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Review

Insights into the pathogenesis of nicotine addiction. Could a salivary biosensor be useful in Nicotine Replacement Therapy (NRT)?

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Abstract

Nicotine has gained the attention of the medical community due to its insidious addictive mechanisms which lead to chronic consumption. The multitude of compounds derived from tobacco smoke have local and systemic negative impacts, resulting in a large number of smoking-related pathologies. The present review offers insights into nicotine addiction physiopathology, as well as social and medical implications, with emphasis on its correlation with Advanced Glycation End Products (AGEs). Therapeutic strategies and new approaches to nicotine assessment and cessation treatment are discussed, noting that such strategies could take into account the possibility of slow and gradual nicotine release from a device attached to a prosthetic piece, based on salivary nicotine-concentration feedback. This approach could offer real-time and home-based self-therapy monitoring by the physician and the patient for follow-up and improve long-term cessation treatment success- Graphical abstract.

Keywords : Pathogenesis, nicotine addiction, salivary biosensor, Nicotine Replacement Therapy, NRT

Highlights

- ✓ Smoking addiction has strong pharmacological, psycho-social, and media support.
- ✓ The development of a double-effect salivary biosensor could represent a useful approach in nicotine addiction therapy.

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Introduction

Nicotine, with the molecular formula $C_{10}H_{14}N_2$ and IUPAC name 3-[(2S)-1-methylpyrrolidin-2-yl]pyridine, is a natural alkaloid found in the tobacco plant, Nicotiana tabacum (1). It has been grown in Native America since 1400 BCE and then brought to Europe via King Philip the 2nd of Spain, through his Spanish Chronicler Hernández de Boncalo. The name "cigar" is derived from "cicadas," the insects that caused plague in the tobacco cultures (2, 3). Over time, nicotine has been used in trading, as a ceremonial tool, as a manner of socializing, for pleasure or relaxation, and for its therapeutic potential in systemic diseases. Nicotine's hazard consists in the fact that it is being used both as an addictive substance and as a medication in smoking cessation therapies. The purpose of the present paper is to provide an update regarding the molecular and pathogenic mechanisms of smoking addiction, with emphasis on its correlation with Advanced Glycation End Products (AGEs). We also discuss smoking cessation strategies and include reference to an innovative approach that associates nicotine addiction therapy with a biosensor inserted in a prosthetic piece, used both as a real-time analyzer and as a treatment option.

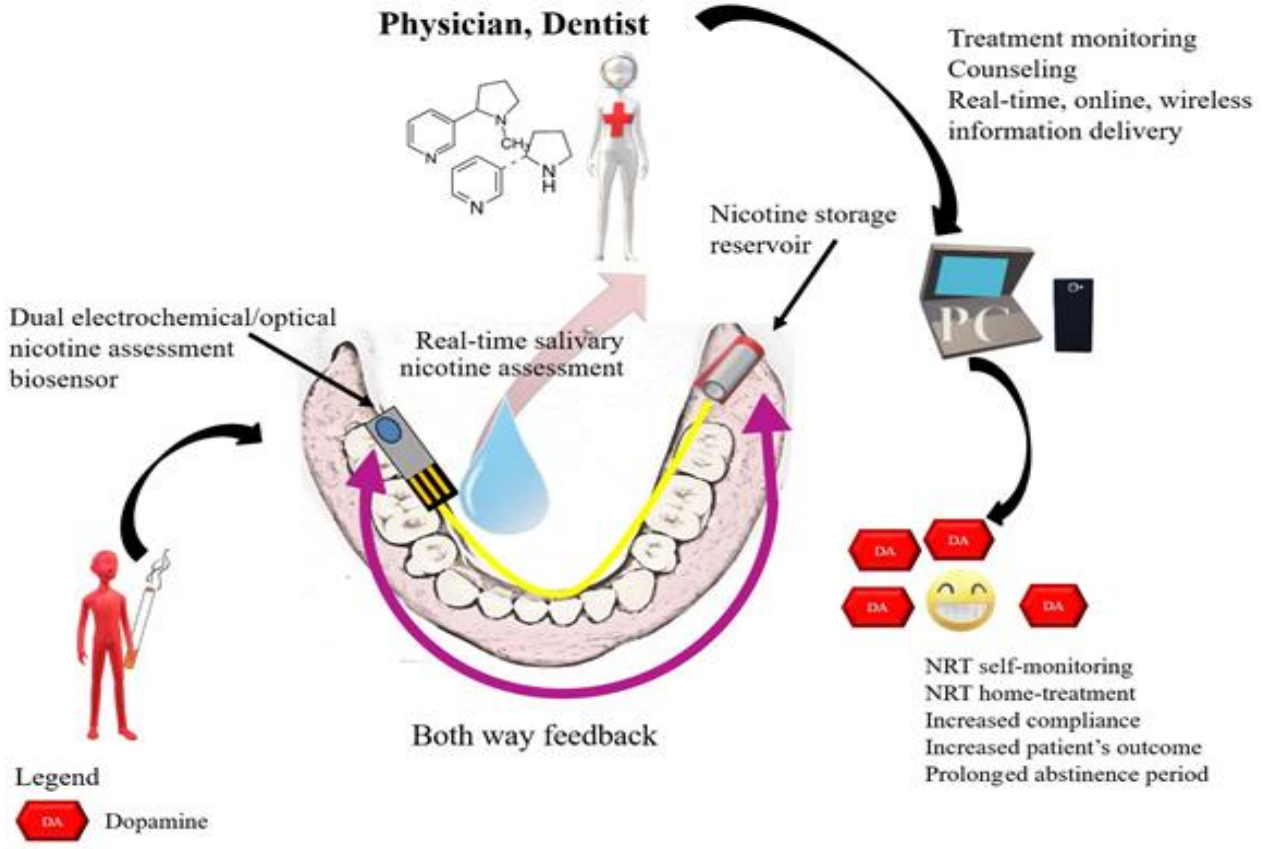
Materials and Methods

This paper is a narrative review of studies involving molecular and pathogenic mechanisms of nicotine addiction, nicotine metabolism, medical consequences, smoke-derived AGEs, cessation treatment options and alternatives, and innovative approaches in nicotine replacement therapy.

The authors used "PUBMED" and MeSH to gather published papers on the above-mentioned aspects. The following keyword associations were used: "nicotine addiction", "nicotine" AND "smoking", "nicotine" AND "pathogenic mechanism", "nicotine" AND "genetic determinism", "nicotine" AND "metabolism", "smoking" OR "nicotine" AND "AGEs", "smoking" OR "nicotine" AND "disease", "smoking cessation" AND "Nicotine Replacement Therapy (NRT)" OR "saliva", "smoking cessation" AND "salivary biosensor".

Inclusion criteria were free full-text articles in English, Spanish, or Portuguese. Human and animal model studies were both included. Only papers from 2000 and onward were included.

There were no exclusion criteria concerning the study design.



Graphical abstract

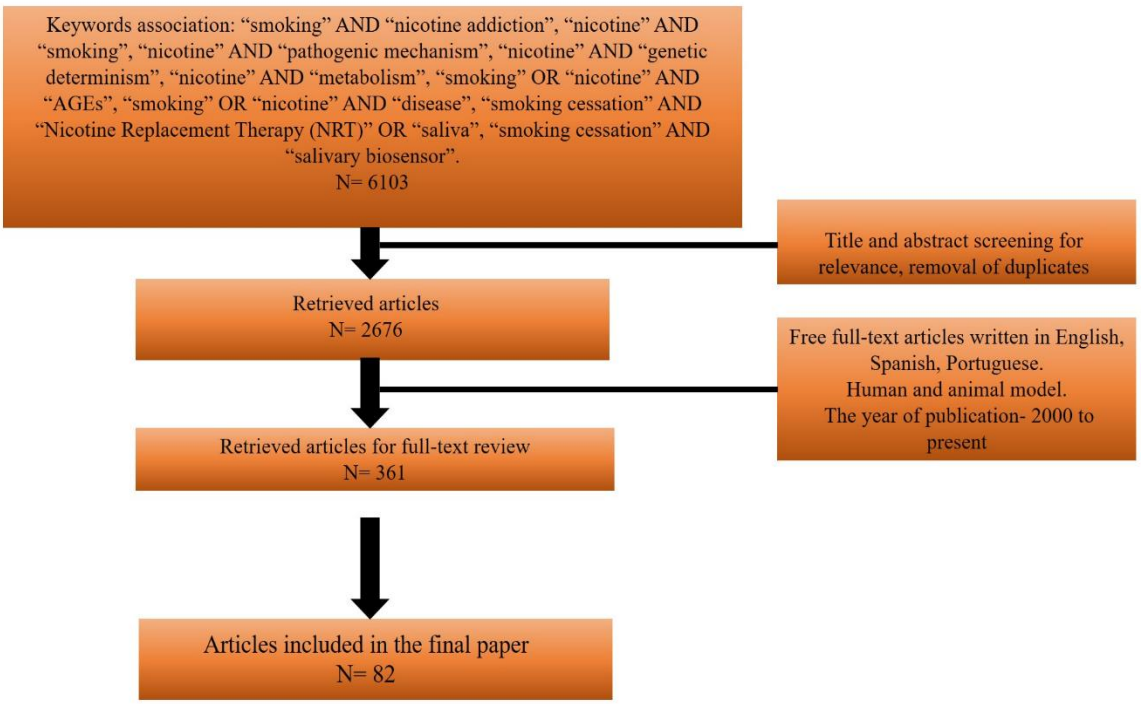


Figure 1. Review extraction - data methodology chart

Results

1. Nicotine addiction

1.1 Nicotine and smoking

Tobacco combustion produces carcinogenic compounds such as benzene, formaldehyde, benzapyrene, carbon monoxide, and cyanide asphyxiants, acrolein, polonium, as well as tobacco-derived pro-inflammatory advanced glycation end-products (AGEs) (4). Lewis et al. identified three types of smoking: active smoking, passive smoking or second hand smoke (SHS), and third hand smoke (THS), referring to the oxidized compounds that turn into carcinogens, along with tobacco-derived nitrosamines, polycyclic aromatic hydrocarbons (PAH), deposited on objects and surfaces humans come in contact with, which can also be inhaled, absorbed through the skin, or ingested (4). THS, also named Residual tobacco smoke or Aged tobacco smoke, has been measured using liquid or gas chromatography, along with mass spectrometry and has a 6-month lifetime in indoor spaces and on surfaces. These residuals induce DNA alteration, cytotoxicity, increased exhaled Nitric Oxide (NO), liver metabolism dysregulation, and thrombosis.

DiFranza and co-workers elaborated a sequence of wanting-craving-needing smoking pattern in chronic consumers (5). The authors stated that in the first stage of nicotine dependence, the early symptom is to want a cigarette, the second stage is an intense craving for a cigarette, which disturbs daily activity and thoughts, and the third stage is needing, an independent intense demand. The period of latency after smoking a cigarette is followed by an active symptomatic stage with manifestations such as anxiety, anger, restlessness, insomnia, difficulty in focusing, and increased appetite. These researchers also found that nicotine dependence is suggested by the shortening of the latency time (6). Cerebral stimuli are driven towards the increase in tobacco input, to maintain balance, and the latency period thus decreases in time, because nicotine's half-life is approximately two hours. Hormones have a modulating effect on nicotine via dopamine, and one hormone, estrogen, is known to influence time perception and cognition. Specifically, time can be perceived as either faster or slower, an important aspect regarding the perceived time period between two smoked cigarettes. Cognition may be affected in terms of decision making and delay discounting (7). Females metabolize nicotine and cotinine faster than men, and their metabolism is influenced by hormonal therapy, with oral contraceptives slowing tobacco smoke-derived compound disintegration (8, 9). A study conducted on active smokers, aged 18 to 65 years, with a history of at least 10 cigarettes/day for at least 6 months, demonstrated that men overestimated the abstinence period compared to women (10) (Figure 2).

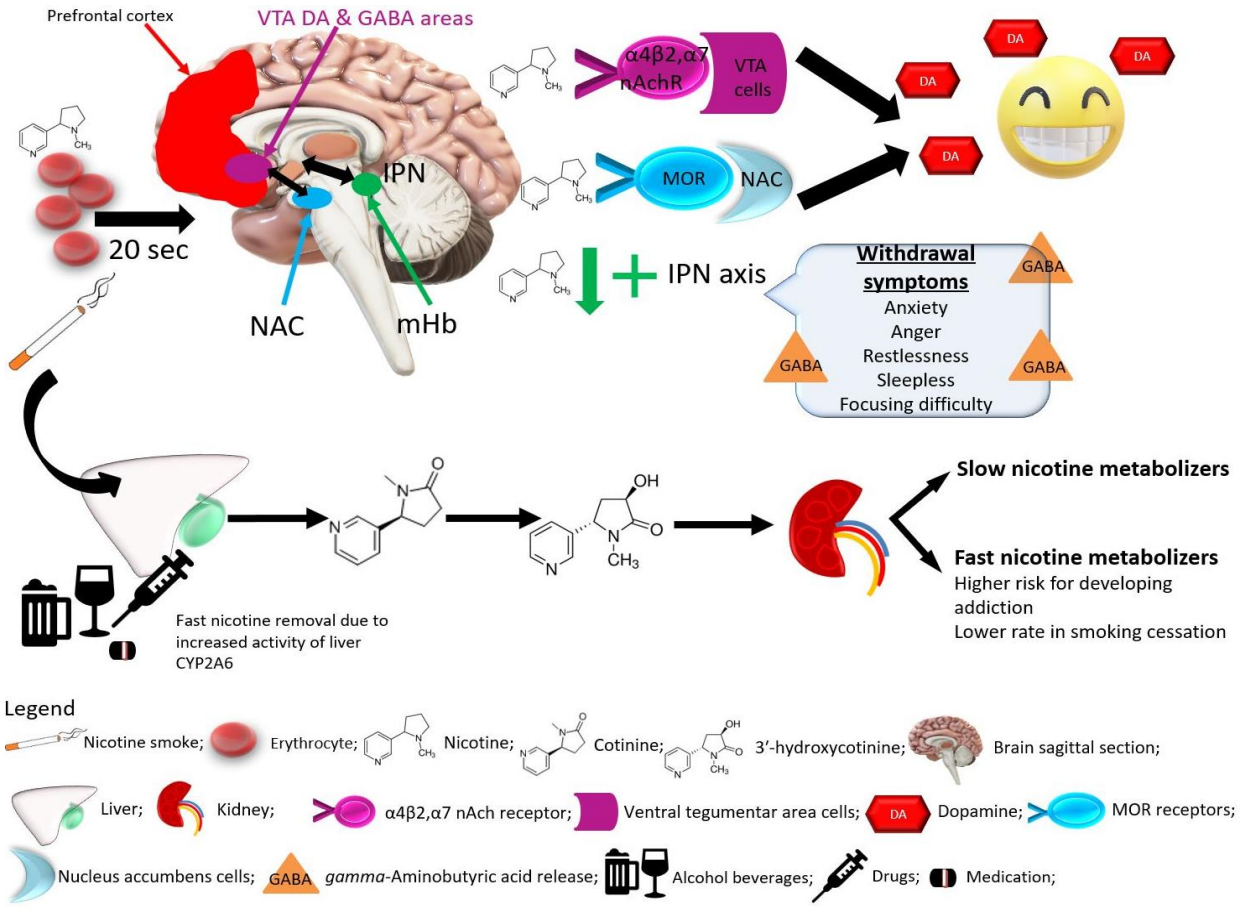


Figure 2. Nicotine addiction

1.2 Pathogenic molecular mechanisms of nicotine addiction

Nicotine enters blood circulation and binds to pre- or postsynaptic acetylcholine receptors (nAChR); these receptors are responsible for acetylcholine (Ach), dopamine (DA), serotonin, and norepinephrine release. In the brain, the most expressed receptors are α4β2 and α7 nAChR (11). When ventral tegmental area (VTA) DAα4β2 nAChR is stimulated by nicotine, VTA cells enter a phasic condition, with increased DA release in the nucleus accumbens (NAc) and prefrontal cortex, and through this mechanism, nicotine mediates relaxing and pleasure effects, considered to be the key point in nicotine addiction (12). Nicotine also stimulates μ-opioid receptors (MOR) from gamma-Aminobutyric acid (GABA) in the VTA area, decreasing GABA secretion and increasing DA release from NAC (11). Molas et al. demonstrated that the interpeduncular nucleus (IPN) axis from the medial habenula (mHb) regulates acute nicotine activity, due to its high nAChRs concentration (13). IPN controls fear and anxiety-related reflexes, which are among the nicotine withdrawal effects and are also nAChR mediated. In chronic consumers, nAChRs are regulated by either cholinergic or GABA neuron sub-populations of mHb-IPN, which increase the parasympathetic activity and lead to IPN stimulation as a final result, increasing withdrawal symptoms.

1.3 Nicotine metabolism

The oral mucosa absorption of nicotine and consequently its pulmonary alveoli and blood flow are influenced by its concentration and free-form. The alkalinity of saliva enhances nicotine absorption, which has a 8.02 dissociation constant that splits nicotine into two halves, one ionized and one non-ionized, the latter being the absorbed form (14). It takes only 15 seconds for nicotine to pass the lipophilic blood brain barrier and reach 50% of its concentration in the cerebral areas (15). Nicotine input is regulated by the consumer, by his smoking habits (frequency and depth of inhaling), the wellness of the pulmonary system, and the environmental quality. After absorption, nicotine is highly concentrated in the hepatic tissue, kidney, lung, spleen, and slightest concentration in fat tissue, whereas for cotinine, the highest concentration is found in liver (16).

Cytochrome P450 2A6/5 (CYP2A6/5), which is part of CYP 450 enzyme family, is the main enzyme responsible

for nicotine oxidation and it can induce ROS and oxidative stress; at the hepatic level, nicotine is C-oxidized and inactivated to cotinine and cotinine to 3′-hydroxycotinine (3HC) (16). The assessment of the correlations between CYP2A6 and renal nicotine clearance has revealed two types of smokers: slow nicotine metabolizers and fast nicotine metabolizers; fast metabolizers have a higher risk of developing addiction and a lower rate of success in smoking cessation (17). P450 2A6 and P450 2A13 enzymes also catalyze nicotine methyl oxidation, resulting in nornicotine, N'-nitrosonornicotine, a pulmonary-specific carcinogenic compound (18). Often, tobacco and alcohol are consumed together and they have a mutual metabolic influence. Cytochrome P450 2E1 is increased in chronic alcohol consumption, and the simultaneous consumption of the two substances promotes lipid peroxidation, alcoholic fatty liver, and alcoholic cirrhosis (19). Alcohol consumption increases fast nicotine removal due to the increased activity of the liver CYP2A6 (20, 21). CYP2A5 influences the nicotine and cotinine bioavailability, expressed by the fact that nicotine's concentration is higher in the brain compared to cotinine, because of the slower liver cotinine metabolism and its difficulty crossing the brain barrier (22). Nicotine is actively transported by the renal cells and because of its basic condition, its excretion rate is influenced by urine pH, compared to cotinine which is influenced only by the urinary flow (23) (Figure 3). By means of oxidative stress, nicotine promotes renal impairment and tubular injury, which are expressed more in young renal tissues (24). NAChR are present in mesangial cells, proximal tubular cells, and podocytes. Nicotine downregulates nephrin constitution and increases the pro-apoptotic podocyte Bax enzyme and ROS production in a dose-dependent manner, enhancing the progression of chronic renal disease (25). Regarding nicotine and cotinine metabolism, factors influencing the compound elimination include: grapefruit juice- inhibits hepatic enzymes; menthol increases cotinine's half-life and the metabolism of nicotine; women have a higher tobacco-derived product metabolic rate than men, which is accelerated in the presence of oral contraceptives, age-related delayed clearance; and general diseases that include renal failure, alcoholic liver disease, hepatitis, associated disease inductor and inhibitor medication; and smoking habits (16).

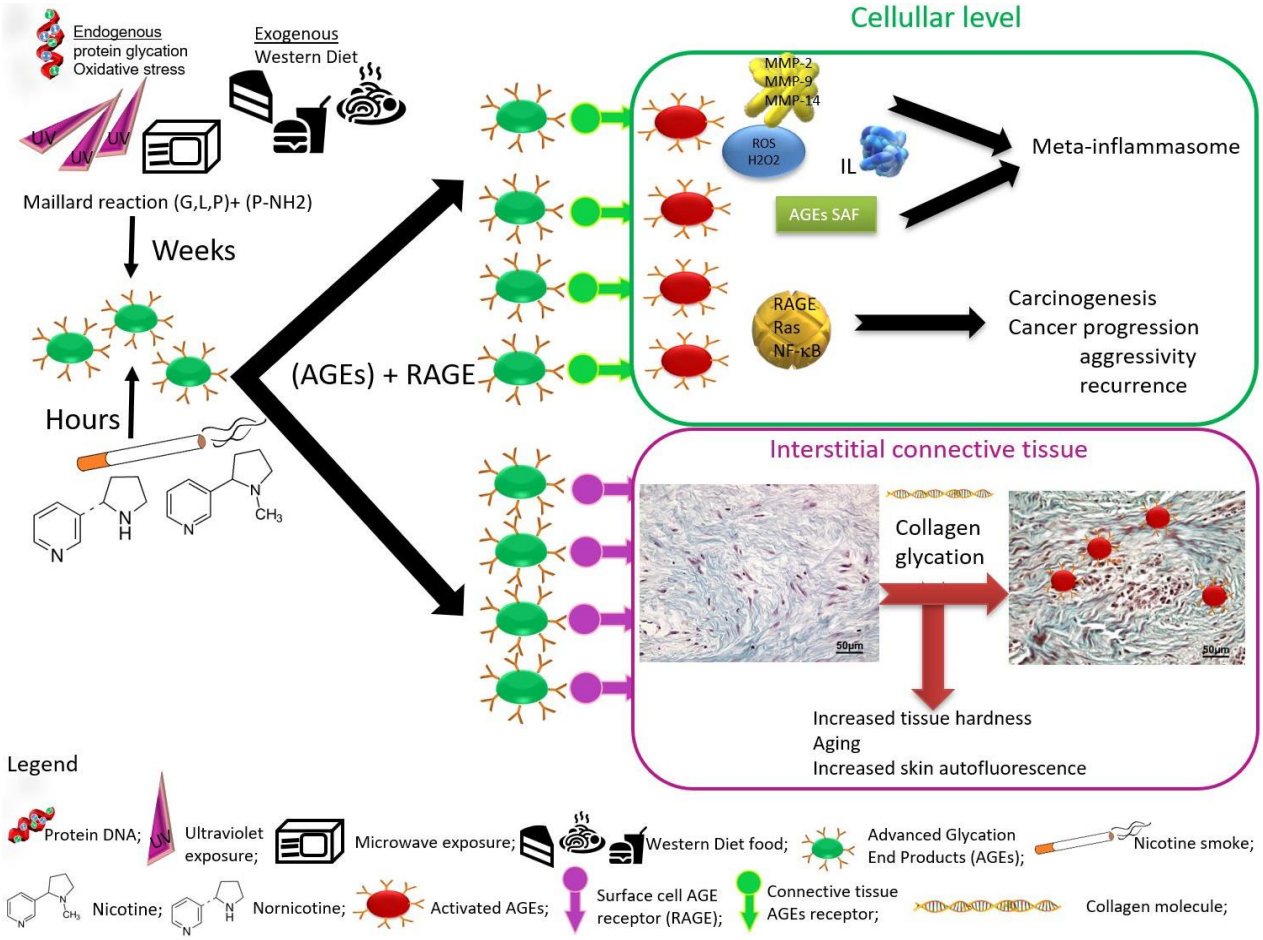


Figure 3. Nicotine metabolism and the pathogenic molecular mechanisms of nicotine addiction

1.4 Genetic determinism of nicotine addiction

Genome-wide association studies (GWAS) have assessed single nucleotide polymorphism (SNP) genes associated with smoking initiation. Results have shown that the following proteins are involved in smoking behavior and addiction: glutamate receptor subunits (GRIN2A, GRIN2B, GRIK2, and GRM8), cell adhesion molecules (CDH23), neurotrophic receptor tyrosine kinase (NTRK2), and the growth factor receptor-bound protein 14 (GRB14) (26). Jensen et al. investigated the relationship between smoking and the SNP in protocadherin (PCDH), a transmembrane protein present in neural synapses, in 3600 patients (27). They administered nicotine intravenously after an overnight abstinence and their results showed that patients with PCDH SNP responded fast and effectively to nicotine infusion. GWAS also found an association between NACHR subunits (CHRNA3-4-5-6, CHRNB2-3-4), dopamine b-hydroxylase (DBH), Flavin-containing monooxygenase (FMO), and nicotine dependence. Smokers with a reduced CYP2A6 allele activity (CYP2A6*2, *4, *9, *12) have a slower nicotine metabolic rate (a higher plasma nicotine concentration) and a decreased hepatic enzyme activity, while CYP2A6*1B smokers have a higher metabolic rate (8).

1.5 Genetic determinism in smoking cessation

A systematic review of 46 papers on the genetic-medication interaction reported that several genes were involved in nicotine addiction, smoking withdrawal, and medication efficacy: CHRNA5-A3-B4, CYP2A6, DBH, CHRNA4, COMT, DRD2, DRD4 and CYP2B6 (28). The SNP in CYP450 2A6, the enzyme that inactivates nicotine to cotinine, is known to have a direct influence on the number of smoked cigarettes, smoking behavior, and the efficacy of varenicline and bupropion treatments, especially in fast nicotine metabolizers compared to slow metabolizers. Researchers have also found the genetic implication for the dopamine pathway, more precisely dopamine COMT enzyme in addiction mechanism (28).

2. Social context and medical implications

Smoking habits are influenced by a number of factors (29). Agaku et al. collected information from Eurobarometer 345 and analyzed the determining smoking factors and the marketing and design elements (30). The initiation of smoking and the brand's choice were enhanced by the pleasant smell and taste of tobacco, its packaging, price, and specific flavors. The analysis further showed that attractiveness was increased by the length, diameter, and additives such as menthol or cinnamon. Cigarette marketing uses terms such as "light", "organic", "silver", which have an appealing effect on buyers, and make them seem less harmful. The World Health Organization's Directives regulate tobacco products' design, flavor, and marketing, including statements which would influence the consumers to choose a specific tobacco brand.

Chronic nicotine consumption leads to tobacco dependence, which pragmatically occurs when the individual "desires" a cigar or cigarette. The degree of dependence is commonly diagnosed with the Fagerström test, which classifies smoking psychiatric disorders, anxiety and depression (31). The World Health Organization (WHO) states that over a million deaths are caused by smoking each year, of which 600,000 are not active smokers, and alerts the population that the number of consumers is increasing and the initiation age decreases (32). The cigar/cigarette smoke and its products induce a chronic inflammatory status (33), a continuous increase in mortality due to pulmonary obstructive disease, cardiac disease, oral cavity and lung cancer, along with other cofactors (34, 35). Carcinogenic, irritating, and asphyxiating nicotine and other smoke compounds are absorbed by means of the pH, so that the high-soluble substances are absorbed in the upper airways, whereas less soluble substances are absorbed in the pulmonary cells (36). Nicotine's cytotoxic effect on oral cavity structures has been tested on human periodontal stem cells (37). Different nicotine concentrations induced autophagic activity, decreased periodontal stem cells viability, and altered the periodontium cell turnover, which, when taken into account, induces and aggravates the periodontal disease. Oral hygiene and exhaled carbon monoxide were assessed on a group of 65 subjects (50 smokers, 15 non-smokers) (38). Plaque, gingival calculus index, and CO were recorded. The degree of nicotine dependence was evaluated using the Fageström test. The study showed that Fagerström scores were directly related to daily tooth brush frequency and gingival index. Smoking was positively correlated with bad oral hygiene as indicated by gingival, plaque, and calculus indices.

3. The correlation between nicotine and Advanced Glycation End Products (AGEs)

Advanced glycation end products (AGEs) are final products of Maillard reaction; in a medical context, AGEs have been associated with the enhanced production of reactive oxygen species (ROS), and the subsequent generation of oxidative or carbonyl stress, thus leading to an inflammatory response. AGEs encompass a large group of products, of which pentosidine, carboxymethyllysine (CML), glyoxal-lysine dimer (GOLD), and methylglyoxal (MG) have been intensely investigated (39). Based on their source, two classes of AGEs are known: the endogenous

AGEs (formed in oxidative stress conditions, hyperglycemia) and exogenous AGEs: dietary AGEs (dAGEs). Moreover, AGEs can be produced by UV (ultraviolet) radiation, nicotine and cigarette smoke, and microwaves and ultrasounds (40). Smoking AGEs are formed in several hours and bind to connective tissue collagen fibers, leading to increased tissue hardness. AGEs mainly act through an immunoglobulin surface receptor (RAGE) mechanism and induce chronic inflammation. Nicotine and nornicotine are enhancing factors for the tissular expression of AGEs. Sanders et al. has shown that gingival epithelial cells exposed to cigarette smoke extract (CSE) exhibited increased RAGE and cytokine mediated inflammatory response, including Ras and nuclear factor kappa B (NF-□B) pathways. This research group used semi-synthetic glycosaminoglycan ethers (SAGEs) and demonstrated the inhibitory effect on AGEs due to the decreased effect on cytokine production in cells stimulated by CSE (41). Chapman et al. evaluated the effect of SAGE in oral squamous cell carcinoma (OSCC) cells exposed to CSE in different concentrations (0.05%, 0.1%, 0.2%, and 0.5%) (42). Smoke extract increased AGEs expression and OSCC cell proliferation. The removal of etiological CSE and SAGE treatment decreased the inflammatory response (the production of matrix metalloproteinases 2, 9, 14) and induced OSCC cell downregulation (Figure 4).

An in vitro study regarding the effect of CSE on rat alveolar epithelial cell lines showed that CSE activated RAGE; Ras is involved in cell growth and differentiation; and NF-□B is related to carcinogenesis and cancer progression (43). Marinucci et al. investigated nicotine, methylglyoxal (MG), a component of cigarette smoke, and AGEs effect on the differentiation and proliferation of human osteoblastic cells, with the focus on osteoporosis (44). They also pretreated osteoblasts with Tiron- an antioxidative and AG- scavenger for MG and its derivatives (MG-H1). Nicotine induced a dose- and time-dependent increase in RAGE and hydrogen peroxide (H2O2). Tiron reduced nicotine induced-apoptosis and the AG pretreatment showed the involvement of MG-H1 in RAGE overexpression and cellular apoptosis. The accumulation of tobacco-sourced AGEs in the skin can be assessed by using the autofluorescence (SAF) technique. Waateringe et al. used the AGE Reader to assess skin AGEs derived from active and secondhand cigarette smoke exposure, along with smoking withdrawal, in healthy individuals and diabetic patients (45). High SAF levels were correlated with diabetic active smokers and SAF intensity was correlated with the hours of cigarette smoke exposure. In contrast, cigarette cessation led to SAF decrease. The authors stated that for a former smoker, it takes approximately 15 years to reach the same SAF levels as a non-smoker.

4. Treatment strategy in nicotine addiction

In the National Socialist Germany, smoking was considered to be un-Aryan, and thus smoking cessation was politically driven. However, the efforts were not effective, because of the stressful living conditions and because cigarettes were used as postwar commercial goods (46). After establishing the direct relationship between cigarette smoke and lung cancer, surveys (47) and research studies regarding smoking and its effects on human physical and mental health were initiated. The most widely used and effective methods in smoking cessation were nicotine patches, bupropion, and varenicline FDA approved medication, sometimes in conjunction with cognitive/active therapy. Varenicline is a partial antagonist which binds to nicotine acetylcholine (ACh) receptors and inhibits the activation of the ACh receptor by nicotine, leading to the lack of satisfaction while smoking (48). Varenicline has a high affinity for a4ß2 nicotinic receptors, blocking the addictive effect of nicotine; this medication has the role of increasing dopamine in the cerebral rewarding areas usually occupied by nicotine (49). A study on 213 subjects compared the effectiveness of pre-quit patches, varenicline (2 weeks before/10 weeks after smoking cessation), and classical patches (50). The pretreatment reduced smoking satisfaction and thus led to a decrease in the number of smoked cigarettes. A more invasive study investigated Nicotine Replacement Therapy (NRT) using high dose nicotine patches (21-84 mg/day) for smoking cessation, without interrupting conventional smoking (51). Researchers found a reduction in pleasure and the number of smoked cigarettes and reported no relapse during the post therapeutic 4 weeks. The results were attributed to the combined effect of high nicotine dose: a nicotine patch pre-load bound to ACo receptors, which led to an unpleasant sensation while inhaling and a secondary side effect of a nicotine overload causing mild nausea or vomiting (51). Other widely used NRT methods are nicotine gum, nicotine inhaler, nicotine nasal spray, where the nicotine inhaler provides up to 4 mg of nicotine, which alone is not enough for a current smoker attempting to quit. The author's analysis showed that combining nicotine patches with the inhaler increases the success rate by two times. Caldwell stated that for achieving the pleasant feeling, nicotine must pass through the pulmonary route, and the association of a metered dose inhaler with nicotine patches is a successful therapeutic approach (52).

The spray and the inhaler's particularity is the fact that their deposition is mainly in the upper airways, while the inferior pulmonary structures are spared, which represents a positive feature especially in pulmonary obstructive diseased chronic consumers (53). Active nicotine spray associated with patches showed a prolonged period of rebound compared to patches only (54, 55). The effect of the sublingual nicotine tablet was compared to transdermal patches, associated with moderate psychological counseling (56).

In a mice model study, Saravia et al. investigated the correlation between nicotine withdrawal and microglial activation in prefrontal cortex and hippocampus, and the effect of cannabidiol in redressing the cognitive damage induced by cessation (57). Inflammatory proteins TNF-α, IL-1ß, IL-10, and IFN increased in hippocampus and prefrontal cortex stratum pyramidal on the 4th day after nicotine withdrawal, while cannabidiol post-treatment normalized TNF-α and IL-1ß levels. The authors suggested that nicotine withdrawal syndrome altered neurogenesis by enhancing the expression of inflammatory proteins, while cannabinoids had a protective effect on cognition impairment. In the same contextual area, Johnson et al. investigated the implication of psilocybin in nicotine withdrawal, the abstinence time, or the reduction in the number of smoked cigarettes in a survey on 358 subjects (58). The authors stated that the 5-HT2A 5-HT1A could exert a psychedelic and endorphin-serotonin releasing effect. Most of the subjects reported a decrease in the number of smoked cigarettes or longer periods of abstinence after the psychedelic experience. The delayed psilocybin effect could alleviate several withdrawal symptoms involving anxiety and craving, and could also exert a parasympathomimetic effect. A meta-analysis by Klinsophon et al. performed on 19 studies focusing on the effect of physical activity on smoking cessation did not reach clear conclusions due to the controversies regarding ß-endorphins release after physical exercise (59). However, the results showed that aerobic and resistance exercises improved the patient's mood, whereas yoga and similar breathing and relaxing exercises led to stress reduction, thus suggesting that parasympathetic stimuli had a positive effect on smoking cessation.

Cigarette/cigar smoke's first contact is with the oral cavity's structures. The negative effect of smoking on the oral mucosa, periodontium, and bone quality and quantity is undisputed, due to the nicotine's toxic metabolites and chronic inflammatory local response. Tobacco-induced local pathology comprises dental caries, tobacco stains, halitosis, hairy tongue, stomatitis, premalignant or malignant lesions (60). The American Dental Association (ADA) has suggested that dentists have the opportunity of helping addicts in cessation therapy by using the 5-A strategy: Ask, Advise, Assess, Assist, Arrange follow-up (61). They can intervene positively because of the multiple visits of the patient to the dental clinic for a direct control of the oral and systemic health outcome. The dentist can make patients aware of their oral health condition which may be affected by smoking, especially periodontal diseases, and the importance of cessation and the absence of relapse in preserving dental treatment outcomes and systemic conditions as well (62).

Due to the technological era and the heavy use of smartphones, smoking cessation applications were considered a positive approach to improving cessation therapy results and a long-term abstinence period, especially in adolescents and young adults. The medical theory, the epidemiological data, the psychotherapeutic aspects, and the user's needs were involved in developing theses apps (63, 64). The apps permit the patient to keep a diary of the symptoms associated with quitting, the quantification of the achievements the addict accumulates during the therapy and especially after, and the online psychotherapeutic characteristics (65). The interactive nature of these applications showed increased patient compliance after NRT therapy, with potential value for such programs either as complementary or as a sequence in smoking cessation programs (66).

4.1. *Electronic cigarettes (ECs) – a healthier alternative?*

ECs originally emerged as a healthier alternative to conventional smoking. ECs contain tobacco specific ingredients and flavors and include the following components: a vaporizer with a heating mechanism, a cartridge and a battery. The higher the voltage, the greater the production of vapors and carcinogenic compounds (67). EC-liquids include nicotine, propylene glycol (PG), vegetable glycerin (VG), and flavors. DeVito et al. found that PG/VG ratio influenced the nicotine input and the concentration of toxic compounds (68). UK Health Ministry asserted that EC vapors contain 95% fewer noxious products than regular cigarette smoke (69). EC vapors also contain nitrosamines, alkaloids, and turpentine (used either as a solvent or as a scent for a pleasant fragrance). Löhler and Wollenberg investigated the differences between classic and electronic cigarettes and their influence on adolescents' and adults' behavior. Their results showed that most of the adult consumers had chosen to adopt ECs due to their lower negative biological effects, or as a way to reduce and quit smoking; another reason was the possibility of smoking in restricted areas. In contrast,

adolescent consumers considered ECs the initial stage, preceding conventional smoking; the risk of changing the ECs for conventional smoking seemed to be correlated with the social, economic and educational status (70).

4.2. Old habits die hard - perspectives?

Nicotine addiction has a multifactorial etiology, from genetic determinants to the context of social acceptance. Daily stress has an obvious impact on the frequency and quantity of nicotine use. Several studies have described the mechanisms of the three stages of nicotine addiction, from the wanting level (self-control) to the craving level in which the receptors and the autonomic nervous system take control. Cigarette consumers seem to ignore the progressive multisystem alterations induced by the metabolism of nicotine and smoke components (carcinogens, AGEs-MG, asphyxiants, proinflammators, irritants). Moreover, it is well known that second-hand and third-hand smoke induce negative delayed effects in non-smokers. The ECs are error-inducers for their users, especially due to the design and the lack of smoke elimination. Nicotine addiction is insidious and tricks patients by an apparent self-control on cigarette input. Clinical studies investigating several single or associated cessation therapies have demonstrated that bupropion, varenicline, and nicotine patches had increased efficacy, and could be combined with physical/psychical therapy. However, there are no studies on long-term follow-up. It is not known when the relapse key moment occurs and especially why many people who had given up smoking eventually return to their unhealthy habit. There is no certain quantity of nicotine or number of smoked cigarettes which make a person become an addict. Further investigations are needed to clarify the neural and psychical factors that cause nicotine addiction and, most importantly, the relapse mechanisms.

Discussions

Biosensors, nicotine assessment and NRT

In biofluids, biomarkers can be used to evaluate the exposure, accumulation of nicotine, and cigarette smoke byproducts, such as aromatic amines, polycyclic aromatic hydrocarbons, acrylamide, benzene, and crotonaldehyde, as well as the efficacy of cessation therapy (71). The assessment was performed using different techniques: liquid chromatography and immunochromatography, in which cotinine is gold labeled nanoparticles combined with an image sensor to quantify the signal of the bounded product (72). Cotinine was mainly chosen as a tobacco biomarker because of the differences between the half-life of the two substances, 2 hours for nicotine and approximately 20 hours for cotinine. The accumulation of nicotine and cotinine in deciduous teeth was assessed using gas chromatography/bmass spectrometry (GC/MS) and liquid chromatography (LC)- tandem mass spectrometry (MS/MS) to monitor tobacco exposure and the cumulative effect of nicotine. To evaluate the efficacy of the cessation therapy, nicotine and cotinine can be analyzed in biological fluids such as saliva and urine. Salivary mouth swab (Oral Fluid Device) cotinine tests were shown to give accurate results of tobacco exposure, in both conventional cigarettes and ECs, even in the case of delayed analysis of the samples (73). It was shown that the concentration of nicotine is higher in unstimulated saliva, and cotinine's concentration in stimulated saliva, because of the differences in the salivary pH and tobacco's ionized and non-ionized metabolites (74). Synthetic receptors, molecularly imprinted polymers bound to nicotine and immobilized to quartz crystal and analyzed using quartz crystal microbalance-dissipation (QCM-D) sensor, use the viscoelastic properties of the investigated substances (75). Researchers developed the molecularly imprinted polymer-carbon nanotube sensor either for the electrochemical heat-transfer-resistance based cotinine detection or for quantification by using the electrical resistance to the substance (76, 77).

Thus, numerous techniques are available for detecting and quantifying nicotine and its metabolites as markers of exposure or for evaluating and monitoring the cessation treatment. There are various treatment approaches, including pharmaceutic nicotine antagonists, NRT using patches, gum, inhalers, sprays, drops, combined with psychotherapy and newly introduced phone applications. The majority of treatment methods use an oral administration route due to the rapid absorption of nicotine through the mucosa in the blood flow. One important negative aspect is the compliance of the patient, because the substances are mainly home self-medications. One patient might underdose, which results in withdrawal symptoms and a higher risk of relapse, or overdose, which is not an effective step for ending the habit. To the best of our knowledge, there is no intraoral device to provide real-time nicotine or cotinine levels. Such a device should be personalized, obtained through the interdisciplinary relation between the dentist and the technician or the orthodontist (78), and adapted to the anatomical characteristics of the patient's oral cavity. It could be represented by a prosthetic piece, for example, a mouth guard made from a biocompatible material in which a small-dimensioned biosensor can be attached (79). For

accurate results, the miniaturized device should be capable of acquiring the essential information, measuring the nicotine level in saliva by processing the received data, and transmitting the results remotely, either wired or mobile. The biosensor would assess real-time salivary smoking biomarkers. For a lightweight, easy-handling device, the power supply should be wireless and small. Various battery dimensions and power are available for medical applications that have low-power consumption - 2uW at 1.2V, so the battery would be active for 6-7 months. Small sized wireless batteries (2 square millimeters) can provide energy from active radio waves (80). Engineers have developed a 3D holographic lithography with a 2D photolithography micro battery, less than 2 inches in dimension, which includes a high-energy material—tin—providing a long-life battery (81). A significant challenge in miniaturizing the device lies in the transmission step, in which an antenna is needed, a component which is difficult or impossible to be miniaturize. Due to the high-frequency of the smartphone use by consumers, the results could be transferred by using an analogue-to-digital convertor, connected by Bluetooth to a phone application (82).

In this manner, the user of the device would know when a new nicotine dose is scheduled, without regard to his own thought processes or clinical symptomatology. The above described nicotine investigation assays are summarized in Table 1.

Authors	Purpose	Technique	Outcome
Gonzalez JM, Foley MW, Bieber NM, Bourdelle PA, Niedbala RS	Salivary nicotine and cotinine detection	Non-centrifuged saliva harvested from patients. CMOS image sensor –detects cotinine mixed with protein A–gold nanoparticles placed on the sample pad. Test line containing BSA–cotinine conjugate.	Cotinine equivalent concentrations of 2 ng mL−1 in < 15 min.
Robson N, Bond AJ, Wolff K.	Nicotine concentration in unstimulated vs stimulated saliva	Salivary samples harvested using Salivette cotton swabs, centrifuged - analysis by LCMS (Liquid Chromatography Mass Spectrometry)	Nicotine reduced in stimulated saliva (mean 1070.6 ± 728.5 ng/ml) compared to unstimulated (mean 2348.7 ± 1261.3 ng/ml). Salivary stimulated cotinine higher (387.9 ± 382.3 ng/ml) compared to unstimulated cotinine (257.5 ± 275.8 ng/ml).
Alenus J, Ethirajan A, Horemans F, Weustenraed A.	Detection of L-nicotine in diluted saliva and urine samples.	Synthetic receptors- Molecularly imprinted polymers (MIPs) combined with quartz crystal microbalances (QCM-D with dissipation monitoring) – detection of Lnicotine (100 mM) spiked in saliva and urine probes. Saliva harvested from patients who chew nicotine with 2, 4 mg of nicotine or without nicotine. Urine mixed with Lnicotine.	Nicotine-free tablet- 1±1 Hz. 2 mg nicotine- 14.5± 1.5 Hz. 4 mg nicotine- 21±3 Hz.
Peeters M, Csipai P, Geerets B, Weustenraed A.	Detection of Lnicotine in unstimulated saliva	Molecularly imprinted polymer (MIP)-type receptors bound to targeted substance- Heat-transfer-based detection of L-nicotine. Saliva harvested from non-smokers+L-nicotine concentrations of 0.25, 0.5, 1.0, 2.5, and 10.0 mM. L-nicotine measurements are performed in phosphate-buffered solution	Lnicotine ranged from 0.2 μM (ΔRth=0.07±0. 01 °C/W) to 50 μM (ΔRth=0.60±0. 03 °C/W).
Antwi-Boampong S, Mani KS, Carlan J, Belbruno JJ.	Detection of cotinine in methanol solution	Single-walled carbon nanotubes coated with molecularly imprinted poly-4-vinylphenol. The imprinted polymers change their resistance proportionally to cotinine concentration.	Resistance increased >30 kΩ
Ciui B, Tertis M, Feurdean CN, Ilea A, Sandulescu R, Wang J, et al.	Direct salivary detection of N$^{\varepsilon}$(Carboxymethyl)lysine	Cavitas printed electrochemical sensor integrated on a customized mouthguard. Differential pulse voltammetry analytical procedure.	A limit of detection of 166 ng/ml (equivalent to 0.81 μM) (over a range of 0.5–2500 μg/ml (equivalent to 2.45 μM–12.24 mM) .
Wu Y, Hao G, Baltus PGM, Bergmans JWM, Linnartz JPMG, Mahmoudi R	Batteryless wireless sensors	60 GHz wireless sensor system- monolithic sensors- chip sensing, transceiving, integrated antenna and energy collection.	17 dB noise ratio achieved from a sensor up to 5 meters distance.
Ning H, Pikul JH, Zhang R, Li X, Xu S, Wang J, et al.	Tridimensional microbatteries for miniaturized power source	3D mesostructured Li-ion microbatteries based on $LiMnO_2$ cathodes- fabricated by 3D holographic lithography and photolithography. NiSn anodes with 3,600 μW cm^{-2}·μm^{-1} peak power.	10-μm-thick microbattery- interdigitated microscaled electrodes with mesostructured pores, electrode shape with an area of 4 mm^2 for 200 cycles.
Farago P, Babtan A, Galatus R, Groza R, Roman MN, Feurdean CN, et al.	Hybrid sensor to identify salivary blood	81 0084 blue fluorescent optical fiber connected to KMAC spectrometer. 3V coin battery. Chibitronix SMD LED. Normal illuminaton conditions.	Selective filtering of the fluorescent radiation (blood filters the evanescent radiation). Selective filtering of incident light (clear saliva propagates fluorescence vs. blood which produces a red peak in the fluorescent spectrum).

Table 1. Saliva, nicotine assessment and biosensors

A useful and innovative approach would be for the nicotine's biosensor prosthetic device to present an alert system, which activates the release of a nicotine dose from a reservoir into the oral cavity where it will be easily absorbed. The dentist could play an important role in monitoring, counseling the patient, and ensuring maintenance of the device. The information provided by the biosensor could be transmitted to the doctor's computing device. The approach would provide a valid, accurate, real-time, and non-invasive evaluation of nicotine use. Its non-invasive properties, combined with NRT, could offer an attractive strategy for both the patient and the physician. Saliva-stimulating slow and gradual nicotine release from a prosthetic device active biosensor would allow a real-time adjusted cure dosage as part of the therapy. This could lead to a possible home-based therapy in which both the attending physician and the patient could have access to the evidence and treatment evolution.

Conclusions

Nicotine has drawn researchers' attention after the findings regarding the correlation between smoking and pulmonary and other diseases. Smoking addiction has strong pharmacological, psycho-social, and media support. Evidence has shown that cigarette/cigar smoke and its products simultaneously induce and aggravate multiple pathologies, beginning with direct contact with the oral mucosa and the upper respiratory airways, to tumoral disease and addictive behavior. Smoking cessation

strategies have a success rate strongly dependent on the patient's compliance. The development of a double-effect salivary biosensor could represent a useful approach in nicotine addiction therapy, both in the real-time monitoring of nicotine levels and in precise nicotine dose administration. This approach represents an innovative and appealing approach in NRT. Future studies would need to demonstrate the device's efficacy and the patient's compliance to such device treatment options.

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Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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