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INSIGHT OF NICOTINE WITHDRAWAL SYNDROME

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ABSTRACT

The biggest preventable cause of disease and mortality globally is tobacco smoking, which is one of the main public health issues. The mortality rate and subsequent cardiovascular events are decreased by quitting smoking. Smoking is a true chronic illness marked by the emergence of a dependency state brought on mostly by nicotine. Because of this problem, smokers typically find it impossible to stop smoking on their own. Treatment options for smoking dependence range from non-pharmacological to pharmaceutical therapy. Currently, it is well acknowledged that smoking cessation medications work well and are secure in everyday situations. The therapist should tailor the smoking cessation strategy based on the most recent scientific data and the patient's preferences, giving particular attention to those patients who have certain cardiovascular and psychiatric comorbidities. Each of these medications has unique properties. The current document aims to provide useful practical guidance to all physicians, particularly those involved in cardiovascular prevention, by summarising the current effective pharmacological strategies for quitting smoking and discussing the contentious issue regarding the use of alternative tobacco products.

Keywords: Nicotine, Tobacco, Smoking, Nicotine addiction, Nicotine abstinence

INTRODUCTION -

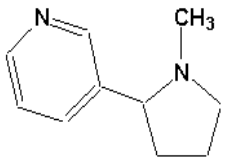
Tobacco dependence is major worldwide health problem and leading preventable cause of death among adults throughout the world **[1]**. The world health organization estimates that one third of global adult population smokes. In developed countries, smoking causes 20% of all premature deaths, and is the cause of more than one-third of all deaths in

men aged 35–69 **[2]**. Epidemiological data suggest that 70% of smokers want to quit, however less than 10% of these quit attempts are successful **[3]**. Smoking causes diseases such as cardiovascular diseases, chronic obstructive pulmonary diseases and lung cancer.

Drug dependence has been defined by the World Health Organisation (WHO) as "A behavioural pattern in which the use of given psychoactive drug is given a sharply higher priority over other behaviours which once had a significantly higher value" **[4] [5]**. Addiction can be also defined as the compulsive use of a drug that may be associated with tolerance and withdrawal symptoms after cessation of the drug **[6]**.

1.1 Nicotine -

Nicotine, [1-methyl-2-(3-pyridyl) pyrrolidine] an alkaloid derived from the leaves of *Nicotiana tabacum* belonging to the family solanaceae has been in use for centuries. It can be smoked, chewed or sniffed. Nicotine, isolated from tobacco leaves although tobacco contains thousands of chemicals, is the most active ingredient and primary component that acts in the brain and produces addiction.



1-methyl-2- (3-pyridyl) pyrrolidine

Nicotine is associated with many well-known pleasurable psychoactive effects, such as arousal, relaxation, and improved mood. Also, nicotine has been shown to act as a positive reinforce of smoking; for example, people are known to smoke only tobacco that contains nicotine, and a regular smoker modifies smoking behaviour to maintain a particular level of nicotine in the body. Nicotine also meets all of the Surgeons General's primary criteria for drug addiction which state that the drug must promote compulsive use, have psychoactive effects and reinforce its own use **[4]**.

1.1.1 Pharmacokinetics

Nicotine absorption can occur through the oral cavity, skin, lung, urinary bladder and gastrointestinal tract **[7]**. The rate of nicotine (pKa-7.9) absorption through the biological membranes is a pH dependent process **[7]**. In acidic environments, nicotine is in ionized state and does not readily cross biological membranes. However, at physiological blood pH (7.4), about 31% of nicotine is non-ionized and rapidly crosses membranes. In basic environments, nicotine is readily absorbed through oral or nasal mucous membranes because of the thin epithelium and rich blood supply results in significant blood nicotine levels, as liver metabolism is bypassed **[8]**. Pipe or cigar smokers do not need to inhale tobacco smoke to achieve significant blood nicotine levels as the pH of the smoke is basic.

On the contrary, the pH of smoke from fluecured tobaccos found in most cigarettes is acidic and there is little buccal absorption from cigarette smoke.

The plasma nicotine level in non-inhaling smokers is around 2.5–8.0 ng/ml, whereas the plasma nicotine levels in inhaling smokers reach 30–40 ng/ml nicotine **[9]**. The absorption of nicotine through the oral mucosa has been shown to be the principal route of absorption for smokers who do not inhale and for smokeless tobacco users. Swallowed nicotine is absorbed in the small bowel and then carried into the portal venous circulation where it undergoes pre-systemic metabolism by the liver which lowers the bioavailability (30-40%). Because of the complexity of smoking behavior, the dose of nicotine cannot be predicted from the nicotine content of the smoke, but approximated by smoking-machine according to the FTC criteria.

Smoking delivers nicotine rapidly to the brain **[8]**. Nicotine is extensively and quickly distributed to other body tissues with a steady state volume of distribution averaging 180 L (2.6 l/kg). Arterial blood and brain concentrations increase sharply following exposure and decline over 20 to 30 min as nicotine redistributes to other body tissues, particularly skeletal muscle. Immediately following nicotine absorption, nicotine levels are higher in arterial than venous blood. Venous blood concentrations subsequently decline more slowly because of redistribution from body tissues and rate of elimination. The brain: venous blood ratio of nicotine is highest during and at the end of the exposure period and gradually decreases due to elimination. In contrast to inhalation, the oral, nasal or transdermal absorption results in gradual increase in nicotine concentrations in the brain.

Nicotine is extensively metabolized in the liver and to small extent in lung and kidney **[8]**. Renal excretion of unchanged nicotine depends on urinary pH and urine flow, typically accounting for 5–10% of total elimination. The half-life of nicotine averages 2 h, although there is considerable inter-individual variability. The primary metabolites of nicotine are cotinine (70%) nicotine-N-oxide (4%), isomethonium ion (17%) and nornicotine. Cotinine formed in the liver in a two-step process involves cytochrome P-450 and aldehyde oxidase enzymes and metabolized to trans-3-hydroxycotinine, cotinine-N-oxide and 5-hydroxycotinine. Nicotine undergoes phase II metabolism by N- and O-glucuronidation. Because of its longer half-life (16 h), cotinine is commonly used as a biochemical marker of nicotine intake. Trans-3-hydroxycotinine, the concentration of which is more than cotinine by 2–3 folds in the urine, is also a useful indicator of nicotine exposure. Assays of

minor tobacco alkaloids, anabasine or anatabine, which are present in tobacco but not in pharmaceutical preparations of nicotine, may be of use in the future in determining smoking status of nicotine replacement therapy (NRT) users **[10]**.

1.1.2 Neurobiology of nicotine addiction

Nicotine is absorbed rapidly into the venous circulation. It then enters the arterial circulation and moves quickly to the brain. Nicotine diffuses readily into the brain, where it binds to nicotinic acetylcholine receptors (nAChRs), which are ligand gated ion channels. Cholinergic agonist binds to the outside of the channel allowing the entry of cations, including sodium and calcium on opening of channels. These cations further activate voltage dependent calcium channels, allowing further calcium entry **[4]**. The nAChRs complex composed of 5 subunit and found in both peripheral and central nervous system **[11]**. In the mammalian brain, there are 9 α-subunits (α_2- α_{10}) and 3 β-subunit (β_2-β_4). The $\alpha_4\beta_2$ receptor subtype is predominant in the human brain and is believed to be the main receptor mediating nicotine dependence **[11]**. Stimulation of central nAChRs by nicotine results in the release of a variety of neurotransmitters in the brain, most importantly dopamine. Nicotine causes the release of dopamine in the mesolimbic area, the corpus striatum, and the prefrontal cortex (Dani and Biasi, 2001 **[11] [12]**. Particular important are the dopaminergic neurons in the ventral tegmental area of the midbrain and the release of dopamine in the shell of the nucleus accumbens (NAc) as this pathway appears to be critical in drug induce reward **[13]**. Nicotinic receptor activation promotes the release of neurotransmitter such as dopamine, noradrenaline, acetylcholine, glutamate, serotonin, beta-endorphine and GABA, which may then mediate various effect of nicotine.

It is believed that most of the release of neurotransmitters occurs via modulation by presynaptic nAChRs, although direct release of neurotransmitters also occur **[14]**. Dopamine release is facilitated by nicotine-mediated augmentation of glutamate release and, with long-term treatment, by inhibition of GABA release **[4]**. Chronic cigarette smoking (but not acute nicotine administration) reduces brain monoamine oxidase A and B activity, which would be expected to increase monoamine neurotransmitter levels such as dopamine and norepinephrine in synapses, thus augmenting the effects of nicotine and contributing to addiction **[15]**. Dopamine release signals a pleasurable experience and is critical to the reinforcing effects of nicotine and other drugs of abuse **[13]**. Chemically or anatomically lesioning dopamine neurons in the brain prevent nicotine self-administration in rats **[14]**. Repeated exposure to nicotine, neuroadaptation occurs to some but not all effects of nicotine **[16]**. Concurrent with this

neuroadaptation is an increase of nAChRs in the brain. This increase is believed to represent upregulation in response to nicotine-mediated desensitization of receptors. This desensitization may play a role in nicotine dependence and tolerance **[16]**.

1.1.3 Nicotine abstinence

The negative aspects of nicotine withdrawal have been hypothesized to contribute in nicotine dependence and high rates of relapse to tobacco smoking. Withdrawal from chronic nicotine administration in humans results in an abstinence syndrome **[17][18][19]**. Nicotine withdrawal is associated with significant increase in intracranial self-stimulation reward threshold, with deficient dopamine release and reduced reward **[20]**. The nicotine withdrawal syndrome is comprised of 'physical' or somatic, and affective components. The most common somatic symptoms include bradycardia, gastrointestinal discomfort, and increased appetite. Affective symptoms primarily include craving, depressed mood, dysphoria, anxiety, irritability, and difficulty concentrating **[19][18]**. The actions of nicotine have been extensively investigated not only in humans, but also in animals and variety of cell systems **[21]**. In animal models, nicotine produces effects that are commonly seen with other addictive drugs like self-administration and place preference, increase in locomotor activity and reward after brain stimulation **[21] [11]**. As mentioned above, rodents chronically treated with nicotine also exhibit signs of withdrawal either after administration of an antagonist of the nicotinic receptors (nAChRs) or after cessation of nicotine **[22] [23]**. Injection of the nAChR antagonist mecamylamine quickly evokes withdrawal signs; on the other hand, the behavioural signs of spontaneous nicotine withdrawal in animal were found to appear within the first few days of abstinence from the drug **[22]**. The most prominent signs of this rodent withdrawal syndrome include abdominal constriction (writhes), rearing, jumping, chewing, facial tremor, eye blinks, ptosis, escape attempts, foot licks, genital grooming, shakes, scathes, yawns **[12][23]** and anxiety **[12]**.

1.1.4 Neurotransmitter system involved in nicotine withdrawal syndrome

1.1.4.1 Acetylcholine

The cholinergic system arises within basal forebrain (medial septum, diagonal band nucleus, and substantia innominata) and pontine (pedunculopontine and laterodorsal tegmental nuclei) sites and projects throughout the brain. The cholinergic system appears to play a significant role in mediating the rewarding actions of acute nicotine. For example, lesioning of the pedunculopontine tegmental nucleus reduced the rewarding effects of self-administered nicotine **[24]**.

Blockade of nAChRs increased the occurrence of withdrawal-related behaviours in rats when treated chronically with nicotine **[20]**. Administration of nicotinic receptor antagonists precipitated withdrawal responses in nicotine naive animals **[20][25]**. This observation suggested that endogenous cholinergic tone, by an action at nAChRs, prevents the expression of somatic and affective signs usually associated with nicotine withdrawal, and that these withdrawal responses arise because of deficits in cholinergic transmission. Direct infusion of nicotinic receptor antagonists into the VTA elevated brain-simulation reward thresholds **[26]** by a similar magnitude to that observed in rats undergoing nicotine withdrawal **[20][25]**. Therefore, reduction in endogenous cholinergic tone may be one of neurochemical adaptation involved in mediating elevations in brain-stimulation reward thresholds observed in rats during withdrawal from chronic nicotine exposure.

1.1.4.2 Dopamine

Evidences suggested that the dopamine fibers that arise within the VTA and project to the NAc, known as the mesolimbic dopamine system, play a major role in mediating the reinforcing properties of acute nicotine. Acute nicotine increased the firing rate of VTA dopamine neurons **[27] [28]** and elevated dialysate dopamine levels in the NAc **[29]**. Direct injection of DHbE into the VTA **[30]**, 6-hydroxydopamine lesions of the NAc (Corrigall *et al*., 1994) **[30]**, or systemic administration of a selective D1 or D2 dopamine receptor antagonist **[14]** attenuated nicotine self-administration in rats. Spontaneous and antagonist-precipitated withdrawal from various drugs of abuse such as amphetamine, cocaine, morphine, and ethanol **[31] [32]** has been shown to produce marked deficits in accumbal dopamine release. These observations are consistent with rewarding properties of drugs of abuse like nicotine, the mesolimbic system also is involved in mediating aversive behavioral states associated with drug withdrawal **[33]**. Hildebrand *et al*. have shown that besides an increase in somatic withdrawal signs, mecamylamine also significantly decreased accumbal dopamine release in rats chronically exposed to nicotine compared with control rats **[34]**. It is likely that deficits in dopamine transmission in the NAc play a role in mediating nicotine withdrawal. Some evidence suggested that dopamine may play a role in mediating nicotine withdrawal, particularly in deficits in reward and motivational processes. It is noteworthy that the recently licensed smoking cessation aid, bupropion (Zyban2) acts, at least in part, by inhibiting neuronal uptake of dopamine and thereby enhancing dopamine transmission **[35] [36]**.

1.1.4.3 Glutamate

Nicotine acts at presynaptic α_7-nAChRs located upon glutamate efferents [37] that arise within the PFC **[38]** to increase glutamate release in the VTA. This enhanced glutamate release then acts at N-methyl-D-aspartate (NMDA) and non-NMDA receptor sites on postsynaptic dopamine neurons and increases their firing rate. Nicotine also acts at α_7 nAChRs located on dopamine cell bodies in the VTA **[28]** and on presynaptic terminals in the NAc **[39]** to increase dopamine release. In addition to its role in mediating the rewarding effects of drugs like nicotine, there is also evidence for a role of glutamate in drug dependence and withdrawal states [40]. The role of glutamate transmission in nicotine withdrawal has been investigated. Group II metabotropic glutamate receptors (mGluR), which include mGluR2 and mGluR3, are inhibitory receptors that are located at presynaptic and postsynaptic locations **[41]**. Stimulation of mGluR2/3 decreased glutamate release throughout the hippocampus, striatum, and cortex **[42] [43]** have shown that the Group II mGluR selective agonist LY354740 ameliorated the increase in acoustic startle response observed in rats undergoing nicotine withdrawal **[43]**. In light of this observation, it was suggested that enhanced glutamate release may play a role in mediating the aversive aspects of nicotine withdrawal that were reflected by an increase in startle reactivity **[43]**. It is interesting that acute nicotine administration increased the release of glutamate in various brain sites including the VTA **[37][39][44][45]** and hippocampus **[46]**, whereas acute LY354740 decreased glutamate release **[41]**. In fact, because withdrawal effects are most often opposite in direction to acute drug actions **[47]**, it might be expected that nicotine withdrawal would be associated with deficits in glutamate transmission. It is therefore somewhat surprising that a drug that acts to decrease glutamate release would ameliorate nicotine withdrawal, particularly because activation of glutamate receptors plays a role in mediating the rewarding actions of nicotine **[48][39]**.

1.1.4.4 Opioid peptide

Reversal of nicotine withdrawal signs by opioid receptor agonist morphine **[49]** and reduction in the naloxone precipitated opiate withdrawal by nicotine and inability of nicotine to produce sensitization in μ receptor knockout mice **[50]** suggest that common neurobiological substrates may mediate nicotine and opiate withdrawal. Accordingly, naloxone and an analog of the endogenous antiopiate, neuropeptide FF, have been shown to precipitate somatic withdrawal signs after chronic nicotine treatment **[49]**.

1.1.4.5 Serotonin

Evidences suggested that serotonin (5-HT), and the 5-HT_1A receptor plays a role in nicotine withdrawal **[51]**. Clinically, the 5-

HT_1A receptor partial agonist buspirone shows efficacy in smoking cessation trials and may reduce withdrawal severity in abstinent smokers **[52] [53]**. Preclinical studies also have investigated the role of 5-HT and the 5-HT_1A receptor in nicotine withdrawal. Nicotine withdrawal significantly increased the acoustic startle response in rats for approximately 4–5 days. It has been suggested that this increased startle reactivity perhaps most closely resembles the increased irritability observed in smokers undergoing nicotine withdrawal **[54]**. Systemic administration of 5-HT_1A receptor agonists such as 8-OH-DPAT exacerbates this response, whereas 5-HT_1A receptor antagonists, such as WAY-100635, alleviate this enhanced response **[55]**. Electrophysiological investigations have demonstrated that the responsiveness to 8-OH-DPAT of neurons in the dorsal raphe nucleus (DRN) was significantly increased during nicotine withdrawal **[56]**. Nicotine withdrawal increases the inhibitory influence of somatodendritic 5-HT_1A autoreceptors located within the raphe nuclei and thereby decreases 5-HT release into forebrain and limbic brain sites which contributes to nicotine withdrawal signs **[56]**.

1.1.5 Pharmacological approaches of nicotine cessation treatment

The drugs currently approved by the US Food and Drug Administration (FDA) for smoking cessation include nicotine-replacement therapy (NRT) in the form of a transdermal patch, gum, nasal spray, oral inhaler, and lozenges and non- nicotine agent **[57]**.

Table 1: Drugs for smoking cessation treatment

Sr. No	Medication	Pharmacological mechanism
1	Nicotine patch	NRT: reduces nicotine craving and withdrawal
2	Nicotine gum	NRT: reduces nicotine craving and withdrawal
3	Nicotine Lozenge	NRT: reduces nicotine craving and withdrawal
4	Nicotine nasal spray	NRT: nACh receptor stimulation rapidly reduces nicotine craving and withdrawal symptoms
5	Nicotine vapour inhaler	NRT: nACh receptor stimulation rapidly reduces nicotine craving and withdrawal symptoms
6	Buproprion hydrochloride	Blocks reuptake of Nor-adrenaline and dopamine
7	Nortryptyline	Blocks reuptake of Nor-adrenaline and 5-HT
8	Clonidine	α_2-adrenoreceptor agonist reduces nicotine withdrawal symptoms
9	Buspirone	Partial agonist of 5-HT_{1A} receptors reduces 5-HT release

CONCLUSION:

This article has focused on a range of novel pharmacological approaches for the treatment of tobacco dependence, pharmacokinetic, Neurobiology of nicotine addiction, Nicotine abstinence, Neurotransmitter system involved in nicotine withdrawal syndrome, Pharmacological approaches of nicotine

cessation treatment. For smoking cessation include nicotine-replacement therapy (NRT) in the form of a transdermal patch, gum, nasal spray, oral inhaler, and lozenges and non-nicotine agent. Drugs with widely differing mechanisms of action can be effective in the treatment of tobacco dependence and/or withdrawal, suggesting that the drug development net be broadened further in the search for medications to treat one of the most devastating epidemics.

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