Nasal snuff: Historical review and health related aspects

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Historical Article

Nasal snuff: historical review and health related aspects

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Abstract
With cigarette smoking declining in the modern world, the tobacco industry has to look for other products that can keep the old customers and attract new ones. Different forms of smokeless tobacco are currently massively promoted and are gaining in importance. Dry nasal snuff – the oldest known form of tobacco in Europe – is one of them. The health risks associated with it are different to those attributed to smoking and oral wet snuff. The nicotine contained leads to dependency. Its resorption rate is similar to that of smoking, so it could be seen as an adequate substitutional therapy. The risk for cardiovascular diseases is lower, compared to that for smokers. Chronic abuse leads to morphological and functional changes in the nasal mucosa. Although it contains substances that are potentially carcinogenic, at present, there is no firm evidence, relating the use of nasal snuff to a higher incidence of head and neck or other malignancies.

Key words: Tobacco, Smokeless; Nicotine; Nasal Mucosa

Introduction

Smoking is a widely recognized major risk factor for lung cancer, upper aerodigestive tract neoplasms and other malignancies, cardiovascular, gastrointestinal and neurological diseases.[1–6] The large majority of smokers are well aware of the devastating effects of this habit on their health and wish to quit. Modern society's intolerance to smoking grows and many different restrictions have been currently imposed on smokers both in the occupational and social environments.[7,8] Quitting smoking is the optimal way out, but it is difficult to achieve, because of the effects of nicotine withdrawal. An acceptable alternative to quitting is to have strategies for reducing the harmful effects of smoking. These may be based on the substitution of cigarette smoking for other ways of nicotine delivery. There are currently four pharmaceutical forms of nicotine replacement – patches, gum, nasal spray and inhaler.[9,10] 'Natural' smokeless tobacco products (tobacco is administered without being burned) are supposed to be helpful as well.[6,11–13] Such products have been massively promoted by the tobacco industry in the last decade and now they present the only growing market segment.[14–17] One of them is nasal snuff – probably one of the oldest forms of tobacco use. The aim of the present paper is to make an overview of the health consequences of nasal snuff.

In the beginning in Europe was snuff

Tobacco, a plant naturally growing all over the Americas, had been cultivated by the native Indians centuries before Christopher Columbus, who in 1492, when searching for a new way to India, brought 'by mistake' the Old and the New Worlds together. The explorers were frightened by the Indians who 'drank fire' (smoked tobacco). However this was only one of the ways the natives used the tobacco plant – they also prepared enemas from it, smoked it in a pipe, chewed it or sniffed it in the form of a powder of dried, crushed tobacco leaves.[5,18] One of the hypotheses for the etymology of the name 'tobacco' is that in a local Indian language 'tobago' means a special pipe, used for inhaling it through the nose. In Europe sniffing tobacco quickly became popular especially in the Spanish and French aristocracy. It was in 1566 the French ambassador to Portugal Jean Nicot (1530–1600), personally convinced of the tobacco's medicinal properties, sent snuff to Catherine de Medici, Queen of France, to treat her migraine headaches. She later decreed tobacco to be termed *Herba Regina*.[18] Apparently this new drug had a beneficial effect on the Queen's disease. Later the most important alkaloid contained in this plant was named after Mr Nicot – nicotine. King George III's wife – Queen Charlotte – was known as 'Snuffy Charlotte' because of her passion for nasal snuff

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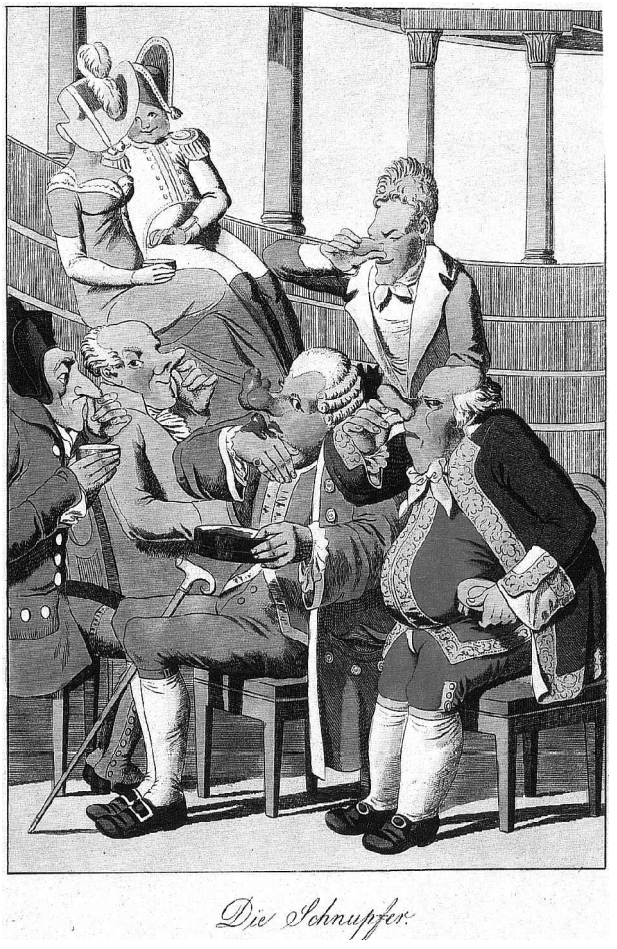

FIG. 1
Caricature of snuff takers. Artist unknown circa 1818.

(Figure 1). It is known that Napoleon sniffed up to over seven pounds a month (1 pound = 16 oz = 0.45 kg). Another passionate snuff user – Admiral Lord Nelson – denied Napoleon his Eastern Empire, and crippled him at sea by winning the Battle of the Nile on July 28th 1798. Snuff also had bad times and opponents – in 1624 Pope Urban VIII threatened excommunication for snuff users, because sneezing was thought to be too close to sexual ecstasy.

Nasal intake of snuff produces a unique short lasting feeling of lightheadedness or slight dizziness, which is not observed in smokers or after oral intake. Another non-pharmacological reason for the snuffers to find their habit significantly more enjoyable than smoking, is probably the fact that smokers have in mind the health risk attributed to smoking.[12] Nasal application of dry snuff comprises intricate sensoriomotor rituals, which provide further motivation for the user.[19] The snuffers place the substance in the anatomical snuff-box (between the tendons of extensor pollicis longus and extensors pollicis brevis) and inhale consecutively through both nostrils (Figure 2). The most popular use of snuff is to take a pinch between the thumb and the forefinger and sniff it into the nose. There are pipe smokers who add a sprinkle of their favourite snuff into their burning bowl of pipe tobacco for an added aroma and nicotine boost.

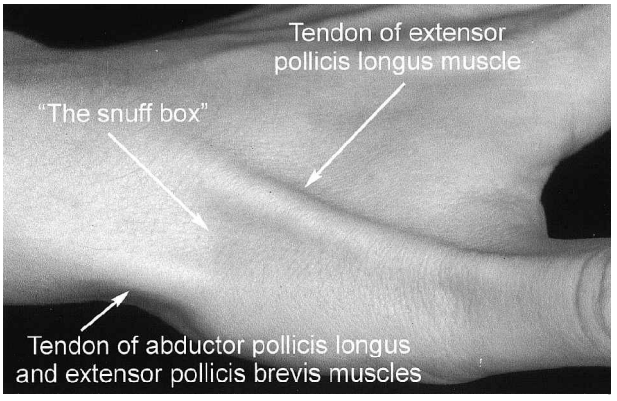

FIG. 2
The anatomical snuff-box (tabatière).

Snuff remained the predominant form of tobacco use throughout the world till the 19th century, the amount used exceeding that for smoking (with a pipe or as a cigar) and for chewing (plug and leaf).[5,17,18] Along with this the production of snuff bottles, boxes or bags was a profitable business for many craftsmen. In Europe and China snuff boxes and bottles were not just simple containers, but highly ornamented objects of art, worn by their possessors as jewellery, or were given as valuable gifts.

The shift towards cigarettes came at the end of the 18th century as the tobacco industry looked for ways of utilizing the scraps left over from the other products. Rolling cigarettes manually was a relatively slow and labour intensive process. The point of no return came with the invention of the cigarette rolling machine by Bonsack in 1880, which could produce up to 120 000 cigarettes per day.[5] The invasion of the cigarette was further speeded up by the introduction of a convenient source of fire – matches. In 1864 Alexander Lagerman constructed an automated machine for their production so their use spread very quickly. In this way the 'noble snuff' slowly gave way to this relatively new occupation – smoking.

Nowadays, when smoking has the characteristics of a pandemic, the use of smokeless tobacco could be defined as endemic, and that of nasal snuff – sporadic.[14] Smokeless tobacco comprises a variety of tobacco-containing products, that are often region-specific. The majority of them are made of *Nicotiana rustica*.[4] There are two major groups of smokeless tobacco products: for oral use – plain tobacco leaves for chewing, American snuff (fermented), Sudanese toombak (with sodium bicarbonate), Indian betel quid (mixed with lime), naswar, gudakhu; for nasal use – the classical rapè from Brazil, English dry snuff, Bayerischer Schnupftabak (Bayrischer Koks), Zulu dry snuff, Sudanese sautè (the first form of tobacco product introduced in this country), 'liquid snuff' in Kenya, burnuthi in Georgia.[4,20,21] People regularly taking snuff account for lower than one per cent of all tobacco users. Sweden has always been a region of particular interest with a more than 300-year-old tradition of producing and using snuff and currently 20 per cent of the Swedish population regularly use snuff.[17] The

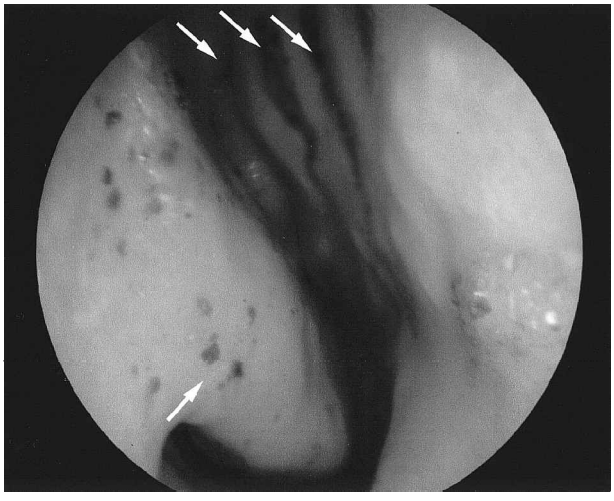

FIG. 3
Snuff particles transported by the mucociliary clearance (arrows) and rests on the inferior turbinate.

predominant form used here is the Swedish moist snuff (snus), which is a non-fermented tobacco product for oral use and should not be confused with dry snuff for nasal use. Other regions with considerable use of smokeless tobacco include the USA, India, Bangladesh, and Southeast Asia.[14]

The 'non-burning' tobacco

The major difference between cigars, cigarettes, pipe and the smokeless forms of tobacco is the absence of carbon monoxide, oxides of nitrogen and tar – all of them being products of the process of burning.[16,19] The composition of smokeless tobacco of the same or analogue kind varies in different countries all around the world.[20] This applies for dry snuff as well. The Zulu snuff produced in South Africa contains charred aloe stems, which give a higher level of the carcinogenic benzpyrene.[16] English and German nasal snuff brands are produced with a wide variety of flavours, including spearmint, raspberry, apricot, lavender etc. In some brands menthol is added. It stimulates the cold receptors and produces a false sensation of decongestion and improved airflow as in medications for the common cold.[22] In comparison with dry snuff for nasal application, wet snuff for oral application contains more nitrosamines and polycyclic aromatic carbons.[16]

It is all about nicotine

Nicotine is the main psychoactive substance in tobacco. The particular properties of this alkaloid are responsible for the typical behaviour of smokers (physical dependence, addiction and habituation) and the control of tobacco use. The nicotine level in the end product is manipulated by the tobacco industry in order to maximize the customer addiction.[7,8] Smoking cigars, cigarettes, pipe, sniffing or chewing are only different forms of delivery of nicotine to the system. In cigarette smoking the nicotine is absorbed through the lungs. Cigar smokers 'puff' it mainly with their mouths and tend not to inhale the smoke, so here the absorption occurs through the oral mucosa as in dipping or chewing tobacco.

When sniffed, the fine tobacco powder is distributed on the surface of the nasal cavity and does not reach other segments of the respiratory system (Figure 3). The nasal absorption of the nicotine is influenced strongly by the pH of the snuff. If alkaline the nicotine is completely protonated and the rate of absorption is very high.[20] These three ways of nicotine administration (through the lung, oral or nasal mucosa) differ significantly in terms of speed. The blood-nicotine level rises most quickly after sniffing or cigarette smoking and is almost four times as slow in cigar smoking.[12,19] It is this nicotine peak that hooks cigarette smokers to their habit. That is why nicotine substitutional therapy, based on nasal nicotine administration with commercially available sprays is considered optimal as means of promoting smoking cessation.[9] In nasal application of snuff or nicotine sprays the blood nicotine peak mimics that of cigarette smoking. On the other hand, the 24 hours average blood concentration of nicotine after nicotine nasal spray is lower than in cigarette smokers, meaning less negative impact on the biomarkers for cardiovascular disease.[9]

Cardiovascular aspects

From the 2500 to 3000 different chemical substances inhaled when smoking, polycyclic aromatic hydrocarbons, the tobacco-specific nitrosamines nitrosonor-nicotine (NNN), 4-(methylnitrosoamino)-1-(3-piridyl)-butanone) (NNK), carbon monoxide, anabasine and cotinine are related to higher cardiovascular risk.[14] Tobacco taken in the form of snuff is considered far less dangerous than smoking. Fibrinogen – a component of the coagulation system and a marker for the risk of coronary heart disease is more elevated after smoking than after smokeless tobacco administration.[9] Snuff does not promote atherosclerosis, does not increase the risk of myocardial infarction and has the same arrhythmogenic effect as the other forms of tobacco intake, the latter having minor clinical relevance.[14] The increased release of catecholamines and the increased blood coaguability are most probably related to smoke components other than the nicotine.[9,12] Nevertheless abuse with nasal snuff or nicotine-containing therapeutic sprays may lead to life-threatening arrhythmias, first because of the doses administered, and second because of the extremely high absorption rate.[9,25]

Effects of dry snuff on the nose

There are very few clinical reports on the problem, because of the limited spread of this form of tobacco abuse today. Probably the physicians from earlier times were more familiar with the snuff-induced changes in the nose. The earliest report found is from the beginning of the 20th century – an era when nasal snuff use was already in decline. In Germany the local form of dry nasal snuff (Bayrischer Koks) was known to cause oedema of the mucosa and the

submucous conjunctive tissue of the turbinates, that did not respond to adrenaline.[23] Recently, Harrison observed in 63 regular long-term users snuff rests in the middle meatus, atrophy of the middle and inferior turbinates and metaplasia of the ciliated columnar to squamous epithelium. In no patient did the biopsy show malignancy.[16] Chetan confirmed these observations and found that snuff inhibits the nasal mucociliary clearance.[24] Nicotine together with lobeline causes vasoconstriction of the cavernous sinusoids with airway enlargement, vasoconstriction of the arterioles with mucosal ischaemia and increased mucosal secretion.[24] Klimek *et al.* proved that this alkaloid is active not only in neuronal cells with specific acetylcholine receptors, but also in the non-excitable nasal epithelium cells.[1] The nicotine acts on the cytoplasma and the intracellular Ca^{2+} channels rather than on a still undefined extracellular receptor. In effect endocytosis, membrane surface area reduction and decrease of the number of the amiloride-sensitive NA^{+} channels occurs, leading to increased water content in the mucus. This is obviously the mechanism which explains the mucolytic properties of tobacco, known and already used in therapy early after the introduction of the plant to Europe. *In vitro* experiments with cartilage explant cultures showed that nicotine could increase cartilage destruction locally or systemically (in the whole body) by influencing the levels of inflammatory mediators. The exact mechanisms of this effect are to be further investigated.[26] Recently Dursun reported a case of blepharospasm improved by nasal nicotine spray, but the underlying mechanism is unknown.[27] In Europe, there were cases of lead intoxication in nasal snuffers. The presence of lead was due to improper packaging and storing.[28]

Does dry snuff cause cancer?

Tobacco smoking is a widely recognized risk factor for cancer of the lungs, the upper airways and the digestive tract.[10,29] In smokers the likelihood for head and neck malignancy is increased fourfold.[4] The effects of smoking on the incidence of cancer are similar for cigarette, cigarillo, cigar or pipe smokers.[3] When smoking is combined with other risk factors (alcohol abuse, presence of inverted papilloma) the resulting risk for development of local neoplasia rises significantly.[3,4,30] There is evidence, that heat, tar, nitroso-nor-nicotine (NNN), 4-(methylnitrosoamino)-1-(3-piridyl)-butanone) (NNK) and other polycyclic aromatic hydrocarbons are capable of inducing malignancy.[4] Obviously the snuff user is not exposed to those, which are products of burning. NNN and NNK are presented in the rough tobacco, and their quantity rises in the process of preparation of snuff, so that contained in 1 g of snuff is higher than in one cigarette.[2] Both NNN and NNK have been found to be carcinogenic specifically in the nose in the mink, when applied systemically. Their combined administration has stronger carcinogenic effect, than any of them given alone. The carcinogenic effects are partially attributed to substances arising from their metabolism by the nasal cells.[2,21,31] The tobacco-specific N-nitrosamines have distant genotoxic effects as well: administered orally, NNN causes nonspecific DNA damage in the nasal cavity, N-nitrosodimethylamine (NDMA) – in the nasal cavity, on the peripheral blood lymphocytes and the liver.[31] Snuff compounds in interaction with herpes simplex virus type 1 could promote distant tumours in rats.[32] Cadmium is another chemical presented in cigarettes. In heavy smokers the daily absorption could be as high as 3-6 μg/day. It causes olfactory dysfunction and has a systemic genotoxic effect.[33] There are no studies on the cadmium absorption in smokeless tobacco users. The genotoxic and carcinogenic effects of nitrosamines have been studied in animal models, but the extrapolation of the results to carcinogenesis in humans is difficult, because of tissue and animal specificity.[34,35,42] Further, most of these experiments show distant, but no local cancer-promoting effects of N-nitrosamines. Nicotine as a chemical substance is generally considered as having no carcinogenic properties. When applied to head and neck cancer cell lines it does not change the speed of proliferation, but has a significant effect on the susceptibility of these cells to DNA-damaging agents such as cisplatin, ultraviolet or gamma radiation. This is clinically manifested by lower rates of response to cytostatic treatment in patients with head and neck malignancies, who continue smoking during radiation.[29]

The clinical evidence of nasal snuff as a carcinogenic factor in the nose and the paranasal sinuses is not convincing. Of course, when reviewing publications from different geographical regions and even different epoques, we should bear in mind that the ways of preparation and the chemical composition of snuff differs from country to country, from brand to brand as well through the times. The first report on nasal cancer, where snuff was suspected as a causal agent was published in 1761 in England.[21] No other publications from Europe or America have since confirmed these observations. From 265 British patients treated over a 20-year-period for malignancy of the upper jaw none had ever used snuff, while none of the observed 63 snuff users had signs of malignancy.[16] Recent trials on Swedish wet snuff dippers failed to prove increased risk for oral cancer.[3,14,16,36] Other forms of oral tobacco use are, however, strongly related to a higher incidence of local neoplasms.[4,14]

Some of the additives used in the different preparations of smokeless tobacco have an exceedingly high carcinogenic potential.[14,42] Publications on the incidence of nasal cancer and its relation to taking snuff concern mainly endemic zones in Africa. An elevated incidence of carcinomas of the maxillary antrum in snuff users was described in South Africa Bantu.[21,37,38] There is clear epidemiological data that the use of Zulu snuff in South Africa rises the risk of cancer.[16] In both groups it is the aloe added to tobacco that is suspected to be responsible for this effect.

Other factors acting locally on the nasal mucosa were proved to be carcinogenic. Large studies showed the close relation between adenocarcinoma of the nose and paranasal sinuses to hardwood dust.[39] In the patients exposed, hyperplasia of goblet-cells and cuboid metaplasia are observed. This effect is related only to this particular histological type. Although the authors state the cause of cancer is a combination effect, they do not present any data on the smoking (or eventually sniffing) habits of the study cohort.

Tobacco free or smoke-free

Smoking imposes an important health burden for the individual and has a significant social and economic cost.[8] Nicotine is to be seen as a prototypic drug of abuse. It is the major mechanism of holding the smokers to their habit. The health risks associated with cigarettes and smokeless tobacco are different. Smokeless tobacco has the advantages of eliminating the smoke-related cancer-causing factors, eliminating the risk for passive smokers, and eliminating the risk of burn injuries and death.[19,40] The negative health effects of smokeless tobacco in all its forms are only two per cent of those of smoking.[13] The whole group of smokeless tobacco products are gaining in popularity in the modern world.[16,37,41] The market growth is mainly attributed to the oral use of moist snuff. Nasal sniffing of dry snuff remains a rare practice. Chronic abuse leads to morphological and functional changes in the nasal mucosa. Although it contains many substances that are potentially carcinogenic, there is no epidemiological evidence for increased incidence of local malignancies in habitual snuff users.

Is switching to snuff a better health alternative for the cigarette smoker? Probably only in terms of avoiding the negative health effects associated with the tobacco combustion products on the cardiopulmonary system.[14,19] The most important pathological mechanism – the one of nicotine dependency and abuse – remains. From this aspect dry nasal snuff and nasal nicotine sprays seem to be a better means for substitutional therapy than transdermal patches because of their particular pharmacokinetic properties. Smokeless tobacco users are most likely to quit using tobacco, with the exception of the concomitant users, who on the contrary are less likely to do so.[6] Optimistic data on smokers shifting to smokeless tobacco and even quitting[13] should be very critically evaluated, for they depend on the study model and the goals defined.[6,10,21] The risk of even stronger drug dependency and associated problems is real.

Even if smokeless tobacco could help smoking cessation in adults, in young people (the most vulnerable target of the promoting campaigns of the tobacco industry) it should be seen as a gateway to cigarette smoking concomitant tobacco abuse and addictive behaviour.[8,11,14,15]

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