

## Tobacco Use: From Brain Probe to Public Mental Health Menace.

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**Abstract:** Drug-abuse has remained a problem of greatest social relevance throughout the history. Tobacco is the drug of recent introduction in the list of psychoactive substances used in the modern world. Tobacco related deaths are around 5 million every year and the toll is likely to double by 2025 if adequate measures are not taken. Nicotine in tobacco is highly toxic and addictive. It is also a gate-way drug for hard-core addictive drugs. The paper attempts to foster communication among nicotine researchers. It explores nicotine as a tool to probe neural activity and tobacco use as a health hazard and social menace.

**Keywords:** Nicotine; Reward pathway; FCTC (Framework Convention on Tobacco Control); NOTE (National Organization for Tobacco Eradication)

### INTRODUCTION

Due to public health advances during the last century, death rates have plummeted and life expectancy has risen sharply everywhere, although more so in the developed countries. Most dreadful infectious diseases have disappeared, decreased drastically or the knowledge to conquer them is available. In the current times there are two major preventable causes of death that are still increasing globally, viz. HIV and tobacco. Tobacco-related diseases cause five million deaths every year and the death toll is likely to increase to 10 million by 2025 if the current trend continues.

In a path breaking judgment in July 1999, the Kerala High Court banned smoking in public places throughout the state for the first time in India. Subsequently, Hon'ble the Supreme Court of India banned smoking in public places throughout the country in November 2001 and directed the Centre and the states to ensure the implementation of the ban.

This paper attempts to foster communication among nicotine researchers working along the continuum from basic to applied science. It also conveys a sense for the special problems and opportunities in the study of nicotine and tobacco use. It explores two themes, (1) nicotine as a tool to probe neural activity, and (2) tobacco use as a health hazard and societal menace, by examining nicotine from pharmaco-chemical, bio-behavioral, and socio-cultural perspectives. The rationale for the integration is that there may be benefits from viewing nicotine in a context broader than those dictated by custom and technological specialization. Tobacco use is surely one of the strangest of human behaviours<sup>1</sup>.

How is it that nearly one-third of world's adult population regularly performs this strange act which is necessary neither for the maintenance of life nor for the satisfaction of social, cultural, or spiritual needs; an act which is acknowledged by its adherents to be harmful to the health and even distasteful<sup>2</sup>. The ubiquity of tobacco use and its persistence in the face of vigorous proscriptions, and, in our own time, despite the generally agreed health risk, is a remarkable phenomenon.

Within a short span after Christopher Columbus, a Spanish navigator and his crewmen first observed this strange behaviour of smoking among the Natives of America in 1492, tobacco use spread worldwide and assumed major social, political, industrial, economic and medical importance<sup>3</sup>. These five hundred years of tobacco's discovery have provided ample opportunity to the commercial forces to dictate its universal availability by way of engineering addiction to tobacco among its users<sup>4</sup>. We know it now adequately that tobacco use not only causes addiction it harms every organ of the body, causes many diseases, compromises users' health in genera, shortens lifespan and leads to premature deaths<sup>5</sup>.

Tobacco is a plant product and the tobacco plant is an important member of *Solanaceae* family of the plant kingdom<sup>6</sup>. Unlike other members of this family, such as tomato and potato, which have an uncontroversial nutritional role, or

the decorative attraction of winter cherry and petunia, tobacco plant carries in its leaves quantities of an alkaloid, nicotine, which gives it instead, power over man's mind<sup>1</sup>.

*Nicotiana tabacum* is the main source of tobacco though most of tobacco in Northern India and Afghanistan comes from *Nicotiana rustica*<sup>6</sup>. Tobacco is grown all over the world; about 100 countries across the globe cultivate tobacco. More than 6 million tons of tobacco are grown worldwide every year. China is the largest tobacco grower with annual production of 2.3 million tons. India is the second largest tobacco producer for domestic use and export (Table 1).

TABLE 1: TOP TEN TOBACCO PRODUCERS

Country	Tobacco Production (in million tons)
China	2.298
India	0.595
Brazil	0.520
United States	0.408
European Union	0.314
Zimbabwe	0.204
Turkey	0.193
Indonesia	0.166
USSR(former area)	0.116
Malawi	0.108
<b>TOTAL</b>	<b>6.137</b>

After harvesting and curing, tobacco leaves are manufactured into consumable products which are smokeless and for smoking. Smokeless products are available for chewing, snuffing and local application while smoking of tobacco is in the form of cigarettes, cigars, *hookah*, *chillum*, *cheroot*, *beedi* etc<sup>2</sup>.

Cigarette smoking is most common both in terms of prevalence and health consequences<sup>1</sup>. In Indian context *beedi* smoking is more common because of economic reasons<sup>2</sup>. From the incandescent tip of the lighted cigarette burning at a temperature of 800°C (1600-1800°F), the smoker with each puff draws into his mouth and lungs a hot potpourri of gases and many sized particles (Figure 1). About 3000 chemicals have been isolated from smokeless tobacco while 4000 have been identified in tobacco smoke, including some that are pharmacologically active antigenic, cytotoxic, mutagenic and carcinogenic. International agency for Research on cancer has identified 55 carcinogens in tobacco smoke<sup>7</sup>. The particulate matter known as tar contains a long list of chemicals, primarily polynuclear aromatic hydrocarbons, aromatic amines and miscellaneous organic compounds. Metabolic activation of nicotine component can incite DNA adduct formation, gene mutations and sequence of events that lead to cancer. Cytochrome P-450 hydroxylates, compounds such as debrisoquine and tobacco specific N-nitrosamines are present in tobacco smoke<sup>8</sup>. Smokers capable to metabolize debrisoquine are 8 times more prone to risk of lung cancer<sup>9</sup>. Cigarette smoke contains 2-6% carbon monoxide (CO), a highly toxic gas, known to interfere oxygen carrying

and utilization. Nicotine is the main chemically active constituent present in tobacco to cause addiction and a number of patho-physiological changes.

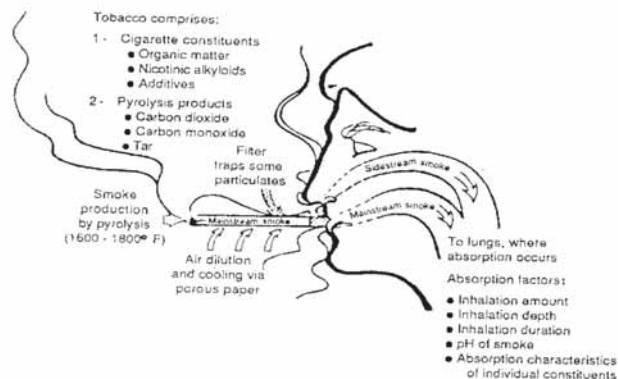


Figure 1: Tobacco Smoking

## NICOTINE IN TOBACCO

Nicotine is an alkaloid (1-methyl-2-[3-pyridyl] pyrrolidine), having carbon, hydrogen and nitrogen in proportion C10, H14 and N2 forming a double ring like structure (Figure 2). In its pure state, nicotine is a colourless, volatile, strongly alkaline liquid which turns pale yellow to dark brown on exposure to air giving it a characteristic tobacco smell<sup>1,2</sup>. It was first isolated from tobacco leaves by Posselt and Reimanbasic in 1828<sup>10</sup> and since then it has been extensively studied.



Figure 2: Structure Of Nicotine

It is highly toxic and potentially lethal chemical responsible for a number of patho-physiological changes in the body and one-drop of pure nicotine is sufficient to kill a dog (or a man) within minutes<sup>11</sup>.

In the smokeless tobacco products nicotine is dissolved in the moisture of tobacco leaf as a water soluble salt while in a burning cigarette, nicotine volatilizes and is present in the smoke as free nicotine suspended on minute droplets of tar. Nicotine not only causes damaging effects it also leads to tolerance to its own action like other dependence producing drugs<sup>4</sup>. It is also a gate-way drug to other drugs of abuse such as marijuana and alcohol<sup>10</sup>.

## NICOTINE IN THE BODY

Nicotine acts on brain and other parts of the nervous system. From tobacco smoke nicotine enters the blood stream through the lungs while nicotine in smokeless tobacco passes through the mucosal membrane of mouth and nose or the skin. Pulmonary absorption, which is the most favoured and perhaps commonest, occurs in a matter of seconds. From the lungs, chemicals in the smoke are absorbed into body's systems and carried quickly to different parts of the body. Oral, snuffs and other smokeless tobacco products are absorbed more gradually<sup>12</sup>. Amount of nicotine intake from one cigarette varies widely, in accordance with the smoker's latitude for adjusting the dose level. Nicotine intake ranges from 10 mg/day to 80 mg/day, or 0.4 mg-1.6 mg/cigarette<sup>10</sup>.

After absorption, nicotine travels rapidly and reaches the brain within seven seconds; it readily crosses the blood brain barrier. This sudden burst of nicotine in the brain causes elevation of blood pressure due to stimulation of adrenal glands resulting in discharge of epinephrine.

There is also sudden release of glucose and increase in respiration, heart

rate, constriction of arteries and increased alertness. Many of these effects are produced through its action on both the peripheral and central nervous system. Nicotine causes release of dopamine, therefore, the psycho-active rewards occur quickly and these rewards are highly reinforced<sup>7</sup>. Nicotine is distributed throughout the body, mostly to skeletal muscles and brain and activates specific receptors known as cholinergic receptors.

Nicotine binds to the receptors in the brain, where it influences the cerebral metabolism. Nicotine is then distributed throughout the body.

If nicotine were not absorbed quickly from the lungs, people would not take it in the form of smoke; if it were not taken up into the brain, it would not exert its psycho-pharmacological effects; if it were not rapidly metabolized and excreted, it would probably not be taken in such often-repeated doses.

## BIOLOGY OF NICOTINE REINFORCEMENT: DOPAMINE AND REWARD PATHWAYS

Nicotine increases activity in prefrontal cortex, thalamus and visual system<sup>13</sup>. It is a powerful reinforcing agent in both animals and humans. The mesolimbocortical dopamine system consists of neurons with cell bodies localized in ventral tegmental area (VTA) and axon projections to nucleus accumbens (NAc) and medial prefrontal cortex.

Nicotinic receptors concentrated in VTA and NAc activate the mesolimbic dopamine system which is responsible for reinforcing behaviour like other dependence producing drugs<sup>14</sup>. VTA and its projections to NAc are involved in reward and mediate the reinforcing actions of drug abuse<sup>15</sup>.

Nicotine stimulates the release of dopamine in the pleasure circuit and increases extra-cellular level of dopamine in NAc<sup>16-19</sup>. It also attenuates locomotor stimulant effect of systemically administered nicotine<sup>20</sup>. Stimulation of central nAChRs by nicotine results in the release of a variety of neurotransmitters in the brain, most importantly dopamine in the mesolimbic area, the corpus striatum and the frontal cortex. Of importance are the dopaminergic neurons in the VTA of the midbrain and release of dopamine in the shell of NAc which is critical in drug-induced reward<sup>21</sup>. Other neurotransmitters, including norepinephrine, acetylcholine, serotonin, Gamma-amino-butyric acid (GABA), glutamate and endorphins, are released as well, mediating various behaviours of nicotine (Table 2)<sup>16</sup>. Release of neurotransmitters occurs via modulation of presynaptic nAChRs along with the direct release<sup>22</sup>. Dopamine release is facilitated by nicotine mediated augmentation of glutamate release and long-term treatment by inhibition of GABA release.

Table 2: Neurotransmitter Release Due To Nicotine Receptor Activation

Neurotransmitter	Behavioural effect
Dopamine	Pleasure, appetite suppression
Norepinephrine	Arousal, appetite suppression
Acetylcholine	Arousal, cognitive enhancement
Glutamate	Learning, memory enhancement
Serotonin	Mood modulation, appetite suppression
Beta-endorphin	Reduction of anxiety and tension
Gamma-amino-butyric acid (GABA)	Reduction of anxiety and tension

## TOBACCO USE AND PHYSICAL HEALTH

Tobacco causes a wide variety of fatal and non-fatal diseases all over the world. Cigarette smoking is the single most important cause of cancer mortality which is more than 30%<sup>23</sup>. Tobacco smoking is responsible for 90% of all lung cancers. Cigarette smokers have 70% higher death rates than non-smokers above 35 years of age. Tobacco smoking is causally associated with higher rates of cancer of larynx, oral cavity and esophagus. Risk of breast cancer is 75% higher in heavy smoker women who begin smoking during adolescence<sup>24</sup>.

Smoking delays conception in women and smoking during pregnancy affects the fetus adversely<sup>2</sup>. Smoking by the mothers during pregnancy has been identified as the single preventable cause of infant morbidity and mortality. Smoking may have long-term effects on surviving children and complications in the mothers including abruptions, placenta praevia, abortion, retarded fetal growth and low birth-weight.

Carcinoma of urinary bladder, kidney, pancreas, stomach and uterine cervix is associated with smoking. 40% of all kidney and bladder related cancers are due to tobacco. 20-30% leukemia cases are tobacco related. Cigarette smoking is a risk factor for coronary heart disease (CHD) with 70% greater CHD death rate. Risk of fatal cerebrovascular disease is 3-times higher in smokers<sup>25</sup>.

Chronic Obstructive Pulmonary disease (COPD) is associated with cigarette smoking as a leading cause of disability.<sup>26</sup> In 1990s about 25% of all male deaths in developing countries were due to tobacco smoking. In women of developing countries deaths have increased from 2% in 1955 to 13% in 1995 and this is continuously increasing. Indian studies are largely on the subjects smoking cigarettes.

## TOBACCO USE AND MENTAL HEALTH

Smoking is 2-4 times higher among psychiatric disorders and substance use disorders<sup>27</sup>. Nearly 41% of current smokers report having a mental health diagnosis in the last month<sup>28</sup>. 60% of current smokers report a past or current history (ever history) of a mental health diagnosis sometime in their lifetime<sup>27</sup>. Heavy smokers report substantially poorer well-being, greater symptom burden, and more functional disability compared to nonsmokers<sup>29</sup>. Public mental health clients have a higher relative risk of death than the general population due, in part, to high rates of tobacco use<sup>30</sup>.

**Most common psychiatric disorders among current (within the last 30 days) smokers are:**

- Alcohol abuse
- Major Depressive Disorder
- Anxiety disorders: simple phobias and social phobias
- Substance Abuse

**Among current smokers, the most common ever mental disorders are:**

- Alcohol abuse
- Major depression
- Substance abuse
- Anxiety disorders: simple phobias and social phobias.

**Quitting smoking among mentally ill:**

- Quit rates among smokers with any *current* mental health diagnosis are significantly lower than smokers with no history of mental illness.
- Quit rates among smokers with *any history* of alcohol and substance abuse and social phobias are significantly lower than smokers without this history.
- Quit rates among smokers with a past history of major depression and simple phobias are similar to smokers without this history.

**Why higher rates of smoking in mentally ill:**<sup>27,31,32</sup>

- **Genetic basis:** Shared genetic factors have been identified for nicotine dependence and for depression. Genetic factors likely contribute to the development of schizophrenia and may contribute to the development of nicotine dependence.
- **Self-medication:** Some researchers speculate that the positive reinforcing effects of tobacco may help manage adverse events due to use of psychotropic medications.
- **Psychological factors:** Smokers with many psychiatric disorders report that smoking reduces their psychiatric symptoms. These smokers are more likely to have higher nicotine dependence levels, have a current history of depression, ADHD, or alcohol dependence.
- **Trauma:** Recent studies have linked a history of grief and PTSD with increased substance use including smoking. In some studies, smokers were found to be more likely to have a history of childhood trauma, which may link to adult depression. Therefore, the initial trauma rather than the later depression could be the risk factor for nicotine dependence.
- **Social factors:** Limited education, poverty, unemployment, peers and the mental health treatment system where tobacco use is generally tolerated and not seen as a health issue may account, in part, for heavier smoking in this population.

## GLOBAL TOBACCO USE SCENARIO

- One-third of the global population or 1.3 billion people around the world use tobacco.
- Although tobacco use has declined in many developed countries, it is increasing in most developing countries.
- Most tobacco use begins during childhood and adolescence.
- No amount of tobacco use is safe and a long-term use has a 50% chance of dying early from tobacco caused disease. 650 million children and adolescents who are smokers today will eventually die prematurely.
- By the year 2020, tobacco will be world's largest single health problem, causing an estimated 8.4 million deaths annually, claiming more lives than HIV, TB, Maternal mortality, Motor vehicle accidents, suicide and homicide, combined.
- 70% victims of tobacco diseases are in the developing world.
- Nicotine is highly addictive and addiction is as potent as any hard-core drug.
- Quitting is not simply a matter of choice for most tobacco users, and tobacco can be physiologically, psychologically and socially reinforcing.
- Quitting has immediate and long-term health benefits Smoking is a ubiquitous personal and environmental pollution.

Environmental tobacco smoke (ETS) is responsible for the preventable diseases, disability and premature deaths. Home and the work-place are the two microenvironments where possibility of exposure to ETS is maximum. Tobacco use is also associated with multidimensional financial loss in the form of tobacco cost, treatment cost of resulting medical illness, loss of buying power food, shelter and education to the children, Tobacco use is certainly a contributory factor towards illiteracy and child-labour. The associated psychological disturbances in smokers' families may lead to anti-social activities and criminality. This behaviour may provide seed and soil for the growth of lawlessness inducing insecurity and instability. The domain of devastating effects of tobacco use are not limited to physical health but the intellectual, social, educational, scientific, and economic development of the society, is at risk.

## Key factors in the treatment of smokers with mental illness

All individuals with mental health disorders should be asked if they are smokers and advised to quit. All identified smokers should have smoking cessation integrated into their overall treatment plan<sup>29-35</sup>. There is increasing evidence that nicotine dependence treatment does not jeopardize recovery from alcohol and other substances and may improve outcomes<sup>33-35</sup>. There are emerging recommendations to treat the mental disorder first before attempting to treat nicotine dependence<sup>29,35</sup>. There are some reports in the literature indicating that psychiatric symptoms can worsen during the acute stages of withdrawal when individuals are not taking pharmacological treatments for nicotine dependence<sup>31,34,35</sup>. There are also reports in the literature indicating that risk for major depression among patients with any history of major depression, increases through the first months following abstinence<sup>33,37-39</sup>. Abstinence from nicotine can increase medication blood levels and risks for medication related adverse events. It is sometimes difficult to distinguish untreated withdrawal symptoms from adverse events from other medications precipitated by a sudden reduction or cessation of nicotine dosing. Therefore, patient monitoring during withdrawal should include consideration of dose adjustments<sup>33,37-38</sup>.

## BEHAVIORAL INTERVENTIONS

There may be a need for more skill development in motivational interviewing and general smoking cessation skills<sup>27,35</sup>.

Protocols for treatment of smokers with mental illness exist for patients seen in mental health facilities and clinics. These protocols rely on prior knowledge of the smoker's diagnosis, medication history, and training to monitor symptoms and make medication adjustments<sup>34</sup>. Protocols for smokers with

a history of mental illness who seek tobacco dependence treatment in settings other than mental health facilities and clinics would follow standard tobacco dependence treatment guidelines. Adjustments in these protocols are needed to take into account special risks to achieving abstinence if we are to improve treatment of smokers with a history of mental illness<sup>40</sup>.

Thus, tobacco causes addiction and severe adverse effects on the body and mind not only the subject for scientific study it draws our attention to its public health implications. There has been a notable lack of dialogue between neuroscientists, who use nicotine in their experimentation, and public policy and health researchers, who view nicotine dependence with increasing dismay and see the continued use of tobacco products as a modern day scourge.

## PREVENTIVE MEASURES

In May 1999, World Health Organization's Framework Convention on Tobacco Control (FCTC) provided basic tool for the countries to enact comprehensive tobacco control legislation. In May 2003, 192 member countries adopted the FCTC backing the resolution. Treaty became international law in February 2005 to address the devastating health, social, environmental, economic and psychological consequences of tobacco consumption world-wide. The objective of the treaty is to protect the present and the future generations from tobacco menace.

In April 2003, the Indian Parliament enacted a far-reaching antitobacco legislation, the Cigarette and other Tobacco Products Act banning tobacco smoking at public places and declaring it as a punishable offence. The Act also bans advertising of tobacco products. The rules framed are:

- Prohibition of smoking in public places
- Prohibition of advertisement of cigarettes and other tobacco products.
- Prohibition of sale to minors.

The Act is in force since May 2004 yet the larger picture is truly alarming. India has turned into a potential market for tobacco industry. According to National Organization for Tobacco Eradication (NOTE) 6000 teenagers start using tobacco products in the country everyday<sup>27</sup>. And out of 100 teenagers smoking today, 50 will eventually die prematurely due to tobacco related diseases. Two third of country's smokers begin at an early age and by the time they realize the risk, they become addicted to nicotine posing public mental health menace. It is not surprising that the Indian Government has banned smoking scenes in movies and WHO has emphasized that the physicians treat tobacco addiction along with other morbid conditions.

Health education efforts against tobacco in India are few. Central and state Health Education Bureaus can play important role to counteract the spreading tobacco menace, which can be largely curtailed through prevention and successful quitting as a result of health education. WHO's regional office supported National Tobacco Control Cell coordinates the activities at the national level to develop strategic media plan to provide health education to the masses.

Tobacco demand is quite high in Indian society and this demand can be possibly reduced by highlighting and emphasizing the harm caused by tobacco. It is the need of the hour to teach each tobacco use to say "no" to tobacco.

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