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CIGARETTE SMOKING, NICOTINE AND PARKINSON'S DISEASE: CONTROVERSIES IN CLINICAL TRIAL DATA AND MEDICAL PRACTICE

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Abstract

It's well known that smoking cigarettes is causally linked to a number of serious mortal diseases. These include laryngeal, lung, bladder, and digestive tract cancers, chronic obstructive pulmonary disease and a number of cardiovascular diseases, such as aortic aneurysm, stroke, and ischemic heart disease.

In 2014, U.S. Surgeon General Report states that smoking is causally associated with inflammation and impaired immune function, and that regular smokers are at higher risk of developing pneumonia, tuberculosis, and other airway infections. So the best way to avoid harm from smoking is to never start, and for smokers to quit.

However, evidence from epidemiological studies suggests a relationship between cigarette smoking and low risk of Parkinson's disease. As a major component of tobacco smoke, nicotine has been proposed to be a substance for preventing against Parkinson's disease risk, with a key role in regulating striatal activity and behaviors mediated through the dopaminergic system. Another data suggests quick deterioration and disease exacerbation after smoking cessation. Animal studies also showed that nicotine could modulate dopamine transmission and reduce levodopa-induced dyskinesias.

Smoking cessation, proposed because of the health issues as certainly reducing the risk of cardiovascular events and cancer, must be definitely accepted as major health paramount procedure, but in the case of Parkinson's disease nicotine-substitute supplements must be provided. As a small amount of nicotine can saturate a substantial portion of nicotine receptors in the brain, nicotine from other sources, such as less harmful smoking advanced devices as well as diet, could be a promising therapeutic substance for motility support and protection against Parkinson's disease.

Keywords: *tobacco smoking, nicotine, Parkinson's disease*

Introduction

Parkinson disease (PD) is an age-related neurodegenerative disorder, with a prevalence of 1-2% among adults aged 55 years and older [*Bezard E et al., 2001*]. Newest data suggest that approximately 1% of individuals older than 60 years are affected by PD, but younger people can also develop PD. Around 60,000 Americans are diagnosed with PD each year, yet this number does not reflect the thousands of cases that go undetected. It has been estimated that 7-10 million people worldwide are

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living with PD [*Thacker E et al., 2007*]. It is predicted to be approximately 9 million PD patients by 2030. The increasing prevalence of PD is associated with higher morbidity, mortality, and health care costs.

It is characterized by a progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta that results in tremor, rigidity, bradykinesia, and possibly dementia [*Olanow C, Tatton W,1999*].

The current evidence related to PD pathogenesis includes defective handling of proteins, mitochondrial dysfunction, oxidative stress, and inflammation [*Bueler H, 2010; Zuo L, Motherwell M, 2013; Camilleri A, Vassallo N, 2014; Connolly B, Lang A, 2014*]. There is no cure for the disease, and only symptomatic relief is available.

Especially in the early stages of the disease, dopamine replacement therapies provide effective control of the motor symptoms with Levodopa/L-3,4-dihydroxyphenylalanine (L-dopa) as the gold standard. However, chronic L-DOPA use does not adequately manage the non-motor deficits and additionally induces a variety of motor and psychiatric side effects that limits its effectiveness [*Huot P et al., 2013; Connolly B, Lang A, 2014*]. These shortcomings strengthen the importance of identifying alternate treatment strategies that delay or halt disease progression, or ideally restore function in PD. Previous reviews reported the association between nicotine and PD risk, but the sources were limited to cigarette smoking and medical use.

While the PD etiology remains poorly understood, numerous studies have shown that environmental factors play key roles in its pathogenesis. We updated epidemiological, own preclinical and clinical data, and studies on nicotine from other sources. We also reviewed the cigarette smoking to understand the potential protective role of nicotine on PD.

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

TOBACCO, NICOTINE AND PARKINSON'S DISEASE: CLINICAL DATA CONTROVERSY

Previous epidemiologic studies have consistently shown that cigarette smoking [*Kelton M et al., 2000; Hernan M et al.,2001; Hernan M et al., 2002; Ritz B et al., 2007; Li X et al., 2015; Veljkovic E et al., 2018*] and smokeless tobacco use [*Benedetti M et al.,2000; O'Reilly E et al., 2005*] are associated with a lower risk of PD. Environmental tobacco smoke exposure is also associated with a significantly lower PD risk among never active smokers [*O'Reilly E et al., 2009; Searles Nielsen S et al., 2012*]. Population-based studies have shown that smoking was associated with approximately 40-50% reduced risk of developing PD [*Hernan M et al., 2002; Ritz B et al., 2007*].

A recent study reported that patients with PD were able to quit smoking more easily than controls [*Ritz B et al., 2014*]. This study suggests that the ease of smoking cessation is an early manifestation of pre-motor PD related to the loss of nicotinic rewards. In this case, quitting smoking could be just a pre-clinical marker rather than a risk factor [*Moccia M et al., 2015*]. However, in a case-control study in France, with 247 cases and 676 controls, when smoking was defined as cigarette smoking 18 years before PD onset, the same inverse association was still present [*Kelton M et al., 2000; Galanaud J et al., 2005*].

Cigarette smoking is suggested to be one of the main protective factors for PD. The risk-lowering effect of smoking on PD has been observed even in ex-smokers. A meta-analysis found that the risk of PD was 58% lower in current smokers and 24% lower in ex-smokers than in never smokers [*Thacker E et al., 2007*]. One case-control study with 196 cases have shown that tobacco use, including tobacco chewing or snuff use, is inversely associated with risk of PD [*Liu Z et al., 2017*].

Consistently, in a case-control study based on 154 PD cases from Washington State, environmental tobacco smoke exposure was associated with 64% lower risk of PD [*Searles Nielsen S et al., 2012*]. Among persons with passive smoking as the only tobacco smoke exposure, risk was inversely associated with years exposed [*Searles Nielsen S et al.,2012*]. One cohort study using parental smoking as the tobacco exposure, has also shown the dose-response inverse association with

PD incidence [*O'Reilly E et al., 2009*]. Because smoke has always been shown as a cause of adverse health outcomes, the inverse association between smoking and the risk of PD was counterintuitive. Some researchers believed that this relation resulted from a true biological protective effect of cigarette smoking. However, some researchers proposed that the reverse association might result from bias. For example, the association between smoking and lower PD risk could be explained by a still-unknown third factor that increases the risk of PD and also causes an aversion to smoking behavior [*Benedetti M et al., 2000; Ritz B et al., 2014*].

Further, one of disadvantages of case-control studies is incidence-prevalence bias. This type of bias could be due to higher smoking-related mortality among incident cases than among controls, leading to a lower proportion of smokers among prevalent PD cases than among controls. However, the results of prospective cohort studies are in agreement with the results of case-control studies, which could minimize this type of bias. In addition, in a prospective study in the Health Professional Follow-up Study with 288 incident PD cases, smoking was not associated with a higher relative risk of death among PD patients than among non-PD patients [*Chen H et al., 2006*]. An alternative hypothesis that genetic polymorphisms that influence tolerance to tobacco smoke may also increase the risk of PD might account this inverse association. Twin studies are usually used to test this type of hypothesis as a gold standard. An inverse relationship between smoking and PD was observed among monozygotic twins, suggesting that genetic factors is unlikely to confound this relationship, moreover direct connections between nicotine deficiency and sleep disorders in PD patients were described [*Bharucha N et al., 1986; Tanner C et al., 2002; Iranzo A et al., 2006; Frenette E, 2010; Wing Y et al., 2012; Postuma R et al., 2012; Schenck C et al., 2013; Iranzo A et al., 2014; Postuma R et al., 2015a; Postuma R et al., 2015b; Wong J et al., 2016; Saeed U et al., 2017*].

With regard to the association between smoking and olfactory function, previous studies (all cross-sectional design) generated mixed results: some [*Murphy C et al., 2002; Vennemann M et al., 2008*], but not all [*Le Floch J et al., 1993; Bramerson A et al., 2004; Liu G et al., 2016; Seubet J et al., 2017; Huang Z et al., 2017*], reported that smokers were more likely to have olfactory dysfunction. It remains unclear whether this is due to a true biological effect of smoking on olfaction or a reverse causality – individuals with olfactory dysfunction may quit smoking.

Extensive literature demonstrates reduced PD risk among current and former smokers. This inverse association between PD and smoking correlates with increased intensity and duration of smoking is more pronounced in current versus former smokers, decreases with years after quitting smoking, and is observed with different types of tobacco products. It has been hypothesized that this surprising effect may be due to the increased mortality associated with smoking related diseases prior to the development of PD. However, several large epidemiological studies have found that this inverse association did not appear to be due to selective survival of PD cases [*Kelton M et al., 2000; Veljkovic E, 2018*].

Constipation and higher risk of developing PD was observed in six population-based studies [*Abbott R et al., 2001; Savica R et al., 2009; Gao X et al., 2011; Lin C et al., 2014; Plouvier A et al., 2014; Schrag A et al., 2015*]. A cross-sectional study with 516 functional constipation cases reported an association between smoking and higher likelihoods of several functional gastrointestinal symptoms, including functional constipation [*Lundstrom O et al., 2016*]. Researchers observed that smoking delayed gastric emptying of solids, rather than liquids, and nicotine was not responsible for the effect [*Miller G et al., 1989*], while acute cigarette smoking in habitual smokers delayed mouth-cecum transit time, an effect most likely due to nicotine [*Scott A et al., 1992*].

After use of trans-dermal nicotine application in nonsmokers, a dose-dependent, significant decrease of total colon transit time was observed, mainly due to an accelerated transit in colon sigmoideum and rectum [*Rausch T et al., 1998*]. Additionally, colonic transit time was significantly shorter in men than in women, and smoking males have prolonged colonic transit time compared with nonsmoking men, while a difference was not observed in women [*Meier R et al., 1995*]. However, in another cross-sectional study with 148 func-

tional constipation cases in Bangladesh, smoking was not associated with functional constipation [*Perveen I et al., 2015*].

Regarding another risk factor for prodromal PD – erectile dysfunction [*Gao X et al., 2007; Schrag A et al., 2015*], multiple human, animal, case series, cross-sectional, and cohort studies support the notion that cigarette smoking is a risk factor for erectile dysfunction. Further, a positive dose-response relation has also suggested that increased quantity and duration of smoking is associated with a higher risk of erectile dysfunction [*Biebel M et al., 2016*].

MECHANISM OF NICOTINE AND PARKINSON'S DISEASE

Findings on the inverse association between cigarette smoking and PD, together with observations that smokeless tobacco users had a lower risk of PD [*O'Reilly E et al., 2005*], support the notion that certain tobacco components, possibly nicotine, could be a promising substance for preventing against PD risk or slowing PD progression [*Quik M et al., 2012*]. The rationale for the candidate role of nicotine is on the basis of evidence demonstrating a close anatomical relationship between the nicotinic cholinergic and dopaminergic neurotransmitter systems in the striatum [*Zhou F et al., 2002*]. Nicotine and its receptors play a key role in regulating striatal activity and behaviors mediated through the dopaminergic system, by activation of nicotinic acetylcholine receptors on dopaminergic terminals and modulating dopamine release [*Quik M, 2004; Grady S et al., 2007; Quik M, Wonnacott S, 2011*].

A number of studies using experimental animal models have shown that nicotine can protect against neurotoxin-induced nigro-striatal damage and improve motor impairments associated with L-DOPA (the gold standard therapy for PD), with dyskinesia as a side effect. In rats, nicotine pretreatment before introduction of lesions reduces neuronal damage, assessed using markers of striatal dopaminergic integrity, including levels of dopamine and its metabolites, tyrosine hydroxylase, dopamine transporters, and vesicular monoamine transporters [*Kelton M et al., 2000; Veljkovic E, 2018*].

The degree of protection against nigro-striatal damage depends on several parameters: lesion size (optimal effectiveness is observed when a moderate damage regimen is engaged), nicotine dose, and timing of administration. Nicotine exhibits a U-shaped dose-response curve. Maximal protection occurs with intermediate nicotine-dosing regimens. Protection was observed with both intermittent and continuous nicotine dosing [*Veljkovic E, 2018*].

Nicotine and its agonists could also reduce levodopa-induced dyskinesias and had been evaluated in rodents and monkeys. In Parkinsonian monkeys, administration of nicotine reduced levodopa-induced dyskinesias by 50-60%, without development of tolerance [*Quik M et al., 2013 a; b; Zhang D et al., 2014 a; b*]. With respect to hemi-parkinsonian rats, which received levodopa injection, nicotine also reduced dyskinesia by more than 50% [*Bordia T et al., 2008; Bordia T et al., 2010*]. These results yield insight that nicotine may inhibit the transport of levodopa by the system L-amino acid transporter. Regarding mechanism of neuroprotection against PD, another hypothesis states that the elevation of brain cytochrome P450 enzymes induced by nicotine may play a role [*Miksys S, Tyndale R, 2006*]. According to this hypothesis, higher levels of cytochrome P450 enzymes in the brain, whether due to genotype or their induction by nicotine, can increase inactivation of neurotoxins, thus delaying development and progression of PD [*Miksys S, Tyndale R, 2006*].

In addition, a novel hypothesis recently proposed that cigarettes may change the composition of the microbiota in the gut in a manner of mitigating intestinal inflammation [*Derkinderen P et al., 2014*]. Dietary nicotine and PD as demonstrated by a neuro-image study, a substantial portion of nicotine receptors became occupied when exposed to relatively small amount of nicotine [*Brody A et al., 2006; Palacios N et al., 2012*]. This notion has further been supported by the observation that long-term smoking is more important than smoking intensity in the smoking-PD relationship. Besides cigarettes, nicotine has a wide distribution in flora and presents in some common vegetables that belong to the biological family of nightshades. They include potatoes, tomatoes, and peppers. Of note, the intake amount from these vegetables is gener-

ally much lower relative to that obtained from tobacco [*Chen H et al., 2010; Palacios N et al., 2012; Nielsen S et al., 2013; Kenborg L et al., 2015*].

Conclusion

Nicotine was a topic of preclinical and clinical investigations into its therapeutic potential because nicotine stimulates dopamine release, a property relevant to PD. Clinical data were inconclusive, with some positive and some negative results following administration of nicotine via different routes (nicotine patch, gum, or intravenous).

Epidemiological data on smoking and alternative nicotine consumption and the incidence of PD have clearly shown an inverse correlation. As a small amount of nicotine can saturate a substantial portion of nicotine receptors in the brain, nicotine from other sources, such as diet, could be a promising therapeutic substance for protection against PD.

Given the roles of different receptors in PD, nicotine should be investigated further for its pharmacological properties. The inconsistency between epidemiological data and clinical trial results obtained with nicotine alone may suggest that other tobacco compounds, separated from combustible tobacco products, may play a role [*Veljkovic E, 2018*].

So, we prove the importance of nicotine supplementation from dietary and/or another sources in patients with PD to sustain the motility and decrease the level of complications, although the constant heavy smokers could suffer from general cardiovascular and oncological diseases.

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2007 *The New Armenian Medical Journal is 15 years-old* 2022

The time flying by so fast and it's seems that our The New Armenian Medical Journal was with us decades, but it's an annual year, and we proudly celebrating our first decade anniversary!

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I am by myself proud to be with the Journal from the creation and all this tempting years, being of the part of it.

Vice Editor-in-chief of "The New Armenian Medical Journal"

Head of the Department of Neurology, , YSMU

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