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EFFECT OF NICOTINE EXPOSURE ON THE RATE OF ORTHODONTIC TOOTH MOVEMENT: A META-ANALYSIS BASED ON ANIMAL STUDIES

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DMD, Gulf Medical University, Ajman, 2015

ABSTRACT

Effect of nicotine exposure on the rate of orthodontic tooth movement: a meta-analysis based on animal studies

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Background: Nicotine exposure has been reported to modify bone metabolism with potential effects on the rate of orthodontic tooth movement.

Aim: To systematically investigate and appraise the quality of the available evidence from animal studies regarding the effect of nicotine exposure on the rate of orthodontic tooth movement in animal subjects.

Materials and methods: Search without language restriction was performed for published and unpublished studies on electronic databases. Controlled studies investigating the effect of nicotine on the rate of orthodontic tooth movement were considered. Following study retrieval and selection, relevant data was extracted, the risk of bias was assessed using the SYRCLE's Risk of Bias Tool and the random effects method of combining treatment effects was used.

Results: From the initially identified records, 5 articles meeting the inclusion criteria were selected. Overall, quantitative data synthesis showed that the rate of orthodontic tooth movement in the nicotine exposed rats was higher than in control the group animals. No effect of the concentration or the duration force application was demonstrated following employment of meta-regression techniques. Many of the risk of bias domains assessed were considered to be unclear.

Conclusion: Rats administered with nicotine showed accelerated rates of orthodontic tooth movement. Although, information from animal studies cannot be fully translated to human clinical scenarios, the orthodontist should be able to identify patients exposed to nicotine and consider the possible implications for everyday clinical practice.

DEDICATION

First of All, I would like to thank God for giving me the wisdom and strength to write this dissertation.

This thesis dissertation is dedicated to my Mother Dr. Sangeeta for her unconditional love and belief in my potential.

To my Dear Father, Dr. Jyothish for being an inspiration and guiding me throughout my career. Your work ethic influences me to improve myself every day.

I would also like to dedicate this work to all my family members who have been by my side, supporting me across my academic and personal endeavors.

Lastly, my special thanks to Dr. Zoya Ali for her continued support and motivation along the years.

DECLARATION

I declare that all content of this thesis is my own work. There is no conflict of interest

with any other entity or organization

Name: Sanjay Kumar Jyothish

Signature:

ACKNOWLEDGMENTS

I wish to express my deepest gratitude to my Supervisor **Dr. Eleftherios G. Kaklamanos**, for his constant mentorship and unwavering support throughout my residency. Your guidance and constant feedback have been instrumental in writing this thesis dissertation.

My sincere thanks To **Professor Athanasios E. Athanasiou** for reviewing my work.

Finally, I would like to take this opportunity to thank all my Professors and teachers throughout my education for their encouragement and motivation.

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1. INTRODUCTION

During the past years, there has been a notable rise in tobacco consumption associated with various health adverse effects (World Health Organization, 2019). Although cigarette manufacturers were trying to withhold important medical information, the association between lung cancer and cigarette smoke became evident in the nineties (Haustein et al., 2017). In the USA and the European Union area, tobacco is related to more deaths than any other substance producing dependence. With the increase of tobacco consumption around the world, developing countries could be possibly facing the same risk in the near future (Lopez et al.,1994).

Tobacco smoke has been reported to contain more than 4,000 substances with important consequences (Dube et al.,1982; Hecht et al.,1988; Hoffman et al., 1990). Nicotine is the key constituent that leads to psychological effects, long-term addiction and other adverse health-related effects (Haustein et al., 2017). Apart from the association with an increased risk for pulmonary malignancy, smoking has also been shown to cause direct harm to the body and has negative effects to the cardiac vasculature, along with glucose intolerance and dyslipidemia (Brunner et al., 2005) Moreover, all forms of tobacco consumption and most importantly cigarette smoking have been implicated in changes to the oral mucosa leading not only to epithelial malignancy but also to gingivitis, periodontitis and increased tooth loss (Haustein et al., 2017).

As modern orthodontics has evolved to cater to a variety of different age groups, many individuals seeking orthodontic treatment may consume tobacco related products and be nicotine dependent. Exposure to nicotine has been shown to have effects like inadequate bracket adhesion (Baboni et al., 2010) and failure of miniscrews (Bayat et al., 2010). Moreover, as nicotine affects osseous tissue cells and bone metabolism in

various ways (Araujo et al., 2018; ; Nagaie et al., 2014; Shintcovsk et al., 2014; Rothem et al., 2013; Tanaka et al., 2013; Saito et al., 2012; Ying et al., 2011; Tanaka et al., 2006; Tanaka et al., 2005;Henemyre et al., 2003; Hollinger et al. 1999), there could be possible repercussions on the rate of orthodontic tooth movement. Although a previous systematic review reported that nicotine administration accelerates the rate of orthodontic tooth movement, they performed only qualitative analysis and did not attempt quantitative data synthesis, nor investigation of the risk of bias of the included studies (Michelogiannakis et al., 2018).

The aim of the present dissertation was to systematically investigate and quantitively synthesize the most recent available evidence from animal studies regarding the effect of experimentally induced nicotine administration on the rate of orthodontic tooth movement.

2. REVIEW OF LITERATURE

According to the WHO, 1.1 billion people consume tobacco in some form or the other and one quarter of the global population aged 15 years and older are current users of some form of tobacco (World Health Organization, 2019). Moreover, passive smokers are potentially being exposed to significant amounts of nicotine (Haustein and Groneberg, 2010). It has been calculated recently that tobacco is responsible for a staggering 6 million deaths per year. Unfortunately, 600,000 of those deaths occur due to chronic and repeated exposure to secondhand smoke (World Health Organization, 2019).

In Europe, approximately 30% of the population consumes cigarettes, cigars, pipe smoke and chewing tobacco. In Germany, in particular, with a population of 17 million people who smoke, around 300 deaths are recorded each day due to the adverse effects of smoking (Haustein et al., 2017). In England, smoking is fairly common as well, with a general prevalence of 21% of adults (National Statistics, 2010). In the United States, one in every five deaths per annum is related to smoking, mainly due to diseases like coronary heart disease, lung cancer and other respiratory tract pathological conditions (US Department of Health and Human Services, 1994). But smoking is not limited to adults. According to recent figures, about 12 of every 100 middle school students and about 31 of every 100 high school students in the United States report current use of a tobacco product. Moreover, nearly 1 of every 4 middle school students and over half of high school students said they had tried a tobacco product (Wang et al., 2019). As modern orthodontics has evolved to cater to a variety of different age groups, many individuals seeking orthodontic treatment may consume tobacco related products and be nicotine dependent.

Dependence can be defined as an illness which needs medical assistance. Nicotine is the only component in a cigarette responsible for dependence (Henningfield et al.,1985). Nicotine is the main alkaloid of the tobacco plant with a liquid-oily consistency at room temperature. On exposure to environmental air, nicotine shows a brownish color change and develops the odor of tobacco. Nicotine therapeutically has been demonstrated to be used as a tool for reduction of smoking. (Haustein and Groneberg; 2010).

Nicotine has minimal psychotoxicity, as opposed to alcohol or heroin, thus making the heavily dependent smoker only minimally conspicuous socially (Haustein and Groneberg, 2010). It has been shown in MRI studies that after intravenous administration, nicotine accumulates in various areas of the brain such as the nucleus accumbens, the amygdala, the cingulate cortex and the frontal lobes. These structures are associated with mood elevation and when activated show the characteristic features of nicotine's behavior-arousing property (Stein et al., 1998). Apart from mood, cigarette smoking influences the ability of the body to metabolize fat and appetite (Haustein and Groneberg, 2010).

According to the Diagnostic and Statistical Manual (DSM-V) of the American Psychiatric Association (American Psychiatric Association (2013), an individual is considered nicotine dependent if he or she presents three or more of the following characteristics:

- Tolerance.

- Withdrawal signs.

- A decreased ability to control the start, the end and the quantity of tobacco consumption.

- An increased neglection of other recreational activities due to consumption.

- Obsessive desire to consume.

- Smoking higher quantities than intended, smoking in spite of having intricate knowledge of its harmful effects to wellbeing.

Heavy nicotine dependence is also known to cause withdrawal symptoms [Haustein and Groneberg, 2010].

The characteristic features of withdrawal are:

- Mild irritation and restlessness.

- Inability to concentrate.

- Pronounced anxious feelings.

- Gaining of weight and an increased appetite.

- Disturbances during sleep and drowsiness.

- Robust craving for cigarettes.

2.1 The nicotinic receptor

The nicotinic acetylcholine receptor (nAChR) has been a subject of long-standing experimental research. It is the prototype ligand-gated ion channel (LGIC). nAChRs are found in the CNS and in peripheral nerve tissues and contain pentametric LGICs, constituted mainly from α and β subunits that come in a large number of variants (α2-α9, β2-β4,γ,δ,ϵ) (Karlin 1993; McGehee et al., 1994). Apart from their primary role in autonomic neurotransmission and the triggering of muscle contraction, nAChRs exhibit numerous modulatory reactions (Karlin 1993). The pathophysiology of various conditions such as Alzheimer's disease, Parkinson's disease, schizophrenia, Tourette syndrome, etc. have shown an involvement of nAChRs (Barrantes 1998). Additionally, they also play a pivotal role in cessation of smoking, analgesia, anxiolysis and

neuroprotection (Barrantes 1998). The nAChR of the human brain is constituted primarily of about 90% of $2\alpha_4$ and $3\beta_2$ subunits (Wonnacott 1990).

The nAChR binds cysteine and nicotine with high affinity (Flores et al., 1990; Williams et al.,1994). The binding site for agonists are found on the C loops of the α subunits and also encompass the aromatic side chains (tryptophan, tyrosine), which initiate cationic π-interactions with them (Grutter et al., 2001). Four hydrophobic transmembrane domains (M1-M4) are enclosed within the polypeptide chain of nAChR subunits, which span the plasma membrane. M2 is an α-helix that includes the cation channel (Grutter et al., 2001).

Nicotinic receptors are adequate to cause the acute and chronic effects of nicotine dependence. Mutant mice engineered with a single point mutation in a4 nicotinic subunits (Leu9'$\rightarrow$Ala9') render a4* receptors hypersensitive to nicotine. Low doses of agonist with selective activation of a4* nicotinic receptors repeat the effects of nicotine, such as dependence, response to acute nicotine administration, as well as tolerance and sensitization stimulated by chronic nicotine use. Thus, the activation of nicotinic receptors is adequate for the development of nicotine caused reward, tolerance and sensitization phenomena (Tapper et al., 2004). Furthermore, prolonged nicotine exposure causes an up regulation of nicotine receptors (Benwell et al.,1998; Collins et al.,1994).

The long intracellular loop that encompasses the centers for the phosphorylation of serine/threonine kinases is responsible for the separation of M3 and M4 from each other (Corringer et al., 2000). Allosteric modulation of the nAChRs occurs during the binding of the agonist (e.g. nicotine) to the receptor (Lena at al.,1993) in which transportation of the cations Na^+, K^+, and Ca^{2+} occurs during the change from the resting conformation to an open state. Agonists bind with a low affinity to the nAChRs when they are in the

open state. The perpetual occurrence of an agonist results in desensitization and channel closure of the receptor, which then becomes refractory to activation (Changeux et al., 1998).

The numerous nAChR subtypes differ significantly in terms of the degree of desensitization and recovery: the α_7 nAChR becomes desensitized very quickly (Mc Gehee et al., 1995) and inactivation with a slow recovery occurs when an agonist is permanently present. Moreover, chronic nicotine exposure can cause the neuronal $\alpha_4\beta_2$ nAChR receptor to become inactive very easily (Kuryatov et al., 2000). Repeated exposure to the agonist might lead to a weakened pharmacological response and permanent desensitization of the receptor (Benwell et al.,1998; Collins et al.,1994).

Various ligands are able to stabilize the conformational receptor state as the transitions from the resting, open and inactive states are interchangeable. The open state is usually stabilized by the agonists, whereas the closed (resting or inactive) state is stabilized by the competitive antagonists (Karlin et al., 1993; Mc Gehee et al.,1995)

2.1.1   Nicotinic receptor agonists and antagonists

Different nAChr subtypes interact with nicotinic agonists that attach themselves to the binding sites, triggering an allosteric modulation of the pentameric complex and opening of the ion channel. Agonists naturally present include cytisine, anatoxin A, epibatidine and anabasine. The affinity of binding of these substances to the $\alpha_4\beta_2$ nAChR subtypes is 100-1000 times higher than to the α_7 subtypes. Their binding affinities (K_i) are 100-1,000 times higher than their functional potencies (EC_{50}) for the activation of the nAChR subtypes. $\alpha_4\beta_2$ nAChR is bound with high affinity by nicotine as it is a prototype nAChR agonist, while the α_7 nAChR reacts 1,000 times less

sensitively (Gotti et al., 1997). The binding activity of the nicotine metabolite cotinine is barely quantifiable (Anderson et al., 1994)

Competitive agonists work in a reversible manner with the nAChR by stabilizing the conformation of the binding site and thus resulting in blocking the action of the agonists. However, D-tubocurarine and dihydro-β-erythroiodine are classic samples of agonists that can overcome the outcome caused the effect of the competitive agonists. This group includes a type of α-conotoxins and numerous snake venoms such as bungarotoxin. D-tubocuranine acts similarly irrespective of nAChR subtypes, and is active at concentrations of 10μM (Chavez-Noriega et al., 1997)

Non-competitive antagonists do not interact with agonists and generate their effect away from the binding center. In their case binding occurs in the vicinity of the ion channel. The most common example of the non-competitive antagonists is the mecamylamine which has the IC_{50} values in the lower μM range (Chavez-Noriega et al., 1997). Analogous effects are also produced by hexamethonium, decamethonium, chlorisondamine which are the other ganglionic blocking agents. Bupropion, an antidepressant, has also been shown to inhibit several nAChR subtypes (α3β2, α4β2, α7) in rats as well as the nAChR-mediated rubidium efflux of the human cell line SH-SY5Y provided the concentrations are in the low range (Popik et al.,1997; Slemmer et al., 2000). The anesthetics ketamine and phencyclidine, as well as the neuroleptic drug chlorpromazine are other substances showing non-competitive effects (Yamakura et al., 2000). Moreover, many steroid hormones such as corticosterone, aldosterone, estradiol and cortisol are capable to inhibit the neuronal nAChR subtypes from the human cell line SH-SY5Y, in concentrations ranging from the upper nM to the lower μM range (Ke et al., 1996). Progesterone inhibits the α4β2 nAChR subtype at concentrations of only 9 μM (IC50) (Paradiso et al., 2000; Valera et al., 1992).

2.2 Nicotine

Nicotine is the primary alkaloid of the tobacco plant, *Nicotiana tabacum.* In 1828, nicotine was first procured by Posselt and Reimann from tobacco leaves. The earliest known pharmacological effects were studied by Prfila in 1843, who conducted and analysis of nicotinic effects. Nicotine is one of the few unique alkaloids remaining at a liquid-oily consistency at room temperature. It is known to have a pale-yellow brownish colour form and contains the odor of tobacco when exposed to air. For medicinal purposes, nicotine has been used to attain cessation of smoking for patients. It is present in two optical isomers- the L-form and the D- form. The L-form is more potent than the D- form (Haustein and Groneberg, 2010)

2.2.1. Pharmacokinetics of nicotine

The different tobacco preparations demonstrated diverse degrees of nicotine absorption. Tobacco chewing or snuffing, results in nicotine absorption that is slower than in the case of a cigarette. With pipe or cigarette smoking, the amount of nicotine absorbed through the mucosa varies and is influenced mostly be the time smoke is kept in the oral cavity. On the contrary, nicotine is quickly absorbed by the epithelium of the pulmonary alveoli and bypasses the liver to reach the brain, resulting in a rise in CO-hemoglobin levels in the blood (Zevin et al., 1998).

The metabolism of nicotine takes place through oxidation and it is eliminated at a rate of 1.5 hour. About 10% of nicotine is eliminated from the body in an unchanged form. The pharmacologically inactive product of nicotine is cotinine. Due to its slow elimination it is used in assays for active and passive smokers. Urine cotinine is measured through various quantitative methods like gas chromatography and mass

spectrometry. These methods are costly and time consuming, but they have a great degree of accuracy and reliability (Hoffmann et al., 1994).

2.2.2. Effects of nicotine in different systems

Nicotine, just like acetylcholine stimulates the receptors of the parasympathetic nervous system. In low doses, nicotine stimulates the Central Nervous System, with an effect that is usually complemented by tremor (Haustein and Groneberg, 2010). Better memory recollection and performance along with a lower aggressive behavior pattern with consumption of nicotine has been demonstrated in experimental animal studies (Jaffe et al., 1985). A feeling of general relaxation has been reported by smoking the first cigarette of the day as reported by smokers, especially in stressful scenarios (Warburton et al., 1998).

The excitatory action is generally produced due to the presynaptic nACh receptors activated by nicotine (Mc Gehee et al., 1995). If these receptors are located on dopaminergic neurons, they increase dopamine metabolism in the mesolimbic and nigrostriatal structures (Wonacott et al., 1990; Balfour et al.,1994). In smokers, the density of nicotinic receptors in the cerebral structures is much greater than in non-smokers and after nicotine infusions, the smoking of even a single cigarette gives rise to the formation of surplus nACh receptors, found in the hippocampus, the gyrus rectus and the cerebellar cortex (Benwell et al., 1985). In heavy smokers, since there is a continuous presence of nicotine, up-regulation of the nicotinic receptors happens in various areas of the brain (neocortex, gyrus rectus, cerebellar cortex, hippocampus, median raphe) (Benwell et al., 1985; Marks et al., 1983; Schwartz et al., 1983; Wonnacott et al., 1990), most likely caused by the reduced internalization and/or degradation of nACh receptors (Marks et al., 1983). The density may almost double,

but their affinity for the ligand does not show any change. The surplus nicotine perhaps binds also to desensitized or inactive receptors (Wonacott et al., 1990).

Nucleus accumbens, the structure which acts as the center for the reward system and plays a pivotal role in caloric intake (Corrigall et al., 1992), shows a marked increase in nAChR density (Clarke et al., 1985). In animal experiments, it has been shown that nicotine administration results in the release of dopamine, suggesting that the development of nicotine dependence is linked with this area (Balfour et al., 1994; Dani et al., 1996). The stimulation of the dopaminergic system by nicotine administration in the mesoaccumbens seems to be especially important, as the enhanced burst firing of the mesoaccumbens neurons causes the release of extra dopamine into the intracellular space resulting in an increased effect on the extra-synaptic dopamine receptors (Balfour et al., 1994). It has also been suggested that the development of nicotine dependence is also determined by their influence on dopaminergic synapses in the mesolimbic system (Wise et al., 1987).

Overall, the amount of nicotine dependence seen among smokers is related to the daily cigarette consumption, the time when the first cigarette has been smoked in the morning and the requirement to smoke at night (Haustein and Groneberg, 2010). Guthrie et al. studied the arterial nicotine levels in 21 smokers who smoked 2 average nicotine (AN) cigarettes and one low nicotine (LN) cigarette (Guthrie et al., 2004). The visual analogue scale (VAS) was used to assess the rating for craving for a cigarette, relaxation, sickness and decreased nervousness before and after smoking each cigarette. Among all the parameters, only craving for a cigarette showed a subjectively different rating. It was seen that after smoking the first cigarette of the day, there was an increase in the plasma arterial nicotine concentrations in blood after which craving was reduced.

Thus, it was suggested that both the pharmacology of nicotine/tobacco consumption along with the psychology are potent factors in craving reduction.

In general, nicotine poses unique distinctive factors that make it different from other addictive substances. Craving to smoke and its dependence stems from ultra-rapid delivery of the nicotinic alkaloid to the brain and can be eradicated by administrations of nicotine over the course of many weeks in a progressively decreased manner of dosage regimen. Antimuscarinic, anticholinergic, or anti-adrenergic activity drugs cannot be used to block out effects caused by nicotine. However, it can be blocked by the antihypertensive ganglion blocking drug mecamylamine (Jaffe et al., 1985).

In the cardiovascular system, nicotine stimulates the cardiac ganglia via the N-receptors, which in turn lead to an elevation in the heart rate. Paralysis of the parasympathetic cardiac ganglia or a discharge of adrenaline from the adrenal medulla may also have the same effect. On the other hand, activation of the parasympathetic system, as well as deactivation of the sympathetic system or a combination of the two may also result in the reduction of heart rate by nicotine. However, these effects are dependent on factors such as the amount of nicotine dose, the route of administration and the time elapsed after the administration. Nicotine in small doses causes slight elevation of the heart rate and blood pressure (Haustein and Groneberg, 2010)

In the gastrointestinal tract, acetylcholine, catecholamines and peptide hormones are the chief mediators affected by presence of nicotine. Tobacco smoking has been suggested to have an ulcerogenic effect, although gastric acids are not consistently stimulated due to smoking. However, the effect of nicotine on intestinal peristalsis leading to multiple bowel movements is well documented (Haustein and Groneberg, 2010).

The stimulation of nAChRs in the carotid bodies is responsible for the stimulation of respiration whereas the stimulation of the receptors located in the aortic bodies stimulates the vomiting center (Haustein and Groneberg, 2010). Nicotine doses which are comparatively excessive have shown to cause convulsions and the consumption of doses which are toxic leads to central stimulation, respiratory paralysis and circulatory failure. Additionally, blockade of neuromuscular transmission occurs due to depolarization caused by nicotine; if the dose is sufficiently high, respiratory paralysis can cause death within a few minutes (Haustein and Groneberg, 2010).

In the hormonal and metabolic level, nicotine has been shown to stimulate the secretion of antidiuretic hormone and β-endorphin. Moreover, in female smokers, premature occurrence of menopause and changes in estrogen secretion have been linked to smoking (Benowitz et al., 1988).

2.3. Effects of nicotine in the oral cavity

Changes in the oral mucosa have been demonstrated widely with cigarette smoking and chewing tobacco (Ragnarsson et al., 1992; Pindborg et al., 1949). In-vitro studies have suggested that nicotine is involved in periodontal destruction by acting synergistically with toxins from putative periodontal pathogens (Sayers et al., 1997). Clinical studies have reached similar conclusions (Regazi et al., 1993). In the USA about 80% of adult smokers is affected by periodontal disease (US Public Health Service, 1987). Smoking has also been implicated as an etiologic factor in acute ulcerative gingivitis (Ragnarsson et al., 1992). It has been suggested that tar and other smoke ingredients cause local injuries to the mucosal surfaces in the oral cavity (Kenney et al., 1977). Moreover, smokers have decreased levels of antibodies IgA and IgG, which indicates a suppression of the immune system (Bennet et al., 1982). Additionally, osteoblastic

proliferation is inhibited in vitro due to nicotine (Fang et al., 1991), along with a decrease in gingival circulation (Clarke et al., 1981).

Smoking affects the oral mucosa in other ways as well. It results in melanosis of the tongue because of the pigmentation of basal keratinocytes (Regazi et al., 1993). Due to the chemical and thermal effects of smoke, smokers may exhibit smoker's palate or stomatitis, a condition which could develop to a precancerous lesion (Regazi et al., 1993). The association of nicotine with the development of squamous cell carcinoma is well established also (Regazi et al., 1993). With a consumption of 20 cigars/day Sigmund Freud was a typical example. He developed leukoplakia with an increased frequency of oral cancers, for which he had undergone numerous surgeries. Freud continued to smoke persistently in spite of wearing prosthetic jaw plates until his demise (Regazi et al., 1993).

Smokers also demonstrate increased discolouration of teeth and abrasion (Regazi et al., 1993). Furthermore, increased tooth loss is commonly seen among smokers (Ragnarsson et al., 1992; Ahlqwist et al., 1989; Holm et al., 1994; Osterberg et al., 1986), which in turn could lead to disturbances in the occlusion (McGowan et al., 1996). When compared with children who have not been exposed to maternal or passive smoking, exposed children have shown an increased risk for the development of caries (Williams et al., 2000).

2.4. Orthodontic tooth movement and nicotine consumption

Orthodontic movement involves an early stage which includes an acute inflammatory response, associated with periodontal vasodilation and migration of leucocytes out of the capillaries. Cytokines, the local biomechanical signal molecules known to network with the entire system of periodontal cells are then produced by local and migratory

cells as a response to the mechanical stimuli. Cytokines are responsible for eliciting secretion and synthesis from target cells of several mediators, such as, growth factors, other cytokines and prostaglandins. Due to this, different biologic effects occur in bone metabolism which result in the remodeling of the osseous tissue in order to accommodate for the movement of the teeth (Krishnan et al., 2006; Meikle 2001)

Nicotine has been shown to affect the metabolism of bone. Fung et al. (1998; 1999) investigated the long- and short-term effects of bone metabolism in 7-month-old female rats. The study measured the calciotropic hormone concentrations (parathyroid hormone, calcitonin, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D) before and after nicotinic administration. The experimental group was administered 0, 3 or 4.5mg/kg/day by subcutaneous implantation of osmotic minipumps. These pumps housed either saline or nicotine for a duration of 2 months (for the short-term experiments) or 3 months (for the long-term experiment). After the duration of the study, the right tibia, left femur, lumbar vertebra and serum were obtained to measure hormonal levels, bone mineral density, bone mineral content and vertebral strength.

Post 2 months of nicotine delivery, treated rats showed lower level of 25-hydroxyvitamin D, but there were no statistical differences in other hormones or in other parameters, like bone mineral density, content etc. After 3 months of nicotine administration, the rats administered nicotine showed substantially lower levels of 25-hydroxyvitamin D. Furthermore, the experimental group of rats given an increased dose had reduced vertebral areas, lower mineral content of bone and reduced tibial endocortical mineral apposition rates, when compared to the control group that received saline. Other results shown were not statistically significant. As per the finding of this study, nicotinic delivery to rats for 2 months did not modify strength, bone mass, formation or resorption in spite of the lower serum levels of 25-hydroxyvitamin D by

about 30%. Nevertheless, a 3-month duration of nicotine can adversely affect the formation of bone and reduce the body storage of vitamin D (Fung et al.,1999). Another experimental research by the same group, using the same methodology on one-month old growing animals showed that nicotine administration for 2 or 3 months had no detrimental consequence on skeletal volume, bone mass or strength (Iwaniec et al., 2000). A number of other studies in human subjects have observed that smoking and consumption of nicotine affect negatively bone mineral density and trigger impaired wound healing and osseous repair (Sanoudos 2001).

Osteoclasts and osteoblasts, the two cells responsible for bone resorption and bone formation process are of paramount importance in the processes associated with tooth movement following orthodontic stimuli. The effects of nicotine have been observed to be inconsistent. Ying et al. (2011) demonstrated that even low concentrations of nicotine considerably stimulate bone marrow cell proliferation and expression of type II collagen. Moreover, nicotine has been reported to stimulate the formation and differentiation of osteoclasts (Tanaka et al., 2006; Henemyre et al., 2003). On the contrary others have shown that a mixture of the components of tobacco smoke induces osteoclastogenesis inhibition in a rat model (Araujo et al.,2018; Nagaie et al.,2014). Shintcovsk et al. (2014), showed an increased percentage of immature collagen, lower blood vessel densities and lower levels of osteoclast-like cells expression in a nicotine administered group compared to the controls.

 Other studies have shown that nicotine stimulates osteoblast precursors but suppresses osteogenesis (Tanaka et al., 2005; 2013). Another study has implied that effect of nicotine on osteoblast cell proliferation is biphasic; high levels of nicotine cause toxic and antiproliferative effects, whereas low levels of nicotine cause stimulatory effects (Rothem et al., 2013). Saito and colleagues (2012), used 24 male Wistar rats who

received subcutaneous injections of nicotine of 3mg/kg, twice a day over a period of 16 weeks. Histomorphometric analysis showed that nicotine considerably reduced the number of larger numbers of osteoblast- like cells, osteoclast-like cells, and micro vessels when compared to the controls. Moreover, nicotine has also been shown to decrease the radiopacity of bone (Hollinger et al. 1999). In this study, 32 mice were split into nicotine and control groups which were exposed to nicotine orally through drinking water for 56 days of continual exposure. Although the study was unable to prove that nicotine affected bone healing, a significant reduction in radiopacity was noted among the nicotine group (Hollinger et al, 1999).

As a variety of different age groups can benefit from orthodontic treatment, many individuals seeking orthodontic treatment may consume tobacco related products and be nicotine dependent. Exposure to nicotine has been shown to have effects like inadequate bracket adhesion (Baboni et al., 2010) and failure of miniscrews (Bayat et al., 2010). Moreover, as nicotine affects osseous tissue cells and bone metabolism in various ways, there could be possible repercussions on the rate of orthodontic tooth movement. Although a previous systematic review reported that nicotine administration accelerates the rate of orthodontic tooth movement, they performed only qualitative analysis and did not attempt quantitative data synthesis (Michelogiannakis et al., 2018).

3. AIM

3.2. Aim of the systematic review

To systematically investigate and quantitively synthesize the most recent available evidence from animal studies regarding the effect of experimentally induced nicotine administration on the rate of orthodontic tooth movement.

3.3. Objectives of the systematic review

To retrieve information on the effect of nicotine, when experimentally administered to rats, on the rate of orthodontic tooth movement.

3.4. Null hypothesis

There is no difference in the rate of tooth movement between nicotine administered and control group animals.

4. MATERIALS AND METHODS

4.1. Protocol development and registration

The present review was based on a specific protocol developed and piloted following the guidelines outlined in the PRISMA-P statement (Shamseer et al., 2015). In addition, conduct and reporting followed the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011) and the PRISMA statement (Moher et al., 2009), respectively.

4.2. Eligibility criteria

The selection criteria followed the PICOS approach. The specific criteria for the domains of study design, participants' characteristics, intervention characteristics and principal outcome measures applying to the present review were followed:

4.2.1. Types of study design

Studies included were prospective controlled studies evaluating the rate of tooth movement in animals exposed to nicotine in comparison to non-exposed animals. Human studies, ex vivo, in vitro, in silico, non-comparative studies (case reports and case series) and reviews (traditional reviews, systematic reviews and meta-analyses) were excluded from the present investigation. The type of study design was assessed using the algorithm available from SIGN (Scottish Intercollegiate Guidelines Network) available from http://www.sign.ac.uk (Appendix I).

4.2.2. Types of participants

The included studies involved healthy naïve animals of any age and gender undergoing any kind of orthodontic tooth movement. Studies in animals undergoing tooth movement in conjunction with other interventions such as tooth extraction etc., on subjects after the cessation of active orthodontic tooth movement or on subjects with co-morbidities were excluded.

4.2.3. Types of interventions

The included studies involved animals who were experimentally exposed to nicotine by any route and concentration.

4.2.4. Types of outcome measures

The studies had to comprehensively report the rate of orthodontic tooth movement (i.e. mean values of the amount of tooth movement during a specific period of time together with appropriate data on dispersion like standard deviation, standard error, etc.).

4.3.   Information sources and search strategy

The principal investigator developed detailed search strategies for each database. These were based on the strategy developed for MEDLINE but revised appropriately for each database to take account of the differences in controlled vocabulary and syntax rules. The following electronic databases were searched (Appendix II): MEDLINE via PubMed, CENTRAL, Cochrane Systematic Reviews, Scopus, Web of Science TM Core Collection, Arab World Research Source, Clinical Trials registry and ProQuest Dissertations and Theses Global database.

There were no restrictions placed on the language, date or status of publication. In addition, efforts were made to obtain conference proceedings and abstracts where possible and the reference lists of all the eligible studies for additional records were searched.

4.4. Study selection

The main investigator and the dissertation principal supervisor assessed the retrieved records for inclusion individually. They were not blinded to the identity of the authors, their institution, or the results of the research. The full text of the records considered by either reviewer to meet the inclusion criteria, were obtained and assessed, again independently, while disagreements were settled by discussion with the dissertation co-supervisor.

4.5. Data collection and data items

The main investigator and the dissertation principal supervisor performed data extraction independently and any disagreements were again resolved by discussion with the dissertation co-supervisor. Data collection forms were used to record the following information:

a. Bibliographic details of the study.

b. Details on study design and verification of study eligibility.

c. Subject characteristics (where available number, gender, age, weight).

d. Nicotine administration characteristics (route, concertation).

e. Tooth movement model.

f. Details on tooth movement measurements and results.

g. Additional information: a prior sample size calculation, reliability assessment.

If clarifications were needed regarding the published data, or additional material was required, then attempts to contact the corresponding authors would be made.

4.6   Risk of bias in individual studies

The main investigator and the dissertation principal supervisor assessed the risk of bias in the included studies, independently and in duplicate, during the data extraction process, using the SYRCLE's risk of bias tool (Hooijmans et al., 2014). Any disagreements were resolved by discussion. The SYRCLE's risk tool assessment tool includes the following domains:

1. Was the allocation sequence adequately generated and applied?

2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?

3. Was the allocation adequately concealed?

4. Were the animals randomly housed during the experiment?

5. Were the caregivers and investigators blinded to the intervention that each animal received?

6. Were animals selected at random for outcome assessment?

7. Was the outcome assessor blinded?

8. Were incomplete outcome data adequately addressed?

9. Are reports of the study free of selective outcome reporting?

10. Was the study apparently free of other problems that could result in high risk of bias?

After entering in the data extraction form the information reported in each study, every domain would receive a judgment of low, high, or unclear risk of bias (Hooijmans et al., 2014).

4.7 Summary measures and synthesis of results

The random effects method for meta-analysis was to be used to combine the rate of orthodontic tooth movement data at each point of observation from each study in appropriate statistical forms (Weighted Mean Difference (WMD) together with measures of dispersion) (Der Simonian and Laird, 1986, Borenstein et al., 2009), since they were expected to differ across the studies due to clinical diversity in terms of participants and intervention characteristics.

To identify the presence and the extent of between-study heterogeneity, the overlap of 95% CI for the results of individual studies was to be inspected graphically, and Cochrane's test for homogeneity and the I^2 statistics were to be calculated (Higgins and Green, 2011). The results of the I^2 statistic were to be interpreted as follows (Higgins and Green, 2011):

- I^2 from 0% to 40%: heterogeneity might not be important.

- I^2 from 30% to 60%: may represent moderate heterogeneity

- I^2 from 50% to 90%: may represent substantial heterogeneity

- I^2 from 70% to 100%: considerable heterogeneity.

All analyses were carried out with Comprehensive Meta-Analysis software version 3 (©2014 Biostat Inc., New Jersey, USA). Significance (a) was set at 0.05, except for 0.10 used for the heterogeneity tests (Ioannidis, 2008).

4.8 Additional analyses

If a sufficient number of trials were identified, analyses were planned for "small-study effects" and publication bias (Higgins and Green, 2011). If deemed possible, subgroup

analyses and meta-regression were planned to explore whether the point of observation

and the nicotine concentration modified the results.

5. RESULTS

5.1. Study selection

The data search took place in July 2019. From the initially identified 498 papers, twenty-three papers were excluded as duplicates and a further 468 were excluded on the basis of their title and abstract. Subsequently, 7 articles were reviewed in full text. However, 2 of them (Li et al. 2016; Schintcovsk et al. 2014) did not provide the quantitative information on the rate of orthodontic tooth movement. The corresponding authors were contacted but no response was received. Ferreira et al. (2018) kindly provided these details. Finally, 5 studies with full text reports were selected for inclusion in the meta-analysis (Sodagar et al., 2011; Bakathir et al., 2016; Kirschneck et al., 2017; Araujo et al., 2018; Ferreira et al., 2018).

5.2. Study characteristics

The characteristics of the studies included in the present meta-analysis, are presented in Table 1.

All papers had been published between 2011 and 2018 and experimented mostly on Wistar rats. Sodagar et al. (2011) used Sprague-Dawley rats and Kirschneck et al., (2017) Fischer 344 rats. Orthodontic tooth movement was accomplished by NiTi closed coil springs between maxillary molars and incisors, apart from Ferreira et al. (2018) that used SS closed coil springs between mandibular molars and incisors.
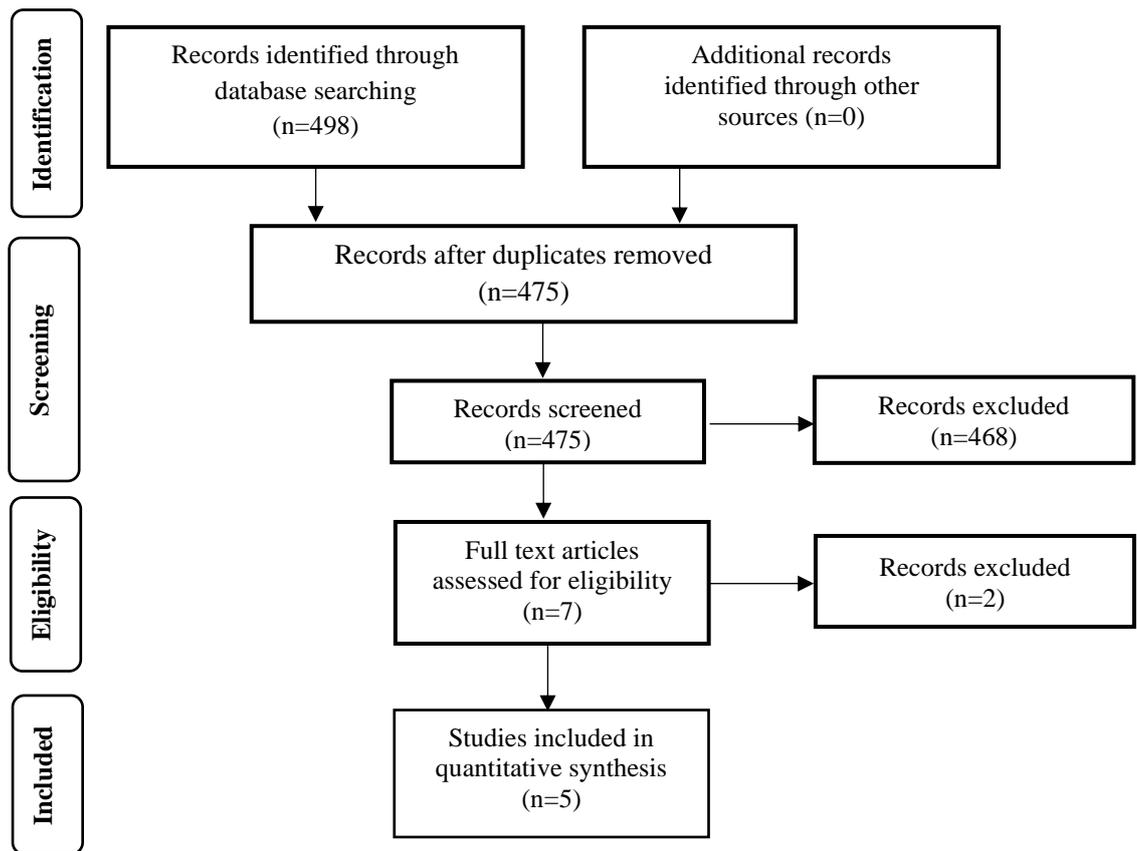
Figure 1. Flow chart of records through the reviewing process.

The generated molar mesializing forces ranged between 25 to 60g and the period of force application between 1 and 4 weeks. Tooth movement was measured clinically (Sodagar et al., 2011; Bakathir et al., 2016; Ferreira et al., 2018), on dental casts (Araujo et al., 2018) or using CBCT radiographs (Kirschneck et al., 2017). Apart from Kirschneck et al. (2017), the rest of the included studies did not report on method of error. Only Kirschneck et al. (2017) and Ferreira et al. (2018) provided calculations on sample size; however, in the latter case the calculations were not based on the amount of tooth movement.

Nicotine was being administered in concentrations ranging from 0.5 to 1.89 mg/kg, for periods of 13 to 74 days, intraperitoneally (Sodagar et al., 2011; Bakathir et al., 2016), subcutaneously (Kirschneck et al., 2017; Araujo et al., 2018) or by inhalation (Ferreira et al., 2018). Apart from the study of Sodagar et al. (2011), the rest included an induction period.

Table 1. Study characteristics.

Study	Animal characteristics Tooth movement model | nicotine administration	Group characteristics	Measurement methodology
Sodagar et al. [2011]	Sprague-Dawley rats [male, adult, 250 ±20g] NiTi CCS from R Mx I to FM [60g] **Force application:** 14d **Nicotine administration:** daily for 13d	**EG₁**: 8; 0.5 mg/kg; IP; 1/d **EG₂**: 8; 0.75 mg/kg; IP; 1/d **EG₃**: 8; 1 mg/kg; IP; 1/d **PG**: 8; 0.1 ml ns; IP; 1/d **Sample size calculation:** NM	**Clinically:** interproximal feeler gauge [d 14] **Method error:** NM
Bakathir et al. [2016]	Wistar rats [male, 12-week-old, 400 ±20g] NiTi CCS from L Mx I to FM [30g] **Force application:** 14d **Nicotine administration:** daily for 14d + 14d	**EG₁**: 8; 0.37 mg/kg; IP; 1/d **EG₂**: 8; 0.57 mg/kg; IP; 1/d **EG₃**: 8; 0.93 mg/kg; IP; 1/d **PG**: 8; 0.1 ml ns; IP; 1/d **Sample size calculation:** NM	**Clinically:** interproximal digital gauge [d 14] **Method error:** NM
Kirschneck et al. [2017]	Fischer 344 rats [male, 6-week-old, 260 ±15g] NiTi CCS from L Mx I to FM and SM [25g] **Force application:** 28d **Nicotine administration:** daily for 10d + 28d*	**EG**: 7; 1.89 mg/kg; SC; 1/d **PG**: 7; 0.1 ml PBS; SC; 1/d **Sample size calculation:** Yes	**Radiologically:** CBCT [d 14, 28] **Method error:** Yes
Araujo et al. [2018]	Wistar rats [male, 9-week-old, 300-3500g] NiTi CCS from L Mx I to FM [25g] **Force application:** 2, 14, 28d [10 an/group] **Nicotine administration:** 30d + 2, 14, 28d [10 an/group]	**EG**: 30; 1 mg/kg; SC; 1/d **PG**: 30; 0.1 ml ns; SC; 1/d **Sample size calculation:** NM	**On dental casts:** digital caliper [d 2, 14, 28] **Method error:** NM
Ferreira et al. [2018]	Wistar rats [male, 12-week-old, mean weight: 300g] SS CCS from R Md I to FM [40g] **Force application:** 7d **Nicotine administration:** daily for 67d + 7d [5d/week]	**EG**: 14 hemi-mand; 1.29 mg/kg; IN§ **CG**: 14 hemi-mand **Sample size calculation:** Yes [but not for the rate of tooth movement]	**Clinically:** digital caliper [d 7] **Method error:** NM

an: Animals; CCS: Closed Coil Spring; CG: Control group without sham procedure carried out; d: days; EG: Experimental group; FM: First Molar; hemi-mand: hemi-mandible; I: Incisor; IN: Inhalation of cigarette smoke; IP: Intraperitoneally; L: Left; Md: Mandibular; Mx: Maxillary; ns: normal saline; PBS: Phosphate Buffer Saline; PG: Placebo group with sham procedure carried out; R: Right; SM: Second Molars

*Initiated 10d before force application; within the first 5d nicotine dose applied increased daily from 1/5 of the final in 1/5 increments to allow adaptation

§The exposure to nicotine per day after cigarette smoke inhalation was converted to mg/kg (Jarvis et al., 2001; Remmer, 1987)

5.3. Risk of bias assessment

Table 2 summarizes the findings of risk of bias assessment. In regard to allocation sequence generation and random housing of the animals, all studies showed an unclear risk of bias apart from Kirschneck et al. (2017). Assessor blinding risk of bias was low for Sodagar et al. (2011), Kirschneck et al. (2017) and Araujo et al. (2018). Other issues potentially creating bias could not be identified, except for Ferreira et al. (2018) where it was clearly mentioned were the compared hemi-mandibles came from the same animals or from different. Bias regarding baseline group similarity, handling of incomplete data and selective reporting was considered low. For the rest of the domains examined the risk of bias was considered unclear.

Table 2. Risk of bias assessment.

Study	Signaling questions									
	1	2	3	4	5	6	7	8	9	10
Sodagar et al. [2011]	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Bakathir et al. [2016]	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Kirschneck et al. [2017]	Low	Low	Unclear	Low	Unclear	Unclear	Low	Low	Low	Low
Araujo et al. [2018]	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Ferreira et al. [2018]	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear

1: Was the allocation sequence adequately generated and applied? 2: Were the groups similar at baseline or were they adjusted for confounders in the analysis? 3: Was the allocation adequately concealed? 4: Were the animals randomly house during the experiment? 5: Were the caregivers and investigators blinded to the intervention that each animal received? 6: Were animals selected at random for outcome assessment? 7: Was the outcome assessor blinded? 8: Were incomplete outcome data adequately assessed? 9: Are reports of the study free of selective outcome reporting? 10: Was the study apparently free of other problems that could result in a high risk of bias?

5.4. Synthesis of results

Overall, nicotine administration tended to increase the rate of orthodontic movement [WMD: 0.178; 95% CI: 0.083 to 0.274; p=0.00] (Figure 2). However, when analysis was repeated per time point, the acceleratory effect after nicotine administration was confirmed only for the observations after 14 days of tooth movement, the time point that included most observations [WMD: 0.317; 95% CI: 0.179 to 0.454; p=0.00]. Furthermore, in an exploratory meta-regression that included the intercept, the duration of tooth movement (in days) and the concentration of the administered nicotine (in mg/kg), no effect was observed (Figures 3-5).

Study name	Time point	Difference in means	Standard error	Lower limit	Upper limit	p-Value	Difference in means and 95% CI
2018 Araujo et al.	[a] 2 days	-0,230	0,246	-0,712	0,253	0,351	
		-0,230	0,246	-0,712	0,253	0,351	
2018 Ferreira et al.	[b] 7 days	0,070	0,074	-0,075	0,215	0,344	
		0,070	0,074	-0,075	0,215	0,344	
2011 Sodagar et al. [0.50 mg/kg]	[c] 14 days	0,260	0,279	-0,286	0,806	0,351	
2011 Sodagar et al. [0.75 mg/kg]	[c] 14 days	0,410	0,192	0,034	0,786	0,032	
2011 Sodagar et al. [1.00 mg/kg]	[c] 14 days	0,570	0,225	0,129	1,011	0,011	
2017 Kirschneck et al.	[c] 14 days	0,200	0,053	0,095	0,305	0,000	
2016 Bakathir et al. [0.37 mg/kg]	[c] 14 days	0,270	0,025	0,221	0,319	0,000	
2016 Bakathir et al. [0.57 mg/kg]	[c] 14 days	0,290	0,022	0,248	0,332	0,000	
2016 Bakathir et al. [0.93 mg/kg]	[c] 14 days	0,590	0,027	0,537	0,643	0,000	
2018 Araujo et al.	[c] 14 days	0,000	0,124	-0,244	0,244	1,000	
		0,317	0,070	0,179	0,454	0,000	
2017 Kirschneck et al.	[d] 28 days	0,300	0,085	0,134	0,466	0,000	
2018 Araujo et al.	[d] 28 days	-0,176	0,192	-0,551	0,200	0,359	
		0,093	0,236	-0,369	0,555	0,693	
		0,178	0,049	0,083	0,274	0,000	

-1,00   -0,50   0,00   0,50   1,00

More in Control Group   More in Nicotine Group
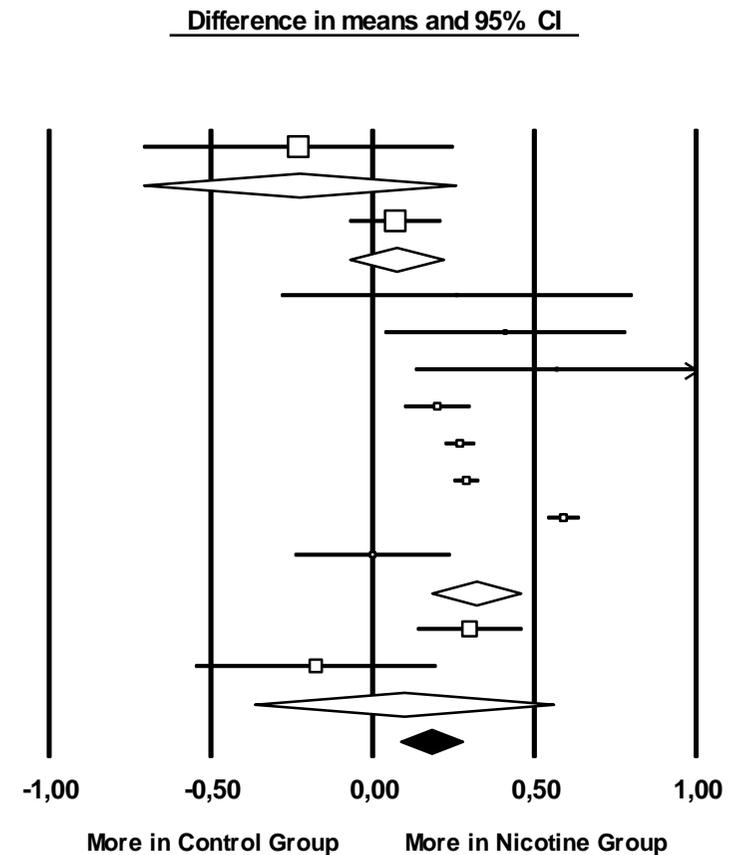
**Figure 2.** Forest plot.
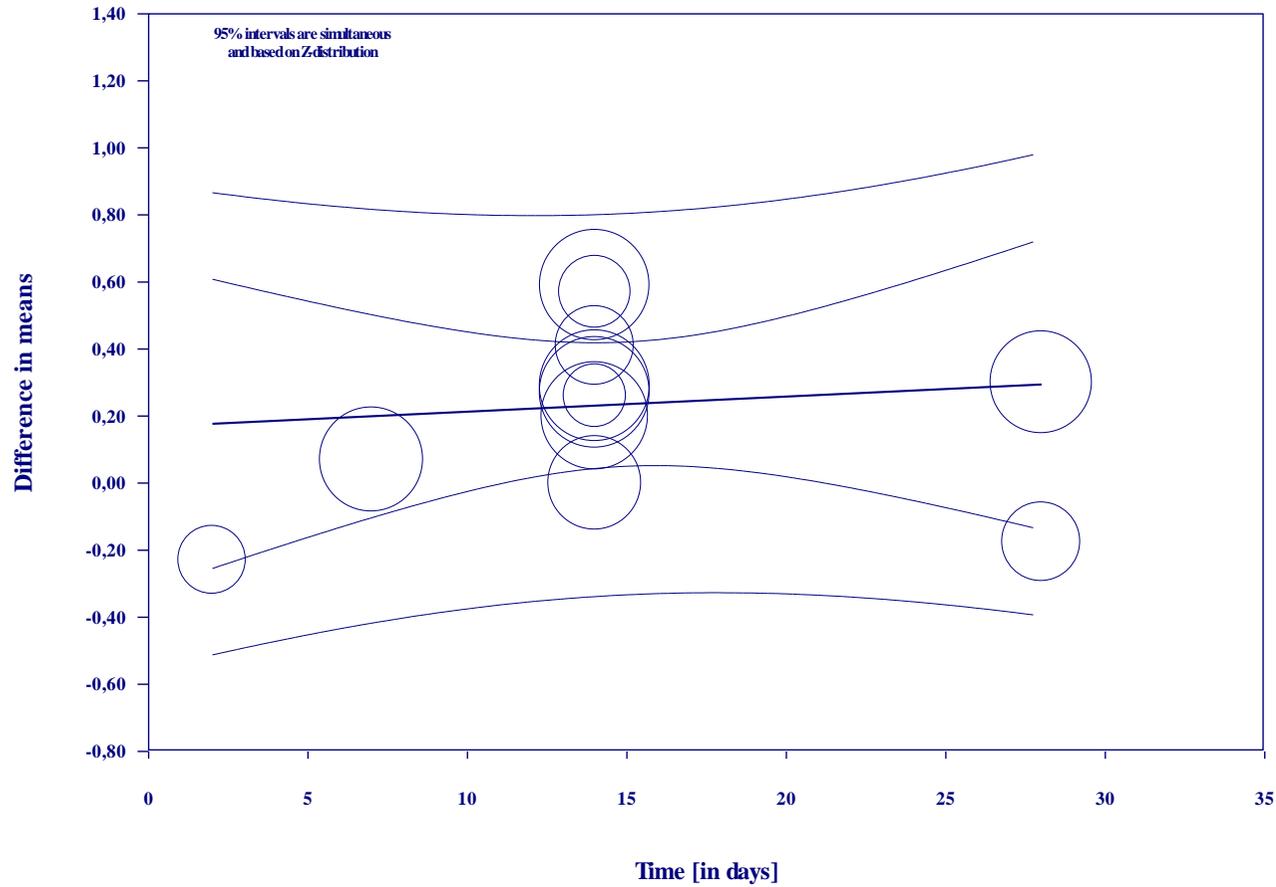
Figure 3. Meta-regression analysis to explore the effect of the duration of force application on the rate of tooth movement.
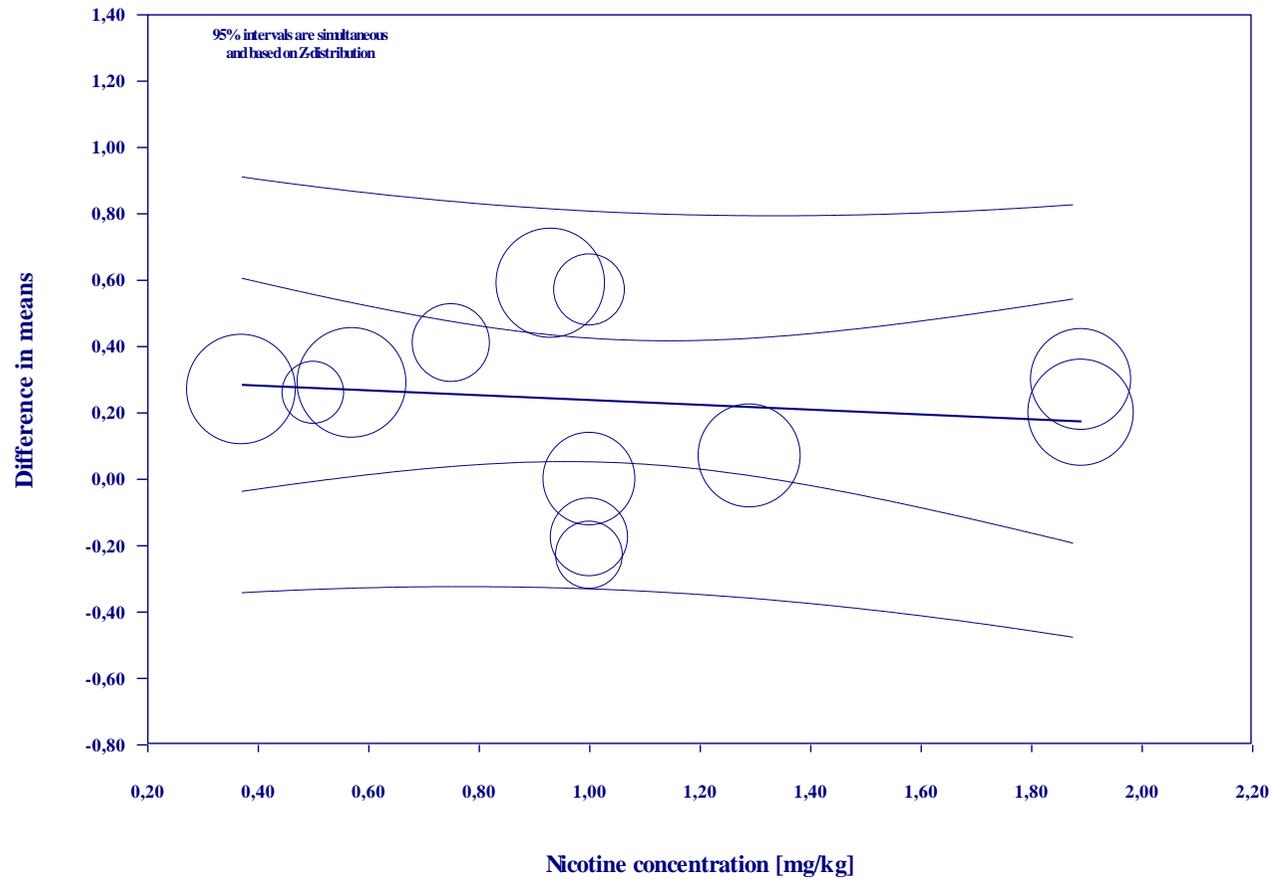
Figure 4. Meta-regression analysis to explore the effect of administered nicotine concentration on the rate of tooth movement.

Main results for Model 1, Random effects (MM), Z-Distribution, Difference in means

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	0,2440	0,1929	-0,1341	0,6221	1,26	0,2060
Time	0,0045	0,0108	-0,0166	0,0256	0,42	0,6742
Nicotine concentration	-0,0724	0,1379	-0,3427	0,1978	-0,53	0,5993

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

$Q = 0,35$, df $= 2$, $p = 0,8387$

Goodness of fit: Test that unexplained variance is zero

$Tau^2 = 0,0370$, $Tau = 0,1924$, $I^2 = 93,55\%$, $Q = 139,64$, df $= 9$, $p = 0,0000$

Comparison of Model 1 with the null model

Total between-study variance (intercept only)

$Tau^2 = 0,0295$, $Tau = 0,1717$, $I^2 = 92,18\%$, $Q = 140,73$, df $= 11$, $p = 0,0000$

Proportion of total between-study variance explained by Model 1

R^2 analog $= 0,00$ (computed value is -0,26)

Figure 5. Meta-regression model and basic statistics.

6. DISCUSSION

6.1.   Summary of available evidence

The use of tobacco products is not only relevant to the increased numbers of adult patients seeking orthodontic therapy and now reported to comprise about a third of the orthodontic population (American Association of Orthodontists, 2016) but also to the older school-aged children that constitute the vast majority of patients under orthodontic treatment. Exposure to nicotine has been reported to modify bone metabolism (Araujo et al., 2018; Nagaie et al., 2014; Shintcovsk et al., 2014; Rothem et al., 2013; Tanaka et al., 2013; Saito et al., 2012; Ying et al., 2011; Tanaka et al., 2006; Tanaka et al., 2005; Henemyre et al., 2003; Hollinger et al. 1999), with potential effects on the rate of orthodontic tooth movement. Based on the data included in the meta-analysis, nicotine administration increased the rate of movement overall. However, no effect of nicotine concentration or the duration of force application on the rate of movement was observed. Although information from animal studies cannot be fully translated to human clinical scenarios and these analyses are exploratory until more scientific information becomes available, it could be safe practice for the orthodontist to be able to identify patients exposed to nicotine and consider the possible implications.

When the difference in the rate of tooth movement between the nicotine administered and the control groups was analyzed per time point, the acceleratory effect following nicotine administration was confirmed for the observations after 14 days of force application. This is the time point that included most observations and can, thus, be considered the most representative of the analysis. Thus, the null hypothesis can be rejected.

Nicotine has been shown to affect the metabolism of bone (Fung et al., 1998; 1999). Even low concentrations considerably stimulate bone marrow cell proliferation (Ying et al., 2011).

Nicotine has also been shown to upregulate the formation and differentiation of osteoclasts in general (Tanaka et al., 2006; Henemyre et al., 2003) and during orthodontic tooth movement (Bakathir et al., 2016; Kirschneck et al., 2017), although opposite reports exist (Araujo et al., 2018; Nagaie et al., 2014; Araujo et al., 2018). Li et al. (2015) demonstrated an increase in receptor activator of nuclear factor-Kappa B ligand levels (RANKL) which is associated with an accelerated rate of bone turnover (Tyrovola et al., 2008), leading potentially to faster orthodontic tooth movement. The RANKL/osteoprotegerin (OPG) system is responsible for the regulatory control of osteoclastogenesis in both tension and pressure sides (Tyrovola et al., 2008). Kirschneck et al. (2017) observed that osteoclast activity and gene expression of inflammatory and osteoclast markers were significantly increased compared to controls under the influence of nicotine. In addition, high levels of nicotine affect adversely osteoblast proliferation (Rothem et al., 2013) and osteogenesis is suppressed (Tanaka et al., 2005; 2013). Nicotine has also been shown to delay angiogenesis, which in turn delays the formation of the connective tissue and osteogenesis (Pinto et al., 2013). Although Shintcovsk et al. (2014) did not observe an upregulating effect of nicotine administration on osteoclast-like cells and Howship's lacunae, they found that nicotine affected adversely the bone remodeling mechanism during orthodontic movement by reducing angiogenesis and delaying the collagen maturation process in the developed bone matrix.

Moreover, nicotine has also been shown to decrease the radiopacity of bone (Hollinger et al. 1999) and negatively affect bone mineral density in humans (Lorentzon et al., 2007). Such effects have been associated with marked reductions in the volume of trabecular bone, trabecular thickness, mineralizing surface, mineral appositional rate and the rate of formation of bone, coupled with increases in the surfaces covered by the osteoclasts. Overall, nicotine affects adversely the general dynamics of trabecular histomorphometric parameters (Hapidin

et al., 2007) and the ability of fracture repair (Kallala et al.; 2013). Effects such those mentioned above could account for the observed acceleratory effect in the rate tooth movement following 14 days of sustained force application.

For the other points of observation, no difference was observed, and the meta-regression did not detect an effect also. Such findings could be attributed to the scarcity of data pertaining to the other time points and should be considered only as exploratory until further research becomes available. Moreover, tooth movement in rats can be summarized in 3 phases: instantaneous tooth movement, delayed tooth movement and linear phase of tooth movement (Bridges et al., 1988). After the early response to the orthodontic force that is depended on the viscoelastic properties of the tissues, a small amount of change occurs in the subsequent delay period due to the hyalinization phenomena. Finally, in the third phase tooth movement occurs. Based on the above observations, the findings of difference in the two groups in the early measurements could be anticipated.

In the 28 days measurements, Kirschneck et al. (2017) observed an acceleration in the rate of tooth movement whereas Araujo et al. (2018) a deceleration, leading to a non-significant statistical result after the application of the quantitative synthesis techniques. In general, Araujo et al. (2018) was the only study not showing more movement in the nicotine administered group compared to the control after the application of orthodontic force systems. Differences in the experimental setting like animal species, as well as nicotine concentration and duration of administration may have influenced the results (Makrygiannakis et al., 2019). Moreover, differences in measurement methodology could play a role. Kirschnek et al. (2017) used CBCT, whereas Araujo et al. (2018) used measurements on dental cast to quantify tooth movement.

According to the findings of Sodagar et al., (2011) and Bakathir et al. (2016), nicotine accelerated the tooth movement in rats in a dose dependent manner. However, in the exploratory meta-regression the concentration of the administered nicotine (in mg/kg) did not show any effect. Once more differences in the experimental setting like animal species, as well as nicotine dosage, route and duration of administration may have influenced the results (Makrygiannakis et al., 2019). Finally, it should not be overlooked that these analyses are exploratory until more scientific information becomes available.

Even from this set of animal data, one could understand that it would be safe practice for the orthodontist to be able to identify patients exposed to nicotine. This group of individuals could involve both active and passive smokers, the latter being potentially exposed to significant amounts of nicotine (Haustein and Groneberg, 2010). Moreover, clinicians might get an insight into the relevant clinical considerations related to treatment. It is possible that the estimation of the duration of treatment should be modified. In terms of mechanotherapy, it must be considered that patients may present increased needs for anchorage preparation. Since it has been reported that orthodontically moved teeth in animals exposed to nicotine exhibit a greater amount of root resorption (Li et al., 2015; Kirschneck et al.;2017), the magnitude of forces should also be controlled. Furthermore, it is possible that clinicians might encounter greater difficulty in planning retention in patients that smoke. Moreover, individuals who smoke exhibit quadruple likelihood to be affected by periodontitis (Tomar and Asma, 2000) and that orthodontic mechanical stimuli in conjunction with inflammation of the periodontium might lead to bone resorption and attachment defects (Nogueira et al., 2017; Ren et al., 2014). Finally, it should not be forgotten that a doctor should always educate the patient in regard to the ill effects of smoking and nicotine, as well as encourage smoking cessation (Haustein and Groneberg, 2010).

6.2.   Strength and limitations of the present review

The present review followed specific guidelines and well-established methodology. Data collection and retrieval was planned with a strategy that was exhaustive, covering electronic, manual and grey literature material up to July 2019. All available studies were included, irrespective of the language, date and status of the publication. The extent of any possible bias was reduced to the extent possible. Moreover, the processes of screening, verification of eligibility, information abstraction and assessment of the risk of bias were conducted in duplicate. The corresponding authors were contacted and consulted for clarifications and queries when needed. Additionally, any disagreement in the process was resolved by discussion with the dissertation co-supervisor.

There were also some limitations present in the study, mainly pertaining to the characteristics and nature of the data collected during the review process. The currently available information is not only indirectly related to humans because the data originates from animal studies but also involves the administration by the administration of nicotine for different amounts time, altered dosages and routes that could have dissimilar effects on the pharmacokinetics and bio-availability when compared to a human setting. The act of smoking creates a different form of systemic drug administration via the pulmonary rather than the portal or systemic venous circulations (Haustein et al., 2017), resulting in different absorption patterns (Benowitz et al., 1988). Only one study exposed the experimental animals to cigarette smoke inhalation, a situation closer to human passive nicotinic exposure (Ferreira et al., 2018). In such cases, it is possible that some of the other chemical compounds included in cigarette smoke other than nicotine, may cause the observed effects (Haustein and Groneberg, 2010). Additionally, the use of specific modes to induce orthodontic tooth movement further circumscribes the

generalizability of the retrieved information to human clinical scenarios. Also, several omissions in the report of the studies led to unclear conclusions regarding the risk of bias in various domains. Consequently, it cannot be still clearly determined, whether exposure to nicotine can affect tooth movement in common clinical scenarios.

6.3.   Recommendations for future research

Since nicotine exposure could be relevant to adults and older school-aged children consuming tobacco products, as well as passive smokers seeking orthodontic treatment, the need for further research is necessitated. Study designs must be standardized, with low risk of bias and as generalizable as possible, in order to mimic the clinical scenarios in daily orthodontic practice.

7.   CONCLUSIONS

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Rats administered with nicotine showed overall accelerated rates of orthodontic tooth movement. Although, information from animal studies cannot be fully translated to human clinical scenarios, the orthodontist should be able to identify patients exposed to nicotine and consider the possible implications for everyday clinical practice.

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9. APPENDICES

Appendix I. Scottish Intercollegiate Guidelines Network (SIGN) algorithm for classifying study design for questions of effectiveness.
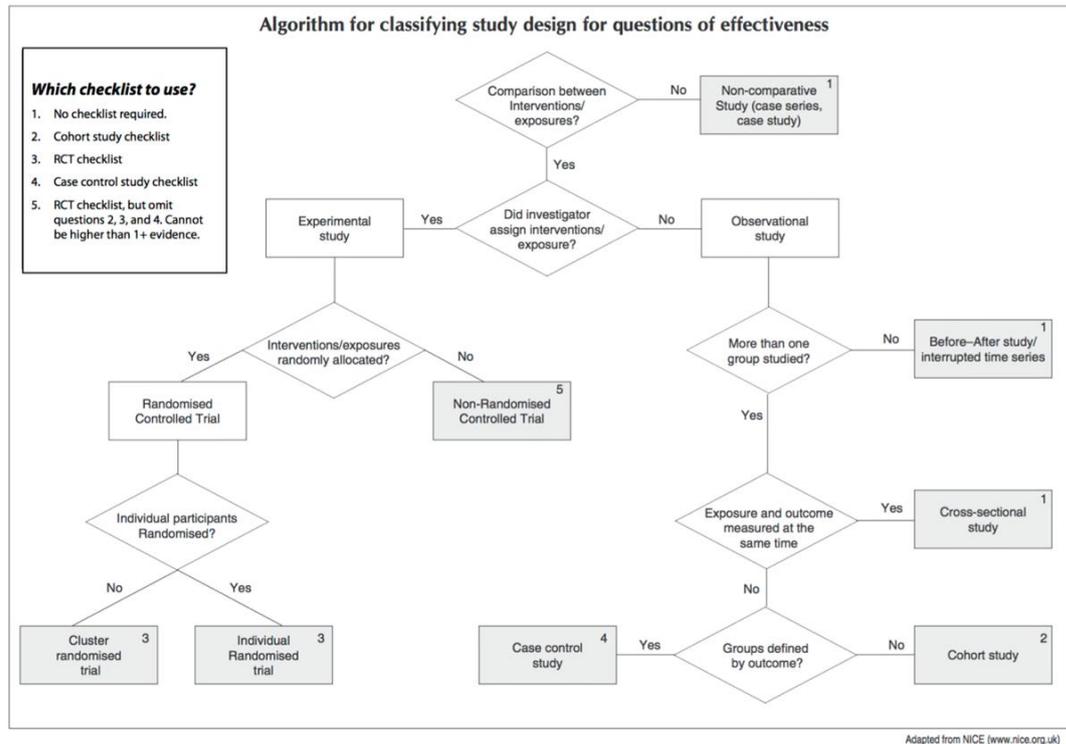
Appendix II. Strategy for database search.

Database [2019 07 09]	Search strategy	Hits
PubMed	(nicotine OR smok* OR cigarette* OR tobacco) AND (orthodon* OR "orthodontic force" OR "mechanical force" OR "tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR "root resorption")	**252**
Cochrane Central Register of Controlled Trials	(nicotine OR smok* OR cigarette* OR tobacco) AND (orthodon* OR "orthodontic force" OR "mechanical force" OR "tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR "root resorption") in Title Abstract Keyword - (Word variations have been searched)	**105**
Cochrane Database of Systematic Reviews	(nicotine OR smok* OR cigarette* OR tobacco) AND (orthodon* OR "orthodontic force" OR "mechanical force" OR "tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR "root resorption") in Title Abstract Keyword - (Word variations have been searched)	**0**
Scopus	TITLE-ABS-KEY((nicotine OR smok* OR cigarette* OR tobacco) AND (orthodon* OR "orthodontic force" OR "mechanical force" OR "tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR "root resorption"))	**213**
Web of Science™	TOPIC: ((nicotine OR smok* OR cigarette* OR tobacco) AND (orthodon* OR "orthodontic force" OR "mechanical force" OR "tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR "root resorption")) Timespan: All years. Databases: WOS, KJD, RSCI, SCIELO, ZOOREC. Search language=Auto	**175**
Arab World Research Source	TI tooth movement AND AB tooth movement	**3**
ProQuest Dissertations and Theses Global	ti((nicotine OR smok* OR cigarette* OR tobacco) AND (orthodon* OR "orthodontic force" OR "mechanical force" OR "tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR "root resorption")) OR ab((nicotine OR smok* OR cigarette* OR tobacco) AND (orthodon* OR "orthodontic force" OR "mechanical force" OR "tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR "root resorption")) in Full Text	**7**