful social interactions can increase sensitivity to rewarding and stressful events.

The social circumstances surrounding tobacco use also play a role in developing dependence. For example, if smoking cigarettes improves social access, the rewarding effects of smoking will be increased.[85] In this respect, smoking's initial functional effect is not physical, but rather enhanced social interaction and camaraderie. The "Water Cooler Effect" of increased workplace cohesion and productivity can be found at office smoke break areas. Interestingly, someone's perceived social status affects how they experience cessation. A study found that people with lower subjective social status had more

withdrawal symptoms, especially symptoms related to negative affect (anger, anxiety).[91]

There are 2 potential explanations for the high degree of clustering of people who use tobacco products. The first explanation provides a hypothesis for the social reinforcement of smoking behavior, as people with similar personalities and behaviors tend to cluster together. The second explanation suggests that smoking is a network phenomenon, sometimes referred to as a social contagion, where a behavior is spread within social networks through interactions.[92] Studies support this theory, showing that smoking behaviors of others in social networks add to the addictiveness of smoking. The consistent visual cues of smoking by members of someone's social network may make it harder for a smoker to quit and more likely relapse.[93]

Youths are at particular risk for experiencing peer pressure, and tobacco use may be required in order to affiliate with particular groups. Kids who are welcomed into a social stratum because they smoke will associate smoking with rewarding peer interaction. Thus, network-based interventions may be promising treatment options for highly social people who want to quit smoking or, in the case of children and teenagers, prevent them from ever starting.

Tendencies toward impulsivity or novelty seeking are predictive of tobacco use, and thrill-seekers are more sensitive to reinforcement and escalation of use.[94] Interestingly, impulsivity and novelty-seeking are modulated, at least in part, by the NAc, which is one of the most significant brain regions for initiation and maintenance of an addiction. One lifestyle factor that could contribute to dependence via this pathway is alcohol consumption. Alcohol dependence among people who smoke predicts less interest in quitting smoking and a higher likelihood of relapse and should be factored into smoking cessation therapeutic protocols.[35] If alcohol use is a contributing factor to TUD, healthcare providers should advise abstinence.

Likewise, other psychoactive drugs can interact with one another to exacerbate the addiction of both. This is particularly true of stimulants like cocaine and methamphetamine, both of which act to increase extracellular dopamine levels in the NAc.[95,96] In addition, nicotine is known to potentiate the effects of cannabis use, perhaps underlying the use of tobacco products in certain preparations of marijuana.[95,97] Therefore, any nicotine cessation program must take into consideration the other substances a person who smokes uses. Intriguingly, 95% of patients recovering from opioid use via methadone treatment reported cigarette smoking in one study, further reinforcing the complex nature of substance use disorders and their treatments.[98]

Tobacco treatment strategies should take social history and psychosocial influences into account. By understanding potential social risk factors that a newly abstinent person may encounter, precautionary steps can be put into place to minimize the risk for stress-primed reinstatement of tobacco use.

For example, cognitive behavioral therapy can teach people how to reframe negative false thoughts with more realistic ones, which is an effective way to ameliorate social anxiety and deal with the underlying cause.

## Conclusion

Research demonstrates that TUD is a complex, heterogeneous condition that does not have a standardized, uniform solution. Interindividual variability plays a major role in smoking initiation, dependence, withdrawal severity, and quitting success. By identifying smoker phenotypes and contributing factors to TUD in an individual, healthcare providers may 1 day have the ability to develop a unique profile for each patient that provides insight into their most appropriate pharmacological and/or behavioral intervention(s).

Current evidence suggests that there is no single best treatment option and that personalized, multifaceted treatment modalities may best serve each individual, possibly with currently available, and often non-pharmacological options. Developing effective ways to identify and treat TUD in diverse groups of people would require a fundamental reimagining of the current, siloed research, development, and treatment paradigm, to a more cross-disciplinary approach.

The framework presented here considers all 5 contributing factors and may help identify the most effective behavioral and/or pharmacological treatment options for subtypes of people who want to quit smoking, using a holistic and comprehensive approach. TUD is not simply a consequence of chemical changes in the brain; there are a number of variables including personality traits, genetics, socioeconomic status, life experiences, and underlying medical conditions that might be driving continued tobacco use. Assessing the individual reinforcers of smoking may reveal a strategy that can precisely target the underlying cause of TUD in each individual.

One way to evaluate the most effective treatments for unique types is to start with a standardized profiling questionnaire that could stratify patients based on tobacco use, habits and preferences, underlying psychological and neurobiological complications, social factors, and their desire to quit, in order to assess each person accurately. By then tracking the treatment strategies and cessation rates of different smoker types over time, we may gain valuable insight into the most effective treatment strategies and be able to make effective personalized recommendations. Implementing such a data-driven strategy to treating TUD requires a holistic approach, rather than the current one-size-fits-all strategy that has failed to improve tobacco cessation rates for many people who want to quit. Doing so may save numerous lives and lead to a future that is less burdened by the human and economic costs of TUD.

## Author Note

This research began in an effort to develop a questionnaire and algorithm that could classify smoker types and recommend a treatment protocol that evidence suggests might be more efficacious for the unique contributing factors.

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