Neuropharmacology of nicotine dependence

Hamdan S. Al-malky*

Pharmacology Department, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Article History:
Received on: 05.08.2019
Revised on: 10.11.2019
Accepted on: 15.11.2019

Keywords:
Nicotine dependence, Nicotine addiction, Tobacco addiction cycle, Neural survival, Pharmacology of nicotine

ABSTRACT
The occurrence of withdrawal symptoms is regarded as the key to mediating smoking relapse amongst smokers. The present study acknowledged the high relapse rates emerging from the inability to address the causes of powerful addiction effects besides identifying chronic disorders caused by nicotine. The present study explored nicotine addiction and its effects on different smoking patterns to provide an informative platform to design interventions that would deliver effective ways of quitting smoking. The study utilized systemic reviews on publications of previous studies obtained from scholarly journal databases, including PubMed, Medline, EBSCO Host, Google Scholar, and Cochrane. Moreover, the study used secondary information obtained from health organizations using filters and keywords to retrieve relevant information. The use of search keywords and filters limited the study to relevant peer-reviewed journals. The study utilized information retrieved from 35 studies obtained from peer-reviewed journals on “nicotine dependence,” “smoking cessation,” and “pharmacology of nicotine dependence and addiction.” The drug tolerance arising in nicotine dependence involved minimized tolerance often occurring during recurrent administration of drugs translated to neuroadaptation. The brain tends to develop challenges in the absence of nicotine, particularly when individuals quit smoking, thus compelling them to backslide from their abstinence. Higher nicotine dependence demotivates individuals from quitting smoking, making the cessation interventions unfruitful, worsened by the inability to understand the causative factors. The solution to overcome nicotine dependence alongside tobacco usage involves a complex treatment technique that would aim to reduce the probability of relapse. Nicotine dependence, Nicotine addiction, Tobacco addiction cycle, Neural survival, Pharmacology of nicotine

INTRODUCTION
Nicotine is a naturally occurring drug found in tobacco making that acts as the leading dynamic element causing addiction. Similar to the use of cocaine and heroin, nicotine causes detrimental effects on human health that are worsened by its very addictive nature (Benowitz, 2010). The three primary findings in the 1998 Surgeon General of the United States report on tobacco and nicotine have been endorsed by several authorities, including the Royal College of Physicians, American Psychiatric Association (APA), and the World Health Organization (WHO). First, cigarettes and tobacco elements have high addictive effects (Zhang et al., 2017). Sec-
Addiction to tobacco arises from repeated use of nicotine that translates into destructive health effects amongst addicts (USDHHS, 2012; Vůňaková et al., 2017). These effects, in turn, result in medical complications, such as cancer, lung diseases, heart complications, and increased vulnerability to secondary ailments (USDHHS, 2012). Most body organs of smokers are exposed to the highly damaging nature of nicotine. Addicts can quit smoking irrespective of their age, thereby decreasing the levels of dangers of nicotine. This awareness explains why a sizable number of smokers in the United States have developed a high interest in quitting smoking (Vůňaková et al., 2017). By contrast, an estimated 80% of individuals refraining from smoking are likely to backslide during their first month of moderation (Benowitz, 2010). Only a mere 3% attain a 6-month abstinence period. Such occurrences demonstrate tobacco having powerful addiction effects besides the identified chronic disorders caused by nicotine (Teitelbaum et al., 2010). This creates the need to explore the nicotine addiction process and its effects varying with the smoking patterns, thereby providing an informative platform to devise the optimal smoking cessation intervention (Berrendero et al., 2010; Hatsuiki et al., 2008).

Nicotine-related statistics

Tobacco usage and developing addiction are among the global leading health dangers identified to cause preventable premature deaths in developed and developing countries (Kühn et al., 2012). Over 4,000 chemicals are estimated to be contained in tobacco smoke, with a sizable portion of them having detrimental properties, including carcinogenic effects and the ability to enhance addictive nicotine effects (Hatsuiki et al., 2008).

Tobacco usage causes an approximated 5 million fatality every year; a number projected to hit double digits by 2025 with the sustenance of present smoking trends (USDHHS, 2012). Although the majority of individuals express the desire to quit smoking, only a few succeed. Factually, individuals backsliding to their past smoking habits is increasing each year to the current high of 80% from their abstinence time, irrespective of quitting medications and non-pharmacological thera-

RESULTS AND DISCUSSION

Overview of nicotine
Figure 1: Flowchart of inclusion/exclusion of studies

Figure 2: The action mechanism of nicotine within the central nervous system: Nicotine binds to the nicotinic acetylcholine receptors present in the mesolimbic–dopamine system of the brain. The presence of nicotine forces the nicotinic receptors located within the tegmental area to release dopamine instantly.

Figure 3: Molecular and behavioral aspects of nicotine addiction

Figure 4: The tobacco addiction cycle

Figure 5: De-nicotinized cigarettes with simple traces of 0.05 mg nicotine levels. De-nicotinized cigarettes entail simply trace nicotine levels (0.05 mg) with low nicotine cigarettes marked by 0.6 mg nicotine. These are obtained by smoking them through 2-FA PET scanning to identify if other smoking elements beyond nicotine deliver $\alpha_4\beta_2$ nAChRs occupancy. This trial revealed $\alpha_4\beta_2$ nAChRs occupancies of 79% for low-nicotine cigarettes and 26% for de-nicotinized cigarettes. The assessment of both de-nicotinized and low-nicotine cigarettes shows smoking to cause $\alpha_4\beta_2$ nAChRs occupancy exclusively.

Figure 6: Evidence of changeable smoking levels in PET images obtained from standard cigarettes. The images showed $\alpha_4\beta_2$ nAChRs occupancy of 0 for no puffs, 33% for 1 puff, 75% for 3 puffs, 88% in full cigarette and 95% in satiety (Brody et al., 2009)
Pharmacology of nicotine

Nicotine properties

Nicotine is a major alkaloid that consists of two tertiary amines, namely ringed pyrrolidine and pyridine. This structural arrangement enables it to bind easily with the acetylcholine receptors [AChRs] located within the neuromuscular joints, ganglia joints, and the brain. The arousal decrement experienced by nicotine users qualifies it as a stimulant (Perkins et al., 2017). The use of nicotine has yielded paradoxical outcomes, i.e., it can act both as a depressant and stimulant. Its stimulation effect is perceived to enhance learning abilities, processing of observed and received information, and boost memory and alertness of users. On the contrary, the use of nicotine has been reported to be associated with increased anxiety and depression levels; moreover, individuals abusing nicotine have reported more pain (Hinrichs et al., 2011). Inhaled nicotine merely takes 7 seconds to reach the brain, making it the quickest and the most preferred way of abuse by most users (Matta et al., 2007; Benowitz, 1996).

Nicotine pharmacokinetics

The uptake of nicotine into the body via inhalation through the lungs occurs in a manner identical to that of intravenous administration (Russell et al., 1981), increasing the dependency of users on it (Kyerematen and Vesell, 1991). The non-ionized nicotine passes through the membranes across the buccal mucosa before reaching the blood-brain barrier. The absorption occurring through the feeble base enables nicotine to convert into a less ionized form, thereby facilitating easier passage across membranes even in alkaline solutions. The transport of absorbed nicotine to other organs and tissues involves several metabolic processes, which take 10 to 20 minutes to transport nicotine to the brain tissues. The extensive volume of distributed nicotine increases its solubility and uptake in the individual, thereby reaching other body tissues (Kyerematen and Vesell, 1991). The presence of nicotine indicates apparent inter-individual changeability effects relative to the metabolic clearance from hepatic blood flow (Kyerematen and Vesell, 1991). While the liver facilitates the metabolism of nicotine, the kidneys function to excrete it from the body.

Nicotine receptor and neurotransmitter release

General mechanism of nicotine

1. The uptake of nicotine into the body tissues involves the distillation of smoke contents from the inhaled cigarette smoke before it is transmitted to the lungs for subsequent absorption across the membranes of pulmonary venous circulation.

2. The nicotine subsequently enters the arterial circulation system, thereby swiftly getting transported into the brain tissues (Maisto et al., 2004).

3. Free distribution of absorbed nicotine is reported to occur within the brain tissues via its attachment to nicotinic acetylcholine receptors [nAChRs], regarded as ligand-gated ion channels.

4. The presence of cholinergic agonists on the external sections of the channels facilitates the entry of cations that take calcium and sodium forms. The cations facilitate the activation of voltage-dependent calcium pathways, thereby aiding calcium entry into the tissues.

Nicotinic receptors

Nicotine accomplishes pharmacological outcomes by activating nAChRs through the central nervous system (CNS). Receptors are considered ligand-gated ion channels owing to the following facts,

1. The intricate nicotinic acetylcholine receptors have five subunits present on the peripheral and central regions of the nervous system.

2. The existence of threefold β subunits [β2 to β4] and nine α subunits within the range of α2 to α10 (Millar, 2009).

3. Human beings are identified to have α4/β2, α3/β4, and α7-homomeric for their copious abilities. The α4/β2 is the dominant subtype, thus acting as the primary mediator of nicotine dependence in the human brain.

4. The binding of nicotine to receptors occurs through mesolimbic dopaminergic and nigrostriatal neurons. These neurons possess the ability to stimulate nicotine receptors to facilitate the release of ACTH, nor-epinephrine, serotonin, acetylcholine, dopamine, growth hormone, and vasopressin. Furthermore, nicotine possesses equally delineated abilities that facilitate the dopamine reward pathway in the brain, as shown in Figure 2 (Unwin, 2005).

5. The β2 subunit gene appears to eliminate behavioral effects exerted by nicotine in mice, as hindering the release of dopamine in the
brain tissues would sustain self-discharge. Consequently, the α4 subunit is regarded to play an active role in determining nicotine sensitivity levels (Albuquerque et al., 2009; Zhou et al., 2003).

**The nAChRs and other neurotransmitters**

1. The involvement of the modulation section by nAChRs is noted to enhance the performance of neurotransmitters within the presynaptic terminals, dendrites, and neural cells.

2. Nicotine-activated nAChRs facilitate the production of neurotransmitters, including norepinephrine, glutamate, acetylcholine, dopamine, and GABA, amongst others (Pontieri et al., 1996; Walters et al., 2005; McGehee et al., 1995; Yang et al., 1996).

3. Further release of neurotransmitters, including acetylcholine, GABA, serotonin, norepinephrine, endorphins, and glutamate, helps to regulate different behaviors exhibited by nicotine.

4. The presynaptic nAChRs are involved in modulating nicotine-mediated discharge simultaneously with the neurotransmitter discharges.

**Neuroparmacology of nicotine dependence**

**Nicotine-mediated desensitization of receptors**

1. Neuroadaptation has been reported to occur, leading to increased tolerance with the exposure of receptors to nicotine, though this phenomenon is not observed in all nicotine effects (Wang and Sun, 2005).

2. The affiliation with the neuroadaptation sites facilitating connections in the brain tissues to experience increased number. The emergence of such an increase supports the up-regulation occurring within the nicotine-mediated desensitization in the receptors. This is essential in strengthening the reliance and tolerance levels of nicotine in the brain tissues (Cha et al., 2017).

3. Typically, it is feasible to pair both reasoning to allow smokers to retain their daytime smoking to achieve stabilized nicotine levels in the plasma, thereby preventing withdrawal symptoms. Similarly, fruitful outcomes could be obtained by overcoming habituated reinforcers identified with smoking, including feeling and tasting smoke (Dani and Heinemann, 1996).

**Nicotine addiction and dependence**

The APA and the WHO have, in the past, reported nicotine addiction and dependence phrases. The drug tolerance arising in nicotine dependence involves minimized tolerance often occurring during recurrent administration of drugs. This leaves the individual requiring more nicotine to derive effects experienced when they used lesser doses (Sesia and Grace, 2012). This leads to neuroadaptation as the brain becomes used to the existence of nicotine, thus treating the administration of nicotine as necessary to sustain its normal functions. The brain tends to develop challenges in the absence of nicotine, particularly when an individual quits smoking, thus compelling him/her to backslide from their abstinence (Milani et al., 2012). Higher nicotine dependence demotivates the individuals from quitting smoking, making the interventions unfruitful, which are worsened by early morning smoking with initial cigarettes and leading to a subsequent increase in the daytime smoking Figure 3.

**The tobacco addiction cycle**

Smoking the first cigarette causes substantial pharmacologic impact, which is experienced as arousal effects responsible for subsequent tolerance to nicotine. The individual smokes the second piece upon realization of a declining tolerance rate in the brain tissues (Grieder et al., 2012). The recurrence of this feeling orients the smoker to increasing nicotine levels in their bodies as they develop increased tolerance intensities. Such occurrences reveal themselves as withdrawal symptoms visible during subsequent smoking Figure 4 (Henningfield, 1993).

The shade displayed in Figure 4 shows the effective region of neutrality involving nicotine threshold level, necessary to derive arousal and pleasure against threshold levels where withdrawal symptoms would arise. The smoker may experience transitory effects as nicotine levels increase in the brain over tolerance levels; however, basic euphoric influences decrease throughout the day (Borrello, 2010). Benowitz found evidence of self-denial responsible for resensitization toward nicotine effects (Benowitz and , 2001).

**Brain imaging of nicotinic acetylcholine receptors**

Conducting an in-depth study of the effects of tobacco smoking and nicotine on the brain is essential for eliminating backsliding and enhancing smoking alleviation treatments. A number of scanning techniques have been applied to examine the occurrence of chronic and acute effects caused by smoking
cigarettes. The following tools are among the widely used.

1. Positron emission tomography (PET)
2. Single-photon emission computed tomography (SPECT)
3. Functional magnetic resonance imaging

Application of the above imaging techniques tests the radiotracers affinities and specificity connections involving α4β2* to nAChRs. The 5-IA SPECT and 2-FA PET experiments in assessing acute effects associated with nicotine intake have found functional connectivity on α4β2* nAChR occupancy from cigarette smoking (Koren et al., 1998; Kimes et al., 2008).

**Up-regulation of nicotine receptors**

Literature reports the chronic effects of nicotine intake from continued smoking as up-regulation of nAChRs in the human brain as typical α4β2* nAChR. Studies examining the postmortem of human beings report chronic smokers to have higher α4β2* nAChRs when compared to non-smokers who successfully quit smoking, and had nAChR intensities similar to that of non-smokers. The literature on SPECT and PET assessments revealed up-regulation amongst smokers with higher α4β2* nAChRs, unlike the levels in non-smokers (Wüllner et al., 2008).

**Occupancy of nicotine receptors**

The ability of receptors to assume varying stoichiometries and existence of potential connection areas in ligands during high and low sensitivities leaves α4β2 nAChRs pharmacology experiencing intricate conditions. The emergence of such combination increases the occupancy levels of such receptors occurring in different allosteric conformations while revealing subsequent sensitivity from ligand binding. This demonstrates the nicotine effect amongst smokers alongside addiction phases, as demonstrated in Figure 5 and Figure 6 (Brody et al., 2009; Cummings and Hyland, 2005).

**Pharmacological intervention of nicotine dependence**

The knowledge derived from pharmacotherapy helps in addressing nicotine dependence. Besides, pharmacotherapy is useful in enabling smokers to avoid smoking, although it has no effect on special addictive situations (Jiloha, 2014). Nicotine replacement therapy (NRT) is among the highly engaged pharmacotherapy solution used in overcoming nicotine reliance. However, pharmacologic therapies in use today to reduce nicotine addiction have yielded not much success. The failures emerging in pharmacotherapy arise from frequent quitting attempts, where individuals fail to stop smoking, and hence, fail to engage the majority of requisite termination aids.

**Nicotine replacement therapy**

The need to reduce the harm surfacing as withdrawal symptoms from nicotine usage reflects the reason behind the use of NRT to treat nicotine dependence. This involves taking advantage of enhancing and optimizing the quitting process, specifically by replacing nicotine previously obtained from tobacco and, hence, delivering nicotine-mediated neuropharmacological effects (Cummings and Hyland, 2005). The NRT process reduces withdrawal symptoms while reducing the reinforcing effects obtained from tobacco-delivery nicotine. In this regard, nicotine medications seek similar outcomes for patients dependent on cigarettes to deliver a pleasing mood and continued alert state, a highly demanding and tedious exercise (Koren et al., 1998; Jiloha, 2014).

**Nicotine in drug therapy**

Dysfunctions arising in neuronal nicotinic receptors have been reported to cause diverse neurodegenerative ailments, such as Parkinson's disease (PD), schizophrenia, autism, and Alzheimer's disease (AD) (Dineley et al., 2015).

**Alzheimer’s disease**

The initial stages of AD are characterized by cholinergic deficits manifested as cognitive symptoms, confusion, lost memory, impaired reasoning, and thinking (Cupertino, 1928). Its occurrence results in severe primary cholinergic losses in the brain regions responsible for attention, and episodic and spatial memory during initial AD phases. Consequently, the ability of nicotine and nicotine analogs in delivering augmented cholinergic performances using nicotinic receptors support the therapeutic approaches in addressing AD (Cupertino, 1928). Thus, it is applicable during the initial stages of the ailment and seen as a general therapeutic approach in treating AD (Schneider et al., 2014).

A number of in vitro and in vivo studies illustrate nicotine possessing the potential to facilitate survival through reactionary processes when exposed to several neurotoxic insults. Recent literature shows enhanced learning and memory induced by nicotine transmitted through the neuropeptide receptors found in the AD rat model. The study of human beings has shown the effect of administering nicotine through intravenous and subcutaneous means on individuals identified with AD (Cupertino,
There emerges a similar possibility of nicotine exhibiting preventive actions against AD that hinders clinical dementia from setting in through minimizing frequent neuronal losses or enhancing its corresponding functional outcomes (Ziaad-dini et al., 2009). Examination of aged individuals has shown abilities to reduce brain Aβ from chronic nicotine levels from dependent usage of tobacco, although the action mechanisms involved have remained unclear. The aforementioned findings reveal that the occurrence of nicotinic cholinergic stimulations necessitates performing additional examinations as potential solutions for AD (Durazzo et al., 2014). Considering that nicotine is identified to cause negative impacts, such as enhancing cardiovascular risks, disrupted behavior, and sleep disorders, it is prudent to conduct further examination of safety and competence levels amongst patients suffering from AD.

**Parkinson’s disease**

There is a likelihood of cholinergic dysfunction, translating to neurotransmitter imbalances identified as PD. A review of existing literature affirms that dopaminergic and cholinergic systems execute their functions simultaneously, leaving the cognitive functions and control of motor alignment from likely impairment in PD cases (Jain et al., 2013). The beginning of particular subunits of nicotinic receptors can induce anti-inflammatory pathways while facilitating the survival of neurons (Barreto et al., 2015). Such receptors have the potential to highly overcome neuroinflammation while facilitating neural survival in the brain regions impaired by PD. The capability of the subtypes of nicotinic receptors is a reason for being considered as therapeutic objectives against PD. A number of epidemiological assessments performed on tobacco users demonstrated reduced prevalence and severity of PD, with a 40% reduced rate of suffering from PD when compared to non-smokers (Hurt et al., 2009). Further examinations have shown smoking to overcome motor complications striking PD patients. This finding emerges from nicotine intake rather than cigarette smoking (Baker et al., 2012). While several studies have demonstrated nicotine to cause asymptomatic effects in PD, these are found to have negligible effects with signs of variations (Baker et al., 2012; Reuck et al., 2005).

The use of modern data obtained from examining non-human primates indicates dyskinesias occurring through levodopa-induced attenuation caused by nicotine, though regarded as emerging from negative side effects associated with patients undergoing levodopa therapy (MacQueen et al., 2014). Simultaneously, the assessments and perceptions above show the tendency of either CNS-selective nicotinic receptor ligands or nicotine having the capability to improve disease progression and facilitate symptoms while suppressing levodopa-induced dyskinesias, thus enhancing PD therapy (Thiriez et al., 2011).

**Autism**

Irregularities occurring in the cholinergic system are considered to cause autism. This is affirmed by an in-depth examination of the brain performed during the post-mortem of adults who suffered autism. It showed declined delineation within the cerebral cortex, affecting several subunits of nicotinic receptors, responsible for their reduced expressions as noted in the neurochemical pathology of autism cases (Greenbaum et al., 2013; Schalkwyk et al., 2015). The loss of cholinergic activity, associated with the autistic brain, leads to likely restoration and improved cholinergic transmission induced by nicotinic receptor ligands to counter the imbalance arising from the loss with highly declined cognitive variations noted in autism (Martin-Ruiz et al., 2004).

**Schizophrenia**

The occurrence of dysfunction cases occurring in the hippocampal cholinergic system is heritably linked with schizophrenia. More smokers are reported to dominate the list of schizophrenia patients compared with the normal population. This occurrence is considered to deliver self-medication, resulting from normalization and alleviation of sensory and cognitive deficits from nicotine intake. The emergence of undesired smoking health effects creates a need for a secondary response for nicotine receptors. Previous research conducted to examine schizophrenia patients identified nicotine by causing alleviated negative symptoms and cognitive deficits alongside neuroleptic side effects (Basu and Nebhinani, 2013). Smoking causes momentarily reduction of negative schizophrenia symptoms by facilitating processes of dopaminergic and glutamatergic transmission (Yee et al., 2015). Uptake of nicotine enhances several cognitive scarcities in schizophrenia patients including shortages occurring in sensory gating alongside irregularities in the smooth eye motion controlled by nicotine administration (Krishnasadas et al., 2012; Hancock et al., 2015). Conversely, smoking is associated with enhancing the non-inhibition observed in schizophrenic patients (Winterer, 2010).

**Recommendations for future research**

1. A number of constraints exist that hinder the specificity of nAChR antagonists and agonists,
leading to the generation of mice expressing genetic nAChR subtypes adjustments to mark a supportive practical approach in assessing their appropriate participation to alter the pharmacologic effects from nicotine intake.

2. The current administration of vaccines in nicotine immunotherapy trails leads to probable errors in addressing nicotine reliance (Wye et al., 2017).

3. Administration of nicotine immunotherapies induces the generation of antibodies in the immune system, thereby reducing the speed and degree of nicotine entry into the brain and modifying nicotine pharmacokinetics while decreasing the reinforced effect of nicotine (Hartmann-Boyce et al., 2012).

4. Further assessment of smoking cessation should be conducted to study the impact of using derived treatments on the genotype and prototype relative to effectually addressing nicotine dependence (Fuxe et al., 2010).

5. There is a need to avail relevant biomarkers and addiction signals to have less toxic and less addictive elements in tobacco products as a solution to overcome the likely expense of complicated, addictive techniques (Fuxe et al., 2010; Zhong et al., 2016).

6. It is indefinite to use phrases, indicating the emergence of relative comparison when examining the abuse potential across products or assessing threshold to gauge abuse capacity levels.

7. It is important to accomplish expanded acceptance on the use of varying design features in tobacco products rather than focusing only on nicotine components inducing addiction to adequately address withdrawal, commencement, and relapse after quitting smoking (Zhang et al., 2011). This mandates the use of current neuro systems statistics identified with conditioning effects and enhancing and ceasing nicotine dependence to generate a feasible approach to anticipate discoveries in the smoking field.

CONCLUSIONS

Tobacco products present efficient conveyance systems in administering nicotine into the body. Nicotine causes extreme addictive effects with a potential of severe pharmacologic effects. It orients the body to the dopamine pathway in the brain, leading to stronger recurrent tobacco use. Individuals who develop nicotine dependence embrace self-standardizing tobacco intake to ensure sustenance of satisfying impacts besides overcoming withdrawal. The occurrence of nicotine dependence is considered a chronic ailment for the brain. Tobacco usage involves intricate disorders involving interchanges between pharmacodynamics and pharmacokinetics, categorized as pharmacology. Overcoming nicotine dependence alongside tobacco use involves a complex treatment technique that would reduce the probability of backsliding.

REFERENCES

Albuquerque, E. X., Pereira, E. F. R., Alkondon, M., Rogers, S. W. 2009. Mammalian Nicotinic Acetylcholine Receptors: From Structure to Function. Physiological Reviews, 89(1):73–120.

Baker, T. B., Breslau, N., Covey, L., Shiffman, S. 2012. DSM criteria for tobacco use disorder and tobacco withdrawal: a critique and proposed revisions for DSM-5*. Addiction, 107(2):263–275.

Barreto, G. E., Iarkov, A., Moran, V. E. 2015. Beneficial effects of nicotine, cotinine, and its metabolites as potential agents for Parkinsonâ€™s disease. Frontiers in Aging Neuroscience, 6.

Basu, A., Nebhinani, N. 2013. Nicotine dependence in patients with schizophrenia. British Journal of Psychiatry, 202(1):74–75.

Benowitz, N. L., ., A. R. 2001. Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine. Smoking and Tobacco Control Monograph. National Cancer Institute, 13:39–63.

Benowitz, N. L. 1996. Pharmacology of Nicotine: Addiction and Therapeutics. Annual Review of Pharmacology and Toxicology, 36(1):597–613.

Benowitz, N. L. 2010. Nicotine Addiction. New England Journal of Medicine, 362(24):2295–2303.

Berrendero, F., Robledo, P., Trigo, J. M., Martín-García, E., Maldonado, R. 2010. Neurobiological mechanisms involved in nicotine dependence and reward: Participation of the endogenous opioid system. Neuroscience and Biobehavioral Reviews, 35:220–231.

Borrello, S. J. 2010. Help your patients with smoking cessation. Nursing Made Incredibly Easy!, 8(2).

Brody, A. L., Mandelkern, M. A., Costello, M. R., Abrams, A. L., Scheibal, D., Farahi, J., Mukhin, A. G. 2009. Brain nicotinic acetylcholine receptor occupancy: effect of smoking a denicotinized cigarette.
Cha, S., Ganz, O., Cohn, A. M., Ehlke, S. J., Graham, A. L. 2017. Feasibility of biochemical verification in a web-based smoking cessation study. Addictive Behaviors, 73:204–208.

Cummings, K. M., Hyland, A. 2005. Impact of Nicotine Replacement Therapy on Smoking Behavior. Annual Review of Public Health, 26(1):583–599.

Cupertino, A. P. 1928. The Impact of Repeated Cycles of Pharmacotherapy on Smoking Cessation: A Longitudinal Cohort Study. Archives of Internal Medicine, 169(20).

Dani, J. A., Heinemann, S. 1996. Molecular and Cellular Aspects of Nicotine Abuse. Neuron, 16(5):80112–80121.

Dineley, K. T., Pandya, A. A., Yakel, J. L. 2015. Nicotinic ACh receptors as therapeutic targets in CNS disorders. Trends in Pharmacological Sciences, 36(2):96–108.

Durazzo, T. C., Mattsson, N., Weiner, M. W. 2014. Smoking and increased Alzheimer’s disease risk: A review of potential mechanisms. Alzheimer’s & Dementia, 10(3):122–145.

Fuxe, K., Marcellino, D., Borroto-Escuela, D. O., Guescini, M., Fernández-Dueñas, V., Tanganelli, S., Agnati, L. F. 2010. Adenosine-Dopamine Interactions in the Pathophysiology and Treatment of CNS Disorders. CNS Neuroscience & Therapeutics, 16(3):18–42.

Hurt, R. D., Ebbert, J. O., Hays, J. T., Mcfadden, D. D. 2009. Treating Tobacco Dependence in a Medical Setting. CA: A Cancer Journal for Clinicians, 59(5):314–326.

Hatsukami, D. K., Stead, L. F., Gupta, P. C. 2008. Tobacco addiction. The Lancet. 371:60871–60876.

Henningfield, J. 1993. Higher levels of nicotine in arterial than in venous blood after cigarette smoking. Drug and Alcohol Dependence. 33:23–29.

Hinrichs, A. L., Murphy, S. E., Wang, J. C., Saccone, S., Saccone, N., Steinbach, J. H., Bierut, L. J. 2011. Common polymorphisms in FM01 are associated with nicotine dependence. Pharmacogenetics and Genomics, 21(7):397–402.

Hurt, R. D., Ebbert, J. O., Hays, J. T., Mcfadden, D. D. 2009. Treating Tobacco Dependence in a Medical Setting. CA: A Cancer Journal for Clinicians, 59(5):314–326.

Jain, R., Majumder, P., Gupta, T. 2013. Pharmacological Intervention of Nicotine Dependence. BioMed Research International, pages 1–8.

Jiloha, R. 2014. Pharmacotherapy of smoking cessation. Indian Journal of Psychiatry, 56(1).

Kimes, A. S., Chefer, S. I., Matochik, J. A., Contoreggi, C. S., Vaupel, D. B., Stein, E. A., Mukhin, A. G. 2008. Quantification of nicotinic acetylcholine receptors in the human brain with PET: Bolus plus infusion administration of 2-[18F]F-A85380. Neurolmage, 39(2):717–727.

Koren, A. O., Horti, A. G., Mukhin, A. G., Gündisch, D., Kimes, A. S., Dannals, R. F., London, E. D. 1998. 2-, 5-, and 6-Halo-3-(2( S )-azetidinylmethoxy)pyridines: Synthesis, Affinity for Nicotinic Acetylcholine Receptors, and Molecular Modeling. Journal of Medicinal Chemistry, 41(19):3690–3698.

Kühn, S., Romanowski, A., Schilling, C., Mobascher, A., Warbrick, T., Winterer, G., Gallinat, J. 2012. Brain grey matter deficits in smokers: focus on the cerebellum. Brain Structure and Function, 217(2):517–522.

Kyeremateng, G. A., Vesell, E. S. 1991. Metabolism of Nicotine. Drug Metabolism Reviews, 23(1-2):3–41.

MacQueen, D. A., Heckman, B. W., Blank, M. D., Rens...
burg, J. V., Park, K., Drobes, J. Y., Evans, D. J., D. E. 2014. Variation in the α 5 nicotinic acetylcholine receptor subunit gene predicts cigarette smoking intensity as a function of nicotine content. The Pharmacogenomics Journal, 14(1):70–76.

Maisto, S. A., Galizio, M., Connors, G. J. 2004. Drug use and abuse. 4th ed.

Martin-Ruiz, C. M., Lee, M., Perry, R. H., Baumann, M., Court, J. A., Perry, E. K. 2004. Molecular analysis of nicotinic receptor expression in autism. Molecular Brain Research, 123(1-2):81–90.

Matta, S. G., Balfour, D. J., Benowitz, N. L., Boyd, R. T., Buccafusco, J. J., Caggiula, A. R., Zirger, J. M. 2007. Guidelines on nicotine dose selection for in vivo research. Psychopharmacology, 190(3):269–319.

McGehee, D., Heath, M., Gelber, S., Devay, P., Role, L. 1995. Nicotine enhancement of fast excitatory synaptic transmission in CNS by presynaptic receptors. Science, 269(5231):1692–1696.

Milani, H. S., Kharaghani, R., Safa, M., Samadi, R., Farhadi, M. H., Ardakani, M. R. K. 2012. The pattern of smoking and nicotine dependence in patients with psychiatric disorders. Tanaffos, 11(1):55–55.

Millar, N. S. 2009. A review of experimental techniques used for the heterologous expression of nicotinic acetylcholine receptors. Biochemical Pharmacology, 78(7):766–776.

Perkins, K. A., Karelitz, J. L., Boldry, M. C. 2017. Nicotine Acutely Enhances Reinforcement from Non-Drug Rewards in Humans. Frontiers in Psychiatry. 8.

Pontieri, F. E., Tanda, G., Orzi, F., Chiara, G., Di 1996. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature, 382(6588):255–257.

Reuck, J. D., Weweire, M. D., Maele, G. V., Santens, P. 2005. Comparison of age of onset and development of motor complications between smokers and non-smokers in Parkinson’s disease. Journal of the Neurological Sciences, 231(1-2):35–39.

Russell, M. A., Jarvis, M. J., Devitt, G., Feyerabend, C. 1981. Nicotine intake by sniff users. BMJ, 283(6295):814–817.

Schalkwyk, G. I. V., Lewis, A. S., Qayyum, Z., Koslosky, K., Picciotto, M. R., Volkmar, F. R. 2015. Reduction of Aggressive Episodes After Repeated Transdermal Nicotine Administration in a Hospitalized Adolescent with. Autism Spectrum Disorder. Journal of Autism and Developmental Disorders, 45(9):3061–3066.

Schneider, L. S., Mangialasche, F., Andreasen, N., Feldman, H., Giacobini, E., Jones, R., Kivipelto, M. 2014. Clinical trials and late-stage drug development for Alzheimer’s disease: an appraisal from 1984 to 2014. Journal of Internal Medicine, 275(3):251–283.

Sesia, T., Grace, A. A. 2012. Shifting pharmacology of nicotine use and withdrawal: Breaking the cycle of drug abuse. Proceedings of the National Academy of Sciences, 109(8):2697–2698.

Teitelbaum, A. M., Murphy, S. E., Akk, G., Baker, T. B., Germann, A., Weymann, L. B. V., Bloom, A. J. 2018. Nicotine dependence is associated with functional variation in FM03, an enzyme that metabolizes nicotine in the brain. The Pharmacogenomics Journal, 18(1):136–143.

Thiriez, C., Villafane, G., Grapin, F., Fenelon, G., Remy, P., Cesaro, P. 2011. Can nicotine be used medicinally in Parkinson’s disease? Expert Review of Clinical Pharmacology, 4(4):429–436.

Unwin, N. 2005. Refined Structure of the Nicotinic Acetylcholine Receptor at 4Å Resolution. Journal of Molecular Biology, 346(4):967–999.

USDHHS 2012. Preventing tobacco use among youth and young adults: a report of the Surgeon General.

Vňuková, M., Ptáček, R., Raboch, J., Stefano, G. B. 2017. Decreased Central Nervous System Grey Matter Volume (GMV) in Smokers Affects Cognitive Abilities: A Systematic Review. Medical Science Monitor, 23:1907–1915.

Walters, C. L., Cleck, J. N., Kuo, Y., Blendy, J. A. 2005. µ-Opioid Receptor and CREB Activation Are Required for Nicotine Reward. Neuron, 46(6):933–943.

Wang, H., Sun, X. 2005. Desensitized nicotinic receptors in the brain. Brain Research Reviews, 48(3):420–437.

Winterer, G. 2010. Why do patients with schizophrenia smoke? Current Opinion in Psychiatry, 23(2):112–119.

Wüllner, U., Gündisch, D., Herzog, H., Minnerop, M., Joe, A., Warnecke, M., Schmaljohann, J. 2008. Smoking upregulates α4β2* nicotinic acetylcholine receptors in the human brain. Neuroscience Letters, 430(1):34–37.

Wye, P. M., Stockings, E. A., Bowman, J. A., Oldmeadow, C., Wiggers, J. H. 2017. Effectiveness of a clinical practice change intervention in increasing the provision of nicotine dependence treatment in inpatient psychiatric facilities: an implementation trial. BMC Psychiatry, 17(1).

Yang, X., Criswell, H. E., Breese, G. R. 1996. Nicotine-induced inhibition in medial septum involves the activation of presynaptic nicotinic cholinergic...
receptors on γ-aminobutyric acid-containing neurons. Journal of Pharmacology and Experimental Therapeutics, 276(2):482–489.

Yee, A., Mohamed, N. N. B. N., Hashim, A. H. B., Loh, H. S., Singh, M. K., Ng, C. G., Jambunathan, S. T. 2015. The Effect of Nicotine Dependence on Psychopathology in Patients with Schizophrenia. BioMed Research International, pages 1–6.

Zhang, T. X., Saccone, N. L., Bierut, L. J., Rice, J. P. 2017. Targeted sequencing identifies genetic polymorphisms of flavin-containing monooxygenase genes contributing to susceptibility of nicotine dependence in European Americans and African Americans. Brain and Behavior, 7(4).

Zhang, X., Salmeron, B. J., Ross, T. J., Geng, X., Yang, Y., Stein, E. A. 2011. Factors underlying prefrontal and insula structural alterations in smokers. Neurimage, 54(1):42–48.

Zhong, J., Shi, H., Shen, Y., Dai, Z., Zhu, Y., Ma, H., Sheng, L. 2016. Voxelwise meta-analysis of gray matter anomalies in chronic cigarette smokers. Behavioral Brain Research, 311:39–45.

Zhou, Y., Nelson, M. E., Kuryatov, A., Choi, C., Cooper, J., Lindstrom, J. 2003. Human α4β2 Acetylcholine Receptors Formed from Linked Subunits. The Journal of Neuroscience, 23(27):9004–9015.

Ziaaddini, H., Kheradmand, A., Vahabi, M. 2009. Prevalence of cigarette smoking in schizophrenic patients compared to other hospital admitted psychiatric patients. Addiction & Health, 1(1):38–42.