
Psychosomatic Effects of Nicotine (Tobacco) in Man – A review of Research Studies

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Abstract

This review was aimed at drawing the attention of the wider public (with special reference to Nigeria) to the unfavourable effects of nicotine in man. This was done by reviewing the research studies conducted by eminent scholars on absorption, distribution, metabolism (breakdown), elimination, and pharmacodynamics of nicotine in man. Results showed that with regular use of tobacco, nicotine accumulates in the body throughout the day and persists at significant levels. The rate of metabolism of nicotine is highly variable among individuals. Therefore this variable should be taken into consideration when determining the smoking behaviour and the smoke related health risks of habitual smokers. Development of tolerance was observed to be one of the effects of tobacco (nicotine) smoking in man. Also the route and rate of administration may have an important influence on the effects and the extent of development of nicotine tolerance. Such considerations may explain differences in subjective and cardiovascular effects of cigarette smoking and nicotine gum chewing. Smoke-rapid brain-uptake process may explain in part the highly addictive nature of cigarette smoking. The dangers and health-risk implications of tobacco (nicotine) smoking are brought to the knowledge of the Nigerian people and recommendations are made to both the Federal Government and the populace at large for corrective measures.

Introduction

The original work on “metabolism, Pharmacokinetics and pharmacodynamics of nicotine in man” was done by Neal et al, 1987 in California. Clinical observations, historical anecdotes, and testimonies, suggest that at least some users of tobacco (nicotine) are unable to permanently abstain, even when ill health is evident, (Connolly et al, 1986). Nicotine exerts several pharmacological actions such as Central Nervous System (CNS) stimulation, and these actions are found both in man and animals. Questionnaire studies suggest that some people smoke tobacco in order to obtain a stimulant effect (Kumar and Lader, 1981). Tobacco (nicotine) share many points in common with prototypic dependence – producing drugs. The behavioural process is orderly. Tobacco self-administration results in the delivery of a centrally active drug (nicotine), and that drug appears critical in the control of the compulsive behaviour of tobacco users. More specifically, these nicotine – delivery substances produce the same functional relations

between drug administration and measures of abuse liability and dependence potential as do the prototypic dependence producing drugs: morphine and cocaine.

A few other characteristics of tobacco products in general may operate to further enhance the number of individuals afflicted by nicotine dependence:

Nicotine – delivery products are widely available and relatively affordable by masses; the self-administration of such products is relatively well tolerated by Nigerian society; nicotine produces a variety of individual specific therapeutic actions such as mood and performance enhancement and the brief effects of nicotine ensure many opportunities for conditioning to occur as the behaviour is frequently associated with the effects of nicotine and concomitant environmental stimuli.

The above characteristics of nicotine effects stimulated the reviewers into exploring the under mentioned questions, why do people habitually consume tobacco? And how does tobacco (nicotine) use influence the health and behaviour of the habitual users? Answers to these questions begin with understanding the Pharmacokinetics (absorption, distribution, metabolism and elimination) and pharmacodynamics of nicotine in man.

Pharmacokinetics

Absorption of nicotine

Nicotine is distilled from burning tobacco and is carried proximally on tar droplets that are inhaled. Absorption of nicotine across biological membranes depends on pH (Armitage and Turner, 1970; Schievelbein et al, 1973). Nicotine is a weak base, and consequently, in acidic environments, it is ionized and does not rapidly cross membranes (Gorrod et al, 1982; Beckett et al, 1971). The pH of smoke from flue-cure tobaccos which are found in most cigarettes is acidic (pH 5.5). At this pH, the nicotine is primarily ionized. As a consequence, there is little buccal absorption of nicotine from cigarette smoke, even when it is held in the mouth, (Gori et al, 1985). The pH of smoke from air-cured tobaccos, such as in pipes, cigars is alkaline (pH 8.5), and nicotine from these products is well absorbed through the mouth (Amitage et al, 1978 and Russell et al, 1980). Chewing tobacco, snuff, and nicotine gum are buffered to alkaline pH to facilitate nicotine absorption. When tobacco smoke reaches the small air ways and alveoli of the lung, the nicotine is rapidly absorbed independent of pH of the smoke. Armitage and co-workers, measuring exhalation of radio labelled nicotine, found that 82-92% of nicotine in mainstream smoke was absorbed by four habitual non inhalers, and 30-66% by three non smokers (who were instructed to smoke as deeply as possible). The rapid absorption of nicotine from cigarette smoke through the lung is presumably because of the huge surface area of the alveoli and small air-ways and dissolution of nicotine into alveolar fluid which facilitates transfer across cell membranes.

Distribution of Nicotine

After absorption, nicotine enters the blood stream where, at pH 7.4, it is about 69% ionized and 31% un-ionized. Binding to plasma proteins is less than 5% (Benowitz et al, 1982) The drug is distributed extensively to body tissues with a steady state volume of distribution averaging 2.6 times body weight (see Table 1). The pattern of tissue uptake cannot be studied in humans, but it was done by measuring concentrations of nicotine in various tissues after infusion of nicotine to steady state, examining tissue uptake in rabbits (see Table 2). Spleen, liver, lungs and brain have high affinity for nicotine while adipose tissue has relatively low affinity for nicotine. After rapid intravenous injection, nicotine blood concentration falls rapidly due to tissue uptake of

the drug. During this phase, blood concentrations are quite high while tissue concentrations would be expected to still be low. Distribution to brain and heart should be rapid because of relatively high rates of perfusion. Thus, direct effects on these organs are expected within 1 or 2 min. Distribution to muscle is by comparison, predicted to be much slower, but muscle represents a storage reservoir of greater magnitude (see Table 2). The consequence of uptake into muscle is that the blood concentration of drug continues to decline at a rate faster than can be explained by metabolism for 20 or 30 min after administration. Thereafter, the blood concentration declines much more slowly, the rate being determined by rate of metabolism and rate of distribution out of tissues. Smoking represents an exposure similar to that of rapid intravenous injection except that the point of entry into the circulation is through the pulmonary rather than the systemic venous circulation. As a consequence of delivery into the lung, the lag time between smoking and entry into the brain is shorter than that after intravenous injection. Thus, after smoking, nicotine will enter the brain quickly, but then brain levels will decline rapidly as nicotine is distributed to other tissues. The distribution half life (about 8 min) rather than elimination half-life (2 hours) determines the time course of central nervous system effects after smoking.

Table 1: Pharmacokinetics of Nicotine

Half-life	120 minutes
Volume of Distribution	180 liters
Total Clearance	1300 ml/min
Renal Clearance (Acid Urine)	200 ml/min
Nonrenal Clearance	1100 ml/min

Average values, based on data from Benowitz et al, (1978).

Tissue to blood nicotine concentration ratio in rabbits based on measurements after 24hr constant infusion of nicotine. Human simulation based on typical organ mass and partition ratios observed in rabbits. V_D = volume of distribution predicted by simulation.

Table 2

Tissue	Rabbit Tissue: Blood Ratio (R)	Mass (M) (kg)	Human Simulation MxR	% Total Body Nicotine
Blood	1.0	5.4	5.4	4.8
Brain	3.0	1.5	4.5	4.0
Heart	2.0	0.3	0.6	0.5
Muscle	2.0	30.0	60.0	53.1
Adipose	0.5	10.0	5.0	4.4
Kidney	21.6	0.3	6.5	5.7
Liver	3.7	1.7	6.3	5.6
Lung	3.7	1.0	3.7	3.2
GI Tissue	3.5	2.0	7.0	6.2
Spleen	9.3	1.5	14.0	12.4
	Total	53.7	113.0	
		$V_D = \sum MxR / \sum M$ =2.1 L/kg		

Benowitz et al, (1978)

Metabolism

Comprehending the pathways of metabolism of nicotine is important in determining if metabolites contribute to actions of nicotine and in understanding factors that influence rate of metabolism in different people. Nicotine is extensively metabolized, primarily in the liver, but to a small extent in the lung and kidney (Gorrod et al 1975 and Turner et al, 1975). Renal excretion depends on urinary pH and urine flow and accounts for from 2-35% of total elimination (Beckett et al, 1980). The major metabolites of nicotine are cotinine and nicotine-N-oxide. Cotinine is formed in a two-step process, the first of which involves oxidation of the 5-position of the pyrrolidine ring in a cytochrome p450-mediated process to nicotine-1(5)- iminium ion (Brandage et al, 1979; Gorrod et al, 1982). The latter is further metabolized by a cytoplasmic aldehyde oxidase to cotinine. Cotinine is also extensively metabolized, with only about 17% excreted unchanged in the urine (Benowitz et al, 1983; Bowman et al, 1962).

Nicotine – 1- N- oxide is a minor metabolite of nicotine. Oxidation of the nitrogen atom of the pyrrolidine ring is dependent upon a microsomal flavoprotein system (Gorrod et al, 1995). After intravenous injection, 100% of nicotine-N-oxide is excreted unchanged in the urine (Beckett et al, 1971). After oral administration, only 30% is recovered unchanged; the remainder is recovered as nicotine and its metabolites. After rectal administration, less than 10% is recovered as nicotine oxide. These findings indicate extensive reduction of nicotine oxide back to nicotine within the gastrointestinal tract, a phenomenon believed to be related to bacterial action.

Nicotine is excreted by glomerular filtration and tubular secretion, with variable reabsorption depending on urinary pH (see Table 2). In acid urine, nicotine is mostly ionized and tubular reabsorption is minimized; renal clearance may be as high as 600 ml/min (urinary pH 4.4), depending on urine flow rate (4.5). In alkaline urine, a larger fraction of nicotine is un-ionized, allowing net tubular re absorption with renal clearances as low as 17 ml/min (urine pH 7.0). With uncontrolled urine pH, renal clearance averages about 100ml/min, accounting for the elimination of about 10% of the daily intake of nicotine. Because urinary pH is a determinant of elimination rate and, hence, body levels of nicotine, it has been suggested that urine pH may influence self-administered nicotine intake (Schachter, 1978).

Pharmacodynamics

The basic pharmacology of nicotine is extremely complex. Several fundamental pharmacological issues of nicotine in the intact organism are complex and difficult to predict from in vitro and animal studies. This is because nicotine can have effects on multiple neuroeffector system and can affect many or all body organs, the effects of which depend on the prevalent autonomic tone of that particular organ. Effects on various organs may have opposing actions, the net effect depending upon the interaction of the two. For example, it is known that nicotine influences heart rate. Based on in vitro and animal studies, it is known that nicotine can influence heart rate by: action on peripheral chemoreceptors (via the central nervous system), direct actions on the medullary center of the brain, direct release of neuronal norepinephrine, facilitation of catecholamine release in response to neural activation, direct peripheral ganglionic stimulation with resultant cardiac sympathetic or parasympathetic (or both) nerve stimulation, release of epinephrine from the adrenal, vagal responses to nicotine-induced stimulation of the emetic chemoreceptor trigger zone in the Medulla, and/or baroreceptor mediated reflex responses to nicotine-induced blood pressure changes (Comroe, 1960; SU, 1982). It is

obvious why it is difficult to predict from basic pharmacologic studies what the influence of nicotine on heart rate will be in the intact human.

A second basic pharmacologic issue is the nature of the dose-response relationship for nicotine. In classical pharmacology, nicotine is commonly discussed as an example of a drug which in low doses causes ganglionic stimulation and in high doses causes ganglinoic blockade (following brief stimulation) (Comroe, 1960). Dose-response characteristics in vivo are often biphasic as well, although the mechanism is far more complex. For example, at very low doses, similar to those seen during cigarette smoking, cardiovascular effects appear to be mediated by the central nervous system, either via activation of chemoreceptor afferent pathways or via direct effects on the brain stem (Comroe, 1960, SU, 1982). The net result is sympathetic neural discharge with an increase in blood pressure and heart rate. At higher doses, there may be direct effects on the peripheral nervous system, such as ganglionic stimulation, with the release of adrenal catecholamines. With extremely high doses, there may be hypotension and heart rate slowing, mediated either by peripheral vagal activation or direct depressor effects mediated by effects on the brain (Ingenito et al, 1972; Porsius, 1978). Before extrapolating pharmacologic observations from animals to humans, blood concentrations should be measured to ensure that the effects are being studied in a portion of the dose-response curve related to smokers.

A third pharmacologic issue of importance is development of tolerance. Smokers know that tolerance develops to some effects of smoking. Smoking the first cigarette as a teenager is commonly associated with dizziness, nausea and/or vomiting, effects to which the habitual smoker rapidly becomes tolerant. Likewise, in vitro pharmacologic studies, tolerance to various effects develops rapidly, although tolerance may not be complete (Loffelholz, 1970; Steinsland et al, 1975). Studies of the human pharmacology of nicotine necessarily take place in people who have a degree of tolerance prior to dosing with nicotine. The extent of tolerance depends on both the level of nicotine, the duration of exposure to a given level, and the rate of increase of nicotine exposure to a particular organ. In designing pharmacologic studies in man, it is essential to consider recent exposure to nicotine and the degree of tolerance that may be present at the time nicotine is administered. Individual differences in degree of tolerance may be important determinants of individual differences in pharmacologic responses observed in experimental studies.

In the light of the foregoing analysis, it is important to consider not only the actions but also dose-response characteristics and tolerance, as well as pharmacokinetics and metabolism, in interpreting studies of nicotine effects in man.

Cardiovascular Effects

The cardiovascular effects of cigarette smoking have been exposed by the researches carried out. Smoking a cigarette activates the sympathetic nervous system and results, in healthy people, in an increase in heart rate and blood pressure (Cryer et al, 1970), cardiac stroke volume and output (Irving et al, 1963), and coronary blood flow (Bargeron et al, 1957). Cigarette smoke or nicotine causes peripheral vascular changes, including cutaneous vasoconstriction (Freund et al, 1960, and increased muscle blood flow (Rottenstein et al, 1960). Smoking results in increased circulating concentrations of norepinephrine, consistent with neural adrenergic stimulation and epinephrine indicating adrenal medullary stimulation (Cryer et al, 1976). Circulating free fatty acids, glycerol, and lactate concentrations increase. Cardiovascular and metabolic effects are prevented by combined alpha and beta adrenergic blockade, indicating that the cardiovascular

effects of cigarette smoking are mediated by activation of the sympathetic nervous system. Nicotine appears to be the substance in cigarette smoke responsible for activation of the sympathetic nervous system.

These pharmacodynamic observations have potential clinical significance: That low concentrations of nicotine increase heart rate to a maximum suggests that heart rate will increase most with the first few cigarettes of the day but subsequently will not vary in relation to the amount of nicotine consumed; that only partial tolerance develops to heart rate acceleration due to nicotine, suggests that effects on heart rate may persist as long as significant levels of nicotine persist; nicotine blood levels were substantially lower while chewing gum than while smoking customary brands of cigarettes but were as high or higher than levels in subjects smoking low yield research cigarettes. Some what unexpectedly, nicotine gum did not produce heart rate acceleration. Throughout the day, although it did increase blood pressure to a similar magnitude as smoking; with prolonged infusion, nearly complete tolerance developed to heart rate acceleration but not to blood pressure elevation; these observations suggest that the route and time course of delivery of nicotine is an important determinant of nicotine effects.

From the results of above studies one may conclude that there is an element of tolerance that persists throughout the daily smoking cycle and which is lost with prolonged abstinence, but that tolerance is rapidly re-established with subsequent exposure.

The psychosomatic effects of nicotine in man as reviewed by the present authors, on the original work on "metabolism, pharmacokinetics and psychodynamics of nicotine in man" done by Benowitz et al, (1982) is meant to bring to the fore of the Nigerian masses, the Federal and State Governments on the dangers and health-risk implications of tobacco smoking.

Tobacco (nicotine) has had a varied use over its history. It has been used in several forms, including cigarettes, cigars, pipes, snuff taking and chewing. In Nigeria, the use of tobacco has been represented by an increase in commercial-type cigarettes and its derivatives or correlates. Cigarette smoke is a complex mixture of particulate phase and gas phase components. The health-risks associated with tobacco use have implicated lung cancer as caused by low-yield cigarette in addition to nutritional deficiencies or imbalances. Cigarette smoking has been established as a risk factor for a number of cardiovascular disorders including arteriosclerosis, which is the underlying cause of coronary heart disease, cerebrovascular disease and atherosclerotic peripheral vascular disease (1983 Report of the Surgeon General). It has been estimated that approximately 40 percent of the deaths due to coronary heart disease in the United States of America are directly attributable to cigarette smoking. It has been reported that cigarette smoke may be responsible for an unfavourable imbalance in prostacyclin and thromboxane ratios, which would favour platelet aggregation, vascular constriction, and pathogenesis of atherosclerosis (Hirsh et al, 1981). The cigarette smoke alkaloid nicotine has been shown to have acute and chronic effects on the cardiovascular systems (Harrison, 1980); these include an increase in heart rate, systolic and diastolic blood pressures, myocardial contraction, oxygen consumption and excitability, coronary blood flow, and peripheral vasoconstriction. As with other smoke-related diseases, the cardiovascular problems appear to be dose related. The longer a person smokes, the greater the health-risk involved.

Implications of the results of these studies for the Nigerian populace

The implication of these findings for Nigerian society appears to be pertinent in view of the recent upsurge of these drugs of abuse in our society. Nigerian nation like most developing nations is faced with harsh socio-economic realities. She is faced with myriads of local and global problems which include tobacco (nicotine) misuse, smoking and self administration of various kinds of drugs of abuse like opium, alcohol, morphine, marijuana, cocaine which contain nicotine. More than half of Nigerian population is under the age of 30 (Ikeme, 2012), therefore, it can be said that the economy of Nigeria is a youth economy. Today's youth will become, in a short decade, tomorrow's parents, leaders, labour force and armies. However, Nigerian youths are confronted with various forms of drug abuse and drug dependence. The problems of Nigerian youths are further worsened by the confusion created by home-videos, bill boards and films. Youths are made to believe that the beautiful and popular are rich (without showing how); drink alcohol, smoke cigarettes which are easily available and affordable. These situations pose great challenges to the very existence of our youths and other individuals in most developing countries especially Nigeria. Furthermore, the unemployed graduates saga in Nigeria who roam about the streets does not help matters either, as some of them organize the youths to venture into one chance bus syndrome in Lagos (a forum through which innocent passengers are robbed inside the bus and pushed down from the bus), armed robbery and restive violence etc.

The proliferation of these drugs of abuse, and their easy reach in the rural villages and urban towns, coupled with their relatively in-expensive nature have rendered our enviable nation almost to an inestimable confusion. The effects on the youths in particular and other questionable individuals in the society have brought about wanton destruction of lives and properties, hired assassins, armed robberies, kidnapping insecurity and "Boko Haran" deadly attacks on the innocent citizens which further worsened the already grave economic situation in the country.

Recommendations

Nigerian youths are pushed into nicotine misuse since they remain without any meaningful means of sustenance. They are confronted with poverty, unemployment, and lack of skills/capacity needed to move the economy forward. Poverty is a driving force for indulgence into nicotine misuse, HIV/AIDS etc. This is because they are faced with unemployment and lack of necessary product skills (Ikeme, 2012). This reality leaves them without any meaningful means of sustenance. To make ends meet, some of these youths indulge in prostitution (both males and females). The home videos recently shot in Nigeria are even worse.

Youthful age is the right time to teach the youths the concept of entrepreneurship to help them develop into wealth creation. Entrepreneurship is the ability to seek investment opportunities (Gana 2001). The entrepreneur takes risks, is focused and energized by certain inner drives. Getting Nigerian youths empowered to acquire skills and ideals for the sake of creating employment for self and others has become a critical challenge for the development of small, medium and large scale businesses that will later metamorphose into national development.

The Federal Government may proscribe these drugs of abuse and dependence including smoking cigarette to create artificial scarcity and make them not easily

affordable. The government can institute long term sentence for offenders (from 10 to 20 years of imprisonment) to serve as a deterrent to others.

Government will endeavour to create more job opportunities for graduates and grant soft loans to entrepreneurs without appendages or collaterals. Everybody must be prepared to make meaningful sacrifice for the good of the nation.

Conclusion

From the research studies reviewed and evaluated, the following conclusions were reached which have several implications with respect to the neurobiology of nicotine and tobacco smoking and chewing of nicotine gum on the health-risks in man:

Quantitative metabolism studies account for only a fraction of the metabolites generated from nicotine. The possibility that unidentified metabolites contribute to the pharmacologic actions of nicotine remains strong.

Pharmacokinetic studies indicate that with regular use of tobacco, nicotine accumulates in the body (and presumably the brain) throughout the day and persists at significant levels overnight.

The rate of metabolism of nicotine is highly variable among individuals. The rate of elimination may be an important determinant of smoking behaviour and possibly of tobacco-smoke related health risks.

Pharmacodynamic studies indicate a nonlinear dose-effect relationship for some (e.g heart rate) but not all responses. The consequence is that many of the cardiovascular effects of smoking, as observed throughout the day, are not dose dependent. This may explain in part why there is a poor correlation between changing yields of cigarettes in the past decades and the smoke related risk of coronary heart disease.

Substantial and rapid development of tolerance to subjective effects (primarily stimulation) and heart rate acceleration occurs during nicotine infusion. Some tolerance reverses after overnight abstinence, but a degree of tolerance persists for days. Short and long-term tolerances need to be considered in planning and interpreting studies of the pharmacology of nicotine.

The route and rate of administration may have an important influence on the effects and extent of development of tolerance to nicotine, such considerations may explain differences in subjective and cardiovascular effects of cigarette smoking and nicotine gum chewing. The smoke-rapid brain-uptake process may explain in part the highly addictive nature of cigarette smoking and other drugs of abuse like marijuana (Indian hemp) morphine and cocaine, and these drugs of abuse have found their ways into the fabrics of Nigerian society, which is a serious danger sign for the inhabitants of such a nation with the recent trend of Nigerian youths having upper hand in the use and application of these dangerous drugs. Where then lies the future of this nation if thus ugly trend is allowed to persist.

There is strong evidence suggesting that nicotine is euphorogenic and serves as positive reinforces to maintain cigarette smoking in man which expresses the strong nature of addictive liability potential of nicotine. When compared with other drugs of abuse, nicotine has been found to produce a profile of subjective reactions in man that is very similar to that produced by morphine and cocaine (Jasinki, 1982).

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