

Advancements in Adolescent Treatments and Recovery for Nicotine Addiction

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Abstract

“Smoking Kills” This headline has been plastered across buildings, buses, subways, advertisements, commercials, for as long as printed media has existed. Every middle school student has sat through countless P.S.A’s about the dangers of substance abuse since the Reagan Administration. The tobacco industry remains to be one of the most economically lucrative businesses, which generates over 816 billion dollars per year selling 5.5 trillion cigarettes to about 1 billion smokers around the world. Despite the general awareness of the dangers and detriment that smoking has on your development and body, the average age of a first-time smoker remains about 14.5 years old. Understanding the roots of addiction is key to developing preventative measures to lower teenage addiction entirely. Nicotine from tobacco induces stimulation and pleasure, and can reduce stress and anxiety. This review covers different aspects of nicotine addiction and recent trends in ways to treat the addiction and possible news to deal with this global challenge.

Keywords: Nicotine addiction; Pharmacology of nicotine; Smoking cessation; Tobacco; Transdermal nicotine; Vaccines for smoking cessation

1. Introduction

“Smoking Kills” This headline has been plastered across buildings, buses, subways, advertisements, commercials, for as long as printed media has existed. Every middle school student has sat through countless P.S.A’s about the dangers of substance abuse since the Reagan Administration. The tobacco industry remains to be one of the most economically lucrative businesses, which generates over 816 billion dollars per year selling 5.5 trillion cigarettes to about 1 billion smokers around the world. Although they may not be marketed or campaigned as heavily as they were in the 1960s, tobacco companies are still able to turn a profit every financial quarter. The dangers, of smoking and nicotine addiction are known for decades [1].

2. Addiction Begins at Early Teenage of the Consumers

Despite the general awareness of the dangers and detriment that smoking has on your development and body, the average age of a first-time smoker remains about 14.5 years old. Understanding the roots of addiction is key to developing preventative measures to lower teenage addiction entirely. Current treatments include FDA approved medication and behavior therapies exist but with varying extents of effectiveness. Since Nicotine addiction mainly stems from social pressures and external factors separate from genetics and demographics, pertinent methods of treatment include Nicotine Replacement Therapy, Combination Pharmacotherapy, as well as toll free quit lines, and individual counseling are typically employed. Smoking cessation methods also have been proven effective, but still have their fair share of caveats. Extended nicotine use can cause an increase in blood pressure, heart rate, flow of blood to the heart, as well as narrowing of the arteries. In a time of global pandemic and disease, it is clearer than ever that we must be more conscious of the substances that we put in our bodies. In an ideal scenario, those who continue to smoke, and abuse drugs will understand how their choices affect themselves and those around them [2].

3. Why Nicotine?

Nicotine from tobacco induces stimulation and pleasure, and can reduce stress and anxiety. When a person decides to stop smoking or is unable to smoke for a prolonged period, they begin to experience withdrawal symptoms. These symptoms include irritability, depressed mood, restlessness, anxiety, difficulty concentrating, increased hunger and eating, an insomnia just to name a few. Nicotine withdrawal in untreated smokers produces mood disturbances comparable to those seen in psychiatric outpatients in terms of intensity. Users may experience heavy mood swings and drastic changes in mood and attitude. Hedonic dysregulation, which is defined as the feeling that there is little pleasure in life and that activities that were once rewarding are no longer enjoyable, can be seen with withdrawal from nicotine and other substances. This is most likely since the deficiency in dopamine release following long-standing nicotine exposure accounts for many of the mood disorders and the anhedonia, as well as the tobacco craving, which are behaviors that may persist in smokers even after they quit [3].

4. Psychological Benefits of Nicotine

The pleasurable feeling associated with nicotine, as well as other inhalants can cause users to feel less stressed or anxious, can cause users to associate their wellbeing with continued use. These, changes, in social behavior and acuity, are what make a substance like nicotine so dangerous. The user believes that they are only capable of feeling basic human emotion and are unable to conduct even the most basic human interactions without the help of an outside substance. Like how some people may seem irritable and cantankerous without their morning coffee, smokers may often avoid social contact altogether until they have had their regular nicotine fix. This inability to conduct basic social interactions is the very definition of an addiction. Another common misconception about users who actively consume nicotine is the notion of a “gateway” drug. Despite figures showing that those who partake in harder and more fatal drugs also consume nicotine, the logic does not go both ways. Gateway drugs are defined as such because of their ability to condition users to social and physical behaviors associated with substance abuse [4].

Adolescence age is really a sensitive developmental period for teenagers moving from child hood to adulthood. It is an interesting stage between these transformations. Due to an attitude to explore the world, it is of enhanced clinical vulnerability

to nicotine, and related products like chewing tobacco, and in recent years' e-cigarettes. While, there are sociocultural influences such as, following the adults in the own houses such as parents or relatives who are addicted to smoking? At this age there is a significant peer pressure of adolescent colleagues and believe it or not but the aggressive marketing by tobacco product companies leads to established data at preclinical and clinical levels indicating that this adolescent sensitivity has strong neurobiological underpinnings. People and scientists have offer definitions of adolescence vary significantly. The most important aspect of this age period is a profound reorganization of brain regions necessary for mature cognitive and executive function, working memory, reward processing, emotional regulation, and motivated behavior. Nicotinic acetylcholine receptors (nAChRs) are the regulating critical facets of maturation of brain from a child to an adult. It is well document argument put forward through the study [4.1] that nicotine exposure, increasingly occurring as a result of Tabaco or similar products including e-cigarette use, may induce epigenetic changes that sensitize the brain to other drugs and prime it for future substance abuse. This is exhibited in adolescent age more prominently that the adults at a later stage [4.1].

5. Crippling Addictions

While consuming nicotine makes the brain more susceptible to more crippling addictions, the social aspect of smoking is more telling. In a cross-sectional national survey between adults of all demographics and genders aged 18 and 25, researchers found that among 455 smokers about 62% of them self-identified as social smokers. Behavior social smoking is defined as smoking in social or group settings and is largely infrequent between consumptions. Although it is far less common in older individuals the study also concluded that those who smoke infrequently are more likely to either start smoking themselves or try more dangerous drugs in casual settings. This is particularly dangerous since those who smoke daily have already built up tolerance for smaller doses and are not as affected by more dangerous substances. Compared to individuals who partake infrequently, a more dangerous substance such as fentanyl laced heroin, the risk of death from even one dose skyrockets to 50%. However, one drawback from studying the research and figures available on social smoking is the fact that is much more difficult to measure and quantify. Since cigarettes and vapes are extremely common in almost every gas station, most of if not all of the sample spaces of research come from varying demographics, socioeconomic backgrounds, levels of education, and ethnicities. Some data suggest that these groups can abstain from tobacco use for days without exhibiting signs of withdrawal, however there are also studies that suggest that intermittent tobacco users may experience sudden urges to smoke and difficulty to quit totally as a result of physiological addiction [5]. For example, a study of adolescent smokers found no evidence to suggest active signs or symptoms of nicotine withdrawal, as measured by changes in heart rate and neuropsychological testing, after 24 hours of abstinence. However, in the 2004 US Surgeon General's report on the health consequences of smoking include information on the dose-response relationship between active smoking and disease indicates that even trivial levels of smoke inhalation or exposure increase the risk of cardiovascular disease, lung and gastrointestinal cancers, lower respiratory tract infections, cataracts, and compromised reproductive health [6].

6. Nicotine Chemistry and Pharmacological Effects

Nicotine is a classified as a tertiary amine comprising of a pyridine and a pyrrolidine ring. (S)- nicotine, a protein found in tobacco ties specifically to nicotinic cholinergic receptors (nAChRs). When an individual breathes in smoke from a cigarette, nicotine is filtered from the tobacco and is delivered in the form of smoke particles into the lungs, where it is retained quickly into the aspiratory venous flow. It at that point enters the blood vessel course and moves rapidly to the mind. Nicotine quickly

diffuses into brain tissue, where it binds to nAChRs. nAChRs are members of the pentameric super group of ligand-gated ion channel receptors that include the 5-hydroxytryptamine₃ (5-HT₃), glycine, and GABA to give some examples [7]. These receptors respond to excitatory amino acids when stimulated. When these receptors are continually activated by nicotine, one of two changes occur. As the receptor is activated, the cations involved move across the plasma membrane, causing it to depolarize and activate the voltage-gated ion channels. This initial binding is what may inhibit the regulation of the activity of some genes or the release of neurotransmitters. Stimulation of central nAChRs by nicotine results in the release of a variety of neurotransmitters in the brain, but most notably dopamine. Nicotine causes the release of dopamine in several parts of the brain including the mesolimbic area, the corpus striatum, and the frontal cortex. Other neurotransmitters, including norepinephrine, acetylcholine, serotonin, γ -aminobutyric acid (GABA), glutamate, and endorphins, are released as well, mediating the various behaviors of continuous nicotine use. Dopamine release signals a pleasurable experience, and is directly responsible for the reinforcing effects of nicotine and other substances [3].

Mechanistic research categorizes nicotine addiction as a chronic and relapsing disorder, which causes neuroplasticity in meso-corticolimbic circuitry, which affects the brain's capacity to mediate motivation, reward, and conditioned reinforcement. Addictive drugs achieve this by providing an expressway to the brain's reward system by flooding it with dopamine. The hippocampus creates memories of this immediate sense of satisfaction, and the amygdala creates a conditioned response to certain stimuli.

In the case of nicotine, addiction and dependence is the result of your brain being flooded with neurotransmitters, specifically an overload of dopamine. Several pharmacogenetic studies focusing primarily on candidate genes related to nicotine reward and nicotine metabolism pathways list many effects of the continuous stream of neurotransmitters. Dopamine release is facilitated by nicotine-mediated augmentation of glutamate release and by inhibition of GABA release. The abundance of dopamine into the brain is one of the most critical components of understanding nicotine addiction [8].

7. Danger of Smoking on Heart, Lung and Fertility of Adolescence

Adolescent smokers are more likely than nonsmokers to develop heart disease, stroke, and lung cancer in their adulthood possibly. Estimates show smoking increases the risk:

- for coronary heart disease by 2 to 4 times
- for stroke by 2 to 4 times
- of men developing lung cancer by 25 times
- of women developing lung cancer by 25.7 times

Smoking causes diminished overall health, increased absenteeism from work, and increased health care utilization and cost.

Smoking not only harms almost every organ of the body but also affects a person's overall health especially if you get addicted to these products at an early or adolescent age.

- A. Smoking can make it harder for a woman to become pregnant with fertility challenges. It can also affect her baby's health before and after birth. Smoking increases risks for

- Preterm (early) delivery
 - Stillbirth (death of the baby before birth)
 - Low birth weight
 - Sudden infant death syndrome (known as SIDS or crib death)
 - Ectopic pregnancy
 - Orofacial clefts in infants
- B. Smoking can also affect men's sperm, which can reduce fertility and also increase risks for birth defects and miscarriage
- C. Smoking can affect bone health
- Women past childbearing years who smoke have weaker bones than women who never smoked. They are also at greater risk for broken bones.
- D. Smoking affects the health of your teeth and gums and can cause tooth loss
- E. Smoking can increase your risk for cataracts (clouding of the eye's lens that makes it hard for you to see). It can also cause age-related macular degeneration (AMD). AMD is damage to a small spot near the center of the retina, the part of the eye needed for central vision
- F. Smoking is a cause of type 2 diabetes mellitus and can make it harder to control. The risk of developing diabetes is 30%-40% higher for active smokers than nonsmokers
- G. Smoking causes general adverse effects on the body, including inflammation and decreased immune function
- H. Smoking is a cause of rheumatoid arthritis [8.1].

8. Pharmacological Basis for Addiction

With repeated exposure to nicotine, tolerance is one of the effects of nicotine concurrent with this neuroadaptation is an increase in the number of nAChR binding sites in the brain. This increase represents reuptake, since the brain is responding to the added stimulus [7]. The weaker constitution of the receptor plays a role in nicotine tolerance and dependence, allowing it to build up easily. Addiction begins in smokers when previously desensitized nAChRs become unoccupied and recover to a responsive state during prolonged periods of not using [3]. This may cause the nicotine binding and desensitization of these receptors during smoking may alleviate craving and withdrawal [9].

According to a brain imaging study showing that cigarette smoking in amounts used by typical daily smokers, a distinct amount of desensitized brain nAChRs was present. Smokers maintain $\alpha 4\beta 2^*$ nAChRs in a desensitized state to avoid withdrawal symptoms. Other research studies have also concluded that conditioned smoking cues maintain smoking behavior during periods of saturation of brain nAChRs. Smokers who continue to smoke throughout the day to maintain plasma nicotine levels that prevent the occurrence of withdrawal symptoms, continue to feel some of the rewarding effects from the conditioned reinforcers associated with smoking such as the taste and sensation of smoke. The physical motion of moving the cigarette or vape device to your lips is also defined as a conditioned motion, causing the physical act to become addicting as well as the active chemicals altering brain chemistry [6].

9. Nicotine Withdrawal

Nicotine withdrawal is associated with drastic varying changes in emotions, including anxiety and the perception of increased stress, which may represent powerful stimuli to relapse to tobacco use. The extrahypothalamic corticotropin-releasing factor (CRF)-CRF1 receptor system contributes to negative affect during nicotine withdrawal. CRF is released in the central nucleus of the amygdala CRF activation produces anxiety behavior, and pharmacologic blockade of CRF1 receptors inhibits the anxiogenic effects of nicotine withdrawal. Inhibiting the CRF1 nicotine receptor prevents the increase in nicotine self-administration that can occur during prolonged periods of not using withdrawal from other drugs of abuse such as alcohol, cocaine, opiates, and cannabinoids is also linked with activation of the extrahypothalamic CRF system, suggesting that this is common precursor to intense withdrawal systems. The hypoactivity of the dopaminergic system and the activation of the CRF system conciliate nicotine withdrawal symptoms that often precipitate relapse to smoking [3].

Although withdrawal symptoms may not cause any fatal results directly, repeated inhalation and larger doses have been proven to lead to premature death in multiple cases. In a recent census in 2019 by the Centers for Disease Control and Prevention, vaping and e-cigarettes have been linked to over 1479 cases of a lung disease dubbed EVALI. This respiratory illness is characterized by chest pain, shortness of breath, nausea, and lung injury. Data as recent as February of 2020 has shown there have been over 2807 reported cases or deaths reported to the CDC across all 50 states. But perhaps the most harrowing aspect from this outbreak is the fact that almost 80% of cases involved users younger than 30 and another 15% were under 18. Despite the fatal results of EVALI there remains about 17.3 million vapers in the U.S alone. The main cause of concern has been identified to be vitamin E acetate, an additive in some THC-containing e-cigarette, or vaping, products, is strongly linked to the EVALI outbreak. Vitamin E is a vitamin found in vegetable oils, cereals, meat, fruits, and vegetables. It can also be found in dietary supplements and cosmetic product such as skin creams. Vitamin E acetate usually does not cause harm when ingested as a vitamin supplement or applied to the skin. However, previous research suggests that when vitamin E acetate is inhaled, it may interfere with normal lung functioning. This happens because inhalants limit and narrow blood flow to the capillaries in human skin. This outbreak has been more than enough reason for governments to actively work towards solving this. A recent statement from Donald Trump reads that he plans to ban e-cigarette flavors that have specific appeal to a younger demographic. This refers to the fruity, colorful, and vibrant flavors such as lychee ice, pink lemonade, peach, mango, mint, and other fruit flavors from being produced. On the surface, this may seem to be an issue of regulation and advertisement and the steps taken against it seem logical, in theory. National and state data from patient reports and product sample testing show tetrahydrocannabinol (THC)-containing e-cigarette, or vaping, products, particularly from informal sources like friends, family, or in-person or online dealers, are linked to most EVALI cases and play a major role in the outbreak [10]. Advertising or brand-awareness has little to do with actual prevention. According to Representative Frank Pallone, the Democratic chair of the U.S. House of Representatives Energy and Commerce Committee. "A flavor bans that exempts menthol and vape shops is no ban at all," Pallone tweeted. As basic economic principles have shown us across all of human history, a demand for a product will always result in profit, leading to competition for those profits. Recent data has already showed that rival companies such as Altria and Puff have already swooped in on the craze with their own line of flavors and advertisements and have seen substantial profit margins. From a historical perspective tobacco companies have notorious in terms of their ability to convince consumers of the necessity of a destructive product. There is a reason that tobacco and e-cigarette companies continue to earn countless profits despite regulations, bans, censorship and laws. There have been famous images and testimonials of doctors, businessmen, athletes, and swimsuit models across many advertisement campaigns of the 1950s to 1960s era. Although

cigarettes were heavily linked to lung cancer and failure, tobacco companies were still able to market them as a social activity for the elite members of society. Smoking was perceived as luxurious and dignified activity. Workplaces, cabs, public parks, and restaurants were all places where people could smoke freely and proudly. According to PRB survey, approximately 42% of Americans were regular smokers. Fortunately for the rest of society, there has been a definite shift in the way that people view smoking conventional cigarettes. Despite the percent of active smokers decreasing by 15% each year, e-cigarettes have proven to be a contemporary nuisance. Unfortunately, the very devices that was meant to slowly wean off smokers became the very cause of one of the highest percent of smoking in underage individuals in the 21st century [11,12].

10. Electronic Cigarette a Global Menace

E-cigarettes are electronic devices that heat a liquid and produce an aerosol, or mix of small particles in the air.

E-cigarettes come in many shapes and sizes. Most have a battery, a heating element, and a place to hold a liquid.

Some e-cigarettes look like regular cigarettes, cigars, or pipes. Some look like USB flash drives, pens, and other everyday items. Larger devices such as tank systems, or “mods,” do not look like other tobacco products.

E-cigarettes are known by many different names. They are sometimes called “e-cigs,” “e-hookahs,” “mods,” “vape pens,” “vapes,” “tank systems,” and “electronic nicotine delivery systems (ENDS).”

Using an e-cigarette is sometimes called “vaping” or “JUULing.”

The use of e-cigarettes is unsafe for kids, teens, and young adults.

Most e-cigarettes contain nicotine. Nicotine is highly addictive and can harm adolescent brain development, which continues into the early to mid-20s.

E-cigarettes can contain other harmful substances besides nicotine.

Young people who use e-cigarettes may be more likely to smoke cigarettes in the future.

Many e-cigarettes come in fruit, candy, and other kid-friendly flavors, such as mango, fruit and crème. A majority of youth e-cigarette users report using flavored varieties, most youth e-cigarette users first start using e-cigarettes with a flavored variety, and flavors are the primary reason youth report using e-cigarettes. E-cigarettes are also advertised using the same themes and tactics that have been shown to increase youth initiation of other tobacco products, including cigarettes. In 2016, about 8 in 10 middle school and high school students-more than 20 million youth-said they had seen e-cigarette advertising. Widespread advertising for these products, including via media for which advertising for conventional tobacco products is prohibited (e.g., TV), and the lower costs of some of these products relative to conventional cigarettes has contributed to the increase in e-cigarette use among youth. Many youths also report using e-cigarettes because they are curious about these new products, and because they believe these products to be less harmful than conventional cigarettes [8.1].

11. Adolescent Youths and E Cig

The last five years have seen significant spikes in youth e-cigarette use rates.

- In 2017, 11% of high school students had used an e-cigarette in the past 30 days. By 2018, that number had risen to 21% and, by 2019, 27.5% of high school students had used e-cigarettes in the past month.
- Compared with the very small amount of youth use in 2011 (1.5%), this represents an increase of more than 1,800% in just eight years, with a substantial increase occurring between 2013 and 2015, when use rose from 4.5% to 16%, coinciding with the emergence of JUUL.
- The current use rate among middle school going children rose from 0.6% in 2011 to 10.5% in 2019.
- Using e-cigarettes has been shown to increase the likelihood of smoking cigarettes among young people, raising concerns that e-cigarettes are acting as entry nicotine products that may lead to use of more dangerous nicotine products. According to a recent study, U.S. youths are 4 times more likely to try cigarettes and 3 times more likely to currently use cigarettes if they previously used e-cigarettes. The study also estimated that e-cigarettes are likely responsible for 22% of new ever cigarette use (trying a cigarette) and 15.3% of current cigarette use for the same group - totaling nearly 200,000 new cigarette initiators.
- Many young e-cigarette users do not know what is in the products they are using. A recent study found that 99% of all e-cigarette products sold at convenience stores, supermarkets and similar outlets contain nicotine. Yet, many young people aren't aware that the products they use, like JUUL, contain nicotine. In fact, a Truth Initiative study showed that nearly two-thirds of JUUL users aged 15-21 were not aware the product always contains nicotine.
- As rates of use increase, we are also seeing the frequency of use (how many times a user vapes in a day) go up, indicating that users are not simply experimenting with e-cigarettes but are instead using them habitually. The 2019 National Youth Tobacco Survey data show that 34.2% of current high school e-cigarette users and 18.0% of current middle school e-cigarette users use e-cigarettes on 20 days or more per month and Monitoring the Future found that in 2019, 11.7% of high school seniors vape every day, suggesting that more users are becoming dependent on these products.
- Youth e-cigarette users cite flavors as a top reason they began using e-cigarettes, second only to use by a family member or friend.
- A study that included middle and high school students reported that 43% of young people who ever used e-cigarettes tried them because of appealing flavors.
- The FDA has also reported that, among current youth users of e-cigarettes, 97% used a flavored e-cigarette in the past month.
- As much as 98.7% of flavored e-cigarette products sold in convenience, dollar, drug and grocery stores contain nicotine.
- Despite JUUL removing some flavors from retail stores in April 2019, they continued to hold a majority of the U.S. e-cigarette sales market share. Research suggests that mint and menthol, which remain available for sale, have continued to increase in popularity. 2019 NYTS data show that mint and menthol e-cigarette use rose to 57.3% from 51.2% in 2018 among high school current users, suggesting a switch to these flavors once mango and fruit medley became harder to obtain [8.2].

12. Young Adults

- Like youth, young adults aged 18-24 are also using e-cigarettes at increasing rates. Young adult use of e-cigarettes every day or some days increased from 2.4% in 2012 and 2013 to 5.2% in 2017, and increased again to 7.6% in 2018 based on a recent analysis.
- A 2016 report from the Behavioral Risk Factor Surveillance System survey found that 44.3% of young adult current e-cigarette users were never smokers before trying e-cigarettes.
- Compared with adults aged 25 and older, young adults are more likely to try e-cigarettes and report having used e-cigarettes in the past 30 days.
- A study in Mississippi suggests that using JUUL leads to more sustained use than other e-cigarettes. It concluded that the continued use of JUUL by Mississippi undergraduate students was more likely than the continued use of other e-cigarettes after an initial trial. The study found that 30-day use was three times higher among those who had tried JUUL than a different e-cigarette.
- The growth in the popularity of e-cigarettes among young adults has caused concerns that use will lead to the initiation of cigarettes and other tobacco products [8.2].

E Cig has become a global menace. It is hard to collect exact impact of e Cig on the population of various countries but the growing consumption is affecting the health of young people worldwide and the impact of this will be clear in coming years.

13. Nicotine Replacement Therapy

In the cases of most nicotine addiction, the severity of each individual must be taken into account, but the methods currently employed are as follows; Nicotine Replacement Therapy, Bupropion, Varenicline. Nicotine Replacement Therapy is the most straightforward out of all of the existing treatments. The main goal of this method is to mimic or replace the effects of nicotine from tobacco. Nicotine replacement medications are typically the most common form of treatment. The main mechanism at work here is the relief of withdrawal symptoms when a person stops tobacco use. Improving of these symptoms is observed with relatively low blood levels of nicotine. Another benefit is positive reinforcement, particularly for the arousal and stress-relieving effects. Positive reinforcement is directly related to the rate of absorption and the peak nicotine levels measured in arterial blood. Positive reinforcement is most relevant to rapid-delivery formulations such as nicotine nasal spray and, to a lesser extent, nicotine gum, inhaler, and lozenge. The use of these products allows smokers to dose themselves with nicotine when they have the urge to smoke cigarettes [13].

Nicotine patches, on the other hand, deliver nicotine gradually and as they are delivered throughout the day, they become less effective since they are not able to sporadically provide the positive reinforcement required to completely treat addiction. The key component of nicotine replacement therapy is that it reconditions the body into producing and secreting neurotransmitters normally.

This is accomplished by the medications ability to desensitize the nicotine receptors in the brain gradually. By infrequently activating those parts of the brain, the user is desensitized over time. If and when a relapse may occur, the cigarette becomes less satisfying and the patient is less likely to resume smoking. A second medication currently employed by health care professionals is bupropion. Bupropion was initially marketed as an antidepressant medication before it was used for smoking

cessation. Bupropion increases brain levels of dopamine and norepinephrine, simulating the effects of nicotine on these neurotransmitters. Bupropion also has the capacity for nicotine receptor-blocking activity, which could contribute to reduced reinforcement from a cigarette in the case of a relapse. However, one of the main drawbacks of this drug delivery system are the plethora of common side effects of bupropion include, difficulty sleeping, agitation, and headaches [14].

Prescribing bupropion is as effective as Nicotine Replacement Therapy but less effective than Varenicline, another common medication. Varenicline is the most effective medication because of the high affinity of the partial antagonist $\alpha 4\beta 2$ nicotinic acetylcholine receptor subtype (nACh) that leads to the release of dopamine in the nucleus accumbens when has the ability to lower craving sensations and withdrawal caused by treatments [15]. According to several studies it is estimated that varenicline helps one out every 11 people who remain abstinent at six months. Nicotine, in this regard is defined as an agonist, causes substantial dopamine release. Varenicline produces less of a response than nicotine but at the same time blocks the effects of any nicotine added to the system [15].

14. Current Medications

Current medications in development are being synthesized with the goal of personal addiction treatment and total rehabilitation. The future medication in development include Rimonabant is a cannabinoid (CB-1) receptor antagonist developed for treatment of obesity and the metabolic syndrome. Clinical studies displayed rimonabant to be effective as an aid for smoking treatments. Cannabinoid receptors contribute to the reinforcing effects of nicotine action. Rimonabant, has not been approved by the U.S. FDA since it may cause adverse neuropsychiatric effects [16].

15. Nicotine Vaccines

Nicotine vaccines are currently undergoing clinical trials and development at NABI Biopharmaceuticals of Rockville, MD. Acute immunization is performed to develop antibodies to nicotine. The antibody binds nicotine and hinders into the brain, reducing the reinforcing effects of cigarette smoking. The nicotine vaccine is the next logical step in total prevention from before the problem even arises. Other potential future medications for smoking cessation include monoamine oxidase inhibitors (MAOA and MAOB), which inhibit the metabolism of dopamine and therefore increase dopamine levels in brain, and dopamine D3 receptor antagonists and partial agonists, which regulate the activity of receptors involved in drug-seeking behaviors. Inhibitors of CYP2A6 activity have also been developed as smoking cessation aids that work by increasing nicotine levels from tobacco use and ultimately reducing urges to smoke.

Methoxsalen and tranlycypromine inhibit CYP2A6 activity and slow nicotine metabolism, but at the cost of them having significant toxicity, making routine clinical use troublesome for health care professionals. Much of the preeminent research is centered around the use of nanoparticle vaccine treatments. Passive transfer of nicotine-specific monoclonal antibodies offers better control of antibody dose, as well as the ability to give very high doses, and an immediate onset of action. However, one drawback is the expensive price point per dose.

The higher price does mean that it has a shorter duration of action than vaccines. Viral vector-mediated transfer of genes for antibody production can elicit high levels of antibody expression in animals and may present an alternative to vaccination or

passive immunization if the long-term safety of this approach is confirmed. Next-generation immunotherapies are likely to be substantially more effective than the current treatments being employed [17].

In recent years several papers have been published on Nicotine vaccines. Raupach et al., have discussed the application of Nicotine vaccines to assist with smoking cessation [18]. Esterlis et al., reported the effect of a nicotine vaccine on nicotine binding to $\beta 2^*$ -nicotinic acetylcholine receptors in vivo in human tobacco smokers [19]. Hoogsteder et al., studied the efficacy and safety of a nicotine conjugate vaccine (NicVAX(R)) or placebo co-administered with varenicline (Champix(R)) for smoking cessation: it was a study using protocol of a Phase IIb, double blind, randomized, placebo controlled trial [20].

Smoking tobacco is globally most widely substance of abuse. Nicotine is responsible for addictive properties of smoking. The currently available medications for the treatment of nicotine addiction have limited efficacy and therapeutic effectiveness. A challenging novel therapeutic concept which has been toyed with is vaccination against nicotine. An efficient vaccine would possibly generate antibodies that will sequester nicotine in the blood and prevent its access to the brain and also control the side effects of the nicotine.

The vaccine would have great potential for treating nicotine addiction and for relapse prevention. The current status of vaccines, against nicotine addiction that are undergoing clinical trials or are in preclinical development. The challenges in development of nicotine vaccines include their efficacy in addiction treatment, challenges and ethical concerns. Existing evidence indicates that nicotine vaccination is well tolerated and capable of inducing an immune response but its effectiveness in increasing smoking abstinence has not been shown so far [21].

16. Conclusion

In conclusion, despite the distressing statistics about underage smoking and premature deaths, the current treatments and preventative methods give hope for the future. We live in a society where drug use is glorified through rap music and clout culture. It has become increasingly easier to acquire and abuse substance privately and much harder for individuals to get the help they need. Drugs and premature overdoses have plagued many lower income neighborhoods and cities for decades. Medicine and technology have rapidly expanding and changing the world at an inconceivable speed. My only hope is that the rest of the world is not left behind.

17. Declaration of Conflict of Interests

The author declares that there is no conflict of interest.

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19. Contribution

All authors equally contributed towards this review paper.

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