The Biochemistry and Pathology of Nicotine Dependence

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Abstract

As the most preventable cause of death and disease in the U.S., nicotine dependency claims 400,999 deaths annually (approximately 40% of all preventable deaths). The pharmacology of nicotine and other psychoactive constituents of tobacco make it a more potent mood and behavior-altering substance than heroin, cocaine, alcohol, and marijuana. Nicotine itself is responsible for some of the pathologic effects of tobacco; other substances like cadmium, carbon monoxide, acetaldehyde, and radioactive metals contribute to the toxicity of this plant. A review of the diseases and conditions related to nicotine dependency are included in this literature review.

> *"Tobacco smoking is probably the most addictive and dependence-producing form of object-specific self-administered gratification known to humankind."*
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> –M.A.H. Russell, Addiction Research Unit, The Maudsley Hospital, London, England (1).

There are many sobering facts about nicotine addiction and its relationship to human health and the economy of health care in the world. To create a context for nicotine addiction treatment in naturopathic medicine, it is important to explore the problem.

Tobacco use has been identified as the most preventable cause of disease and premature death in the U.S., responsible for 400,000 deaths yearly–19% of all deaths and 40% of all preventable deaths. Tobacco is responsible for more deaths in this country every year than all other drug dependencies, AIDS, homicide, suicide, and motor vehicle accidents combined (2). To compare that estimate with alcohol and all illicit drugs, only 135,075 users die annually as a result of the use of alcohol, cocaine, and heroin (3). Smoking is the leading cause of death from civilian fires (1,303 people in 1988) and, in 1990, smoking-related illnesses accounted for 1 in 5 deaths and more than 25% of all deaths in people aged 35 to 64 (4).

A smoking employee costs his or her employer about $4,000 per year in both direct and indirect costs. The direct and indirect costs of nicotine dependency to the community total about 68 million dollars annually (5). These are costs that are passed on to all of us in the higher cost of living, health care costs and insurance fees, lost productivity, taxes, and emotional health (nicotine addiction, like any other drug addiction, affects the emotional welfare of everyone around the user).

Smokers have a death rate 30-80% higher than non-smokers (6). Some of the related health problems smokers face include a 4 to 5 times greater risk for liver cirrhosis, an increased risk for peptic ulcer (and a seriously increased risk for fatality as a result of internal bleeding), ten different cancers, peripheral vascular disease, gastritis, infertility, periodontal disease, chronic stomatitis, increased incidence of respiratory and ear infections, premature menopause, amblyoplia, dysmennorhea, headaches, and the well known increased risk for cardiovascular disease (7). Passive smoking via exposure to environmental tobacco smoke (ETS) is responsible for more than 53,000 deaths yearly. The heart disease deaths combined with the cancer deaths attributable to environmental tobacco smoke make passive smoking the third leading cause of preventable death, behind smoking and alcohol abuse (8). Nonsmoking spouses of smokers have a 20% increased risk of lung cancer and women who are exposed to ETS for 3 or more hours per day carry the same elevated risk for cervical cancer as do

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women who smoke (9). Passive smoking is also linked with sudden infant death syndrome, childhood otitis media, enuresis, asthma, and bronchitis (9). In 1988, 2,552 infant deaths were attributable to their mother's nicotine dependency (5). Smoking, both active and passive exposure, is the reason that lung cancer surpassed breast cancer in 1987 as the leading cause of cancer deaths in women (8).

Despite this alarming reality, about 28% of American men and 23% of American women are still regular smokers (4). Even though the number of Americans who smoke appears to have gone down from 42% in 1965 to 25.5% in 1994, the number of cigarettes produced in the United States is equivalent to that in 1963: 525 billion per year (10). According to the World Health Organization, 2.5 million people internationally currently die from tobacco use each year. WHO predicts that by 2025 there will be 10 million deaths per year. If WHO estimates are correct, 500 million people now alive, that is 10% of the world's population, will die of diseases caused by nicotine addiction (5).

Why is tobacco use, in all its various forms, so tenacious even in the face of such global consequences? The answer lies in the pharmacology of nicotine and other mood-altering constituents of tobacco. The pharmacologic action of nicotine is pervasive, it binds to cholinergic receptors in the central nervous system, the adrenal medulla, neuromuscular junctions, and all autonomic ganglia (11). The specific receptors that nicotine binds to, the nicotinic acetylcholine receptors, are very diverse and have different chemical conductance rates for sodium and calcium and different sensitivities to nicotine and nicotine metabolites (11,12). This may be one of the reasons for nicotine's diverse actions in each individual and nicotine's ability to create opposing effects depending on how it is used. Nicotine is the only known drug that can act as a stimulant or a depressant depending on how it is titrated (inhaled) (13). Rapid, superficially inhaled nicotine generally results in the release of ACTH and concomitant release of epinephrine from the adrenal gland, resulting in an amphetamine-like effect. Conversely, slow deep inhalation results in a predominant beta-endorphin release, resulting in a sedative, barbiturate effect. This is, of course, done unconsciously by the smoker at different times in response to different needs, to achieve differing effects. This ability of nicotine is unique and is one of its strongest dependency producing qualities (13).

The majority of nicotine's effects are mediated through the central nervous system. Smoking is a very effective method of administering nicotine to the CNS. Nicotine from a cigarette reaches the brain in 3-7 seconds if it is inhaled. Intravenous nicotine would take twice as long (5). Nicotine in the brain can affect nearly every neurotransmitter and CNS hormone. Nicotine acts on the CNS and the adrenals to produce increases in catecholamines, dopamine, serotonin, GABA, vasopressin, growth hormone, ACTH, cortisol, neurophysin I, glutamine and beta-endorphin (11). At the same time, nicotine reduces CNS production of LH, FSH, and prolactin (11). Because of the rapid elevation of nicotine in the brain within seconds of inhalation, and the immediate and powerful dopaminergic stimulation in the nigrostriatal regions of the brain, nicotine can produce powerful changes in mood and behavior. The ability of a drug to quickly and effectively stimulate dopamine production is apparently one of the strongest determinants of its addictive capacity (14). It is perhaps this pharmacological effect that makes nicotine 1000 times stronger than alcohol, 5 to 10 times stronger than heroin and cocaine, and 10-100 times stronger than barbiturates in its ability to alter mood and behavior (13). Nicotine's ability to release three major neurotransmitters in the brain, dopamine, norepinephrine, and serotonin, resemble the effects of some antidepressant medications and are probably used by smokers for that purpose (11).

In addition to mood alteration via brain neurotransmitters and hormones, nicotine is a powerful sympathetic stimulant. This produces the obvious: increases in heart rate, blood pressure, cardiac stroke volume and output. A smoker's heart will produce 10,000 extra heartbeats for every pack he or she smokes (15). The phenomena of accelerated heart rate can persist for as long as moderate levels of nicotine are found in the user's body, sometimes as long as overnight (16). The cardiovascular effects of nicotine are important clinically in the pathology of acute myocardial infarctions, especially if smokers who are using nicotine patches are concurrently smoking. The FDA has investigated the possible link between nicotine patches and smoking as a result of incidences of heart attacks in smokers who were on nicotine patches while infrequently smoking (17). Nicotine patches now carry warnings that use in patients who have cardiovascular disease or who are pregnant should be carefully considered. There is considerable debate in the health care community about the use of nicotine-replacement as a smoking cessation strategy due to the lack of long term research on its use and the fact that nicotine itself has adverse health effects (17).

Because nicotine causes vasoconstriction and induces platelet aggregation, it has long been recognized as a cause of impaired wound healing and may cause ischemia in damaged tissue (18,19). Smoking a single cigarette causes a 42% decrease in bloodflow to the fingers (20). Thromboangitis obliterans (Buerger's disease), a smoking-related disease involving ischemia in the extremities and usually necessitating amputation in chronic stages, results from the vasospasms induced by nicotine (21).

Nicotine is responsible for the increased incidence of peptic ulcers seen in smokers; smokers have difficulty healing from peptic ulcers due to increased basal acid secretion, and lowered mucosal blood flow (7). Smokers also have a higher incidence of gastritis, a lower secretion of pancreatic bicarbonate and a lowered transit time (18). It is commonly accepted in medicine that as long as a smoker continues to use nicotine, the healing of his or her ulcer will be very difficult, if not impossible (7).

Nicotine, mainly due to its direct effect on adrenal function, increases the production of several hormones. One of them, adrenaline, can increase up to 83% in the urine after just two cigarettes (22). Corticosteroids are also elevated post-smoking for as long as 2 hours (23) and may exert a mood-altering effect in addition to contributing to osteoporosis (11). Adrenal medullary hormones, released in more frequent and higher amounts as a result of nicotine use, may have the ability to exacerbate hyperthyroidism and insulin-dependent diabetes (18). There

are correlations between smoking and Graves' hyperthyroidism both in incidence and severity and smoking appears to worsen hypothyroidism (9).

Although nicotine alone has pathological effects, there are over 5,000 chemical substances in combusted tobacco, 43 of which meet stringent criteria for the definition of a carcinogen by IARC standards (24). To illustrate the seriousness of the problem of tobacco pollution, in 1988 Chilean grapes were banned from the U.S. because two grapes were found to be contaminated with a few percent of the amount of cyanide found in one cigarette (5). Tobacco also contains another psychoactive compound: acetaldehyde, the principal aldehyde in tobacco smoke. Acetaldehyde is the first metabolite of alcohol and is stored in the CNS where it is further metabolized to tetrahydroisoquinoline (THIQ), which is a well known compound to researchers in the field of alcohol metabolism. THIQ has opiate effects in extremely small doses and is considered a very addicting chemical (25). Acetaldehyde is also a toxic compound due to its oxidant properties, and is implicated in cardiac and pulmonary disease as well as alcoholic cerebellar degeneration (26).

Cadmium, a heavy metal found in tobacco smoke, is responsible for the development of several disease states at high levels of exposure. Smokers appear to carry twice to ten times the cadmium burden of nonsmokers (27). The biological half-life of cadmium is longest in the kidneys and liver where it may remain for 60 years (28). Kidney damage includes proximal tubular dysfunction, Fanconi Syndrome, consequent osteoporosis, calcium oxalate kidney stones, slight anemia, and anosmia (29). Cadmium exposure also causes renal hypertension and may be the reason for hypertension in the percentage of smokers who are hypertensive (28). Cadmium also accumulates in the lens and in the testicles and may be related to the etiology of cataracts and testicular necrosis that are known to occur in long-time smokers (27).

Tobacco also contains certain radioactive elements, the most common being Polonium 210. This is a uranium breakdown product that comes from high uranium phosphate fertilizer. Much of our agricultural phosphate fertilizers are obtained from uranium and other mine tailings (30). The plant is a good selective absorber of polonium 210 and it remains intact when tobacco is combusted. Polonium 210 is considered a carcinogen and reacts synergistically with other carcinogens like benzopyrene and radon daughters. The amount of radiation exposure a smoker obtains from an annual one-and-a-half-pack daily smoking habit is the equivalent of aproximately 300 chest x-rays (31). Tobacco also contains radium-226, lead 210, and potassium-40 (32).

Any discussion of the effect of tobacco on the human reproductive system must include the effects of compounds in tobacco like aldehydes, cadmium, and radioactive elements, because they affect the liver and the liver controls metabolism, synthesis and conjugation of hormones through the P450 enzyme system. There is evidence that carbon monoxide, nicotine and other constituents of tobacco induce or block specific hydrolase and aromatase enzymes that allow for the synthesis of different forms of estrone and estriol from estradiol. Female smokers appear to have difficulty making the active form of estrogen (16a-hydroxyestrone) and instead produce estrogen (2-hydroxyestrone) that has little peripheral estrogenic activity (33). Although many studies have shown that female smokers have the same quantity of urinary estrogens as their nonsmoking counterparts, these studies have not evaluated the biological activity of these estrogens (33). The enzyme that allows for the production of progesterone from pregnenalone is also inhibited by carbon monoxide and second trimester pregnant smokers have been shown to exhibit lower progesterone and estriol levels while post-menopausal women have shown slightly higher levels of progesterone (34).

Male smokers appear to have higher levels of estradiol, estriol, androstenedione and higher mean DHEA levels than their nonsmoking counterparts. Their testosterone levels, however, are roughly equivalent (35). The results of these sex hormone studies suggest that the antiestrogenic effect of tobacco in woman is mediated by adrenal hormones and that when smoking alters the androgen/estrogen ratio, it makes men appear feminized and women more male in their hormone profiles (35).

The importance of tobacco's effects on sex hormones is also relevant in the area of osteoporosis. Studies done in older male smokers show greater rates of bone loss (39% greater in the wrist) (36), and male smokers in one study who smoked one pack per day lost bone mass at twice the rate of non-smokers. Bone loss in this study appeared to occur even with smokers who used 10 cigarettes a day (37). Women who smoke enter menopause an average of 2 years early, have higher rates of vertebral fractures, and have lower bone mass than non-smoking post-menopausal women (38). Female smokers do not appear to benefit from estrogen replacement therapy (39).

Women between the ages of 13 and 25 are now the fastest growing segment of the population, so their health concerns are growing rapidly (4). Fully 1/3 of all cervical cancers are estimated to be caused by mutagens in cigarettes that are absorbed and secreted in cervical mucus (18). The risk for this cancer is equivalent in women who are, as stated above, receiving these mutagens, not as smokers themselves, but as passive smokers (9). Women who use oral contraceptives and smoke increase their risk for myocardial infarction by a factor of ten (40). Women who smoke more than 20 cigarettes daily are 3 times more likely than non-smokers to take more than a year to conceive, with 3 times the risk of primary tubal infertility, and a greater risk for ectopic pregnancy (40). The risk for coronary heart disease and acute myocardial infarctions may be up to 10 times higher in young women who smoke due to the multi-factoral nature of CVD that includes oral contraceptives and substance abuse (40). In countries where smoking has been common for women for several decades, over half of all deaths from cerebrovascular disease in women under 65 are directly related to tobacco use (40).

It is undeniable that nicotine addiction is not only the most preventable cause of disease and death in this country, but also the most preventable cause of disease and death in the physician's office. It is also obvious that simply stopping smoking is not enough to drop an ex-smoker's health risks to that of a "never-smoker," although smokers who quit before age 50 have half the risk of dying in the next 15 years compared with those who continue

to smoke (40). The greater our understanding of the long-term effects of nicotine dependency, the better able we will be to change the lives and prevent early deaths of the 3,000 people who die daily in the U.S. as a result of this disease.

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Biography

Lyn Patrick, ND, a 1984 graduate of Bastyr University, has spoken nationally on the subject of nicotine dependency and worked as a consultant for Sierra Tucson, a nationally known drug and alcohol rehabilitation psychiatric hospital. Dr. Patrick has been in private practice in Tucson, Arizona for the last 13 years.