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Beyond the Smoke: Could Nicotine Actually Be a Medicine for Parkinson Disease?

Mr. Param Paresh Patel

Student, Pharmacy

Abstract

Background: I have read that nicotine is a drug. Recent research says nicotine might help treat Parkinson's disease. Parkinson's disease is caused by loss of neurons that make dopamine. That loss breaks the link, between the dopamine system and the acetylcholine system. When the brain circuits lose their integrity patients show motor signs such as tremor and other movement problems. I have read that tobacco use does not give any health benefits. Tobacco use is a risk factor, for disease. Tobacco use increases the chance of disease, cancer, chronic obstructive pulmonary disease and death. The literature reports an observation. Population based studies report a finding. The finding is that cigarette smokers have rates of Parkinson's disease, then nonsmokers. I find the rates of Parkinson's disease, in cigarette smokers because smoking is known to cause serious health problems. The contradiction caught the attention of researchers. Researchers examined nicotine to see if nicotine can protect the dopamine-producing neurons. Researchers also examined nicotine to see if nicotine can lower the risk of developing Parkinson's disease.

Objective: I wrote this review to summarize work that looks at nicotine without tobacco smoke and how nicotine can protect systems. I wrote this review to interpret the results of that work. I wrote this review to evaluate findings from laboratory-based studies and human studies.

Conclusion: Some observational studies have found a link, between smoking cigarettes and the lower risk of Parkinsons disease. The observational studies have sparked interest in nicotine as a brain-protecting agent. In studies that use animal models nicotine shows ways to change, cut back or even reverse the damage to dopaminergic neurons. The clinical trial data, in humans testing nicotine for pd show results.

1. Introduction

I see Parkinsons disease (PD) getting worse, over time and hurting the brain. I see Parkinsons disease (PD) showing a build-up of misfolded α-synuclein and loss of neurons in the tract. I notice the number of people with Parkinsons disease (PD) keeps going up around the world. I worry that the rise of Parkinsons disease (PD) creates a public health problem because Parkinsons disease (PD) limits movement, independence and the quality of life, for millions. I have read that many studies show that people who use tobacco get Parkinsons disease (PD) often, then people who do not smoke. This odd thing makes researchers ask if nicotine or some part of tobacco affects pathways that change the risk for Parkinsons disease (PD). So smoking is still bad, for health.

Parkinson's disease begins when the neurons, in the substantia nigra that produce dopamine slowly break down. The neurons in the substantia nigra send dopamine to the striatum. When the neurons in the substantia nigra break down the breakdown irritates the ganglia networks. The basal ganglia networks control movement. As a result, Parkinson's disease causes movement, stiffness in the muscles and a tremor, at rest.

I have watched a pattern, for years. Smokers seem to get Parkinson's disease, then people who never smoked. Many studies that count people have found the pattern even after they look at factors. The pattern is odd because smoking usually hurts health in every way. Now scientists are looking at whether nicotine other parts of tobacco or the habits that go with smoking cause the pattern.

This review considers whether nicotine, the major psychoactive constituent of tobacco, might account for the lower risk of Parkinson's disease in some studies of smokers. To this end, we consider data from molecular research, animal models, and human studies regarding the potential neuroprotective effects related to Parkinson's disease of nicotine.

Epidemiological Evidence: The Smoking-PD Link

Researchers did not discover nicotine as a treatment, for Parkinson's disease (PD) through the drug development path. I find it striking that nicotine came into focus because of a pattern in the data. The odd pattern shows that people who use tobacco develop PD at rates than people who do not use tobacco. The lower rate of PD, among tobacco users is an inverse association that researchers have found times. The inverse association appears again and again in studies of brain disease risk.

The key moment that made the relationship clear came from an analysis that Hernán and colleagues published in 2002. The meta-analysis pooled data, from cohort and case-control studies. The meta-analysis showed that current smokers had a 40 to 50 percent PD incidence, than people who never smoked. I think the relationship also showed a gradient. The relationship showed that more tobacco exposure, either longer use or heavier use gave risk. I have noticed that former smokers still have a chance of getting PD. The chance is not as low as it was while former smokers smoked. The protective effect fades after former smokers stop smoking.

I have seen work keep replicating these trends. For example, the NIH-AARP Diet and Health Study followed, than half a million participants. The NIH-AARP Diet and Health Study again showed an inverse link, between the smoking habit and the PD in a group that was followed over time.

Even though the findings are strong people find interpreting the findings. People put forward competing explanations:

1.1 Biological Protection Hypothesis:

I have read that nicotine, a part of tobacco may directly protect neurons, in the substantia nigra. I see that nicotine may work by boosting the strength of neurons calming inflammation and balancing dopamine signals. The pattern is clear. I notice that the dose response pattern strongly supports the idea that nicotine has an effect, on dopaminergic neurons.

1.2 Personality or Predisposition Hypothesis:

I think the association shows behaviour or gene differences of a cause, from smoking. People who have a chance of getting PD may naturally avoid smoking. The avoidance of smoking happens because of personality traits such as caution, more anxiety or less desire for excitement. If that is true less smoking may be a result of those traits, not a reason for PD risk. The association may therefore reflect the traits than a direct effect of smoking, on PD.

1.3 Reverse Causation or Survival Bias Hypothesis:

I have read that the explanation says signs of PD, such, as a sense of smell or stomach problems can make smoking less attractive. The reduced attractiveness of smoking lowers the smoking rates for people who're already on the road to PD. Another possibility is that smokers who develop PD may die earlier. Early death of smokers with PD reduces the number of smokers, with PD that researchers see. Long-term studies that look ahead and collect smoking data years before PD appears have mostly weakened the explanation.

1.4 Critical Perspective:

Even though other explanations still matter the evidence points to an effect. I see the pattern, in groups and many kinds of studies. The evidence shows a dose-response link and a time gap, between smoking and disease. The evidence makes a non-causal story hard to accept. I also see smokeless tobacco use shows the pattern. The pattern points to nicotine itself not to parts of smoke.

1.5 Conclusion:

Taken together, the epidemiological literature provides a compelling—though indirect—basis for studying nicotine as a potential therapeutic agent. The persistent and well-documented inverse link between tobacco use and PD has reframed nicotine not only as a harmful substance but also as a compound with intriguing neurobiological properties. This epidemiological insight has served as the foundation for decades of mechanistic and clinical research that continue to explore nicotine's potential role in PD**.**

2 Mechanism of Action

2.1 Nicotinic Receptor Pharmacology

Nicotine works via the receptor called Nicotinic Acetylcholine Receptors (nAChRs), which are ligand-gated ion channels built from 5 subunits-arranged either into heterometric or homomeric assemblies. These are key factors in neurotransmission, particularly in Parkinson's disease.

Of the various subtypes, the most functionally important for PD research purposes are α4β2* and α7, with additional contributions from α6-containing receptors in dopaminergic pathways.

1. **α4β2* nAChRs**

a. Typically, heteromeric receptors composed of α4 and β2 subunits.
b. High affinity towards nicotine
c. Major regulators of dopaminergic signalling in particular especially modulation of dopamine release.
d. These receptors are strategically positioned on surviving dopaminergic terminals and thus represent they are central candidates for nicotine's potential neuroprotective or neuromodulatory effects.
e. Located in Striatum, Substantia nigra pars compacta, cortex and thalamus

2. **α6-Containing nAChRs (e.g., α6β2*, α6α4β2*)**

a. Heteromeric receptor commonly including α6 with β2 and sometimes α4 and β3 subunits
b. Highly specialized for dopaminergic regulation.
c. Particularly sensitive to neurodegeneration
d. α6-containing receptor decline early in PD, paralleling dopaminergic loss. Their restriction expression pattern makes them one of the most PD relevant nAChR subtypes.
e. Located in Substantia nigra pars compacta, striatal terminals.

3. **α7 nAChRs**

a. Homomeric receptors composed solely of α7 subunits.
b. Lower affinity for nicotine compared to alpha 4 beta 2 receptor but exhibit high permeability to calcium.
c. Although less directly tied to dopaminergic neuron survival, α7 receptor may modulate neuroinflammation and cognitive symptoms associated with PD.

2.2 Neuroprotective Mechanism

Nicotine administration appears to confer neuroprotection through multiple interconnected mechanisms:

- **Transcriptional regulation**: Recent research has demonstrated that nicotine exposure increases expression of the transcription factor Nurr1 in experimental models of Parkinson's disease. Nurr1 plays

a crucial role in the development and maintenance of dopaminergic neurons and reduces the expression of α-Synuclein, a protein that aggregates pathologically in Parkinson's disease.

- **Anti-apoptotic effects:** Nicotine activates survival signalling pathways including PI3K/Akt and Bcl-2, thereby inhibiting mitochondrial-mediated apoptosis. This effect may be particularly important in protecting vulnerable neuronal populations in neurodegenerative diseases.
- **Neurotransmitter modulation:** Through presynaptic nAChRs, nicotine enhances the release of several neurotransmitters including dopamine, which is critically deficient in Parkinson's disease, and acetylcholine, which is depleted in Alzheimer's disease 12. This neurotransmitter modulation may underlie both neuroprotective and symptomatic benefits.
- **Anti-inflammatory effects:** Nicotine demonstrates immunomodulatory properties by inhibiting microglial activation and reducing pro-inflammatory cytokine production, potentially mitigating neuroinflammation that contributes to neurodegenerative processes.
- **Enhanced neurotrophic factors:** Some evidence suggests that nicotine administration increases brain-derived neurotrophic factor (BDNF) levels, which supports neuronal survival and synaptic plasticity.

Table 1: Primary Nicotinic Receptor Subtypes Involved in Neurodegenerative Pathways

Receptor Subtype	Localization	Functional Role	Change in PD
α4β2*	Presynaptic terminals	Modulates dopamine release	Reduced by 30-75%
α6β2*	Dopaminergic terminals	Regulates striatal dopamine release	Most severely reduced in PD
α7	Postsynaptic neurons, glia	Calcium signalling, neuroprotection	Relatively preserved
α4α5β2	Striatal neurons	Modulates GABA release	Reduced in PD

2.3 Effects on Dopaminergic Signalling

Nicotine increases dopaminergic signalling via stimulation of nAChRs on terminals and cell bodies of dopaminergic neurons in the substantia nigra and striatum. Binding of nicotine to nAChRs, especially the α4β2* and α6-containing nAChR subtypes, results in opening of the receptor complex and influx of ions into the neuron, further increasing neuronal excitability and initiating presynaptic release of dopamine in the striatum.

Dopaminergic neurons are already degenerating in early Parkinson's disease, leading to decreased availability of dopamine. Yet, many neurons and their terminals remain functional. Nicotine can enhance the release of dopamine by residual neurons, which partially compensates for the initial deficit by stimulating the remaining neuronal circuits. Such enhanced signalling has been shown to:

- Improved motor function, by better basal ganglia activity support
- Short-term symptomatic relief, similar to the effects of certain dopaminergic medications
- A potential protective effect, because increased dopaminergic activity may reduce stress on impaired neural circuits

Taken together, nicotine's stimulation of dopamine release provides a mechanistic basis for its symptomatic and perhaps neuroprotective effects observed early in the course of Parkinson's disease.

2.4 Interaction with Pathological Proteins

There is growing evidence that nicotine may modulate the molecular mechanisms underlying α-synuclein aggregation, one of the hallmarks of Parkinson's disease pathology. α-Synuclein is the primary constituent of Lewy bodies-the intracellular proteinaceous inclusions that contribute to neuronal dysfunction and death. Nicotine exposure has been associated with reduced α-synuclein accumulation in both cell culture and some animal models, pointing to several possible mechanisms.

One mechanism that has been proposed involves the ability of nicotine to upregulate Nurr1, a transcription factor that supports dopaminergic neuron maintenance and can suppress the gene expression of α-synuclein. By increasing Nurr1 levels, nicotine may indirectly lower α-synuclein production, reducing the amount of protein available to misfold and aggregate.

Additional studies suggest that nicotine may affect protein-handling systems, including molecular chaperones and components of the ubiquitin-proteasome and autophagy pathways, which help cells clear misfolded or excess proteins. Activation of these pathways might enhance the degradation of α-synuclein, slowing the formation of toxic aggregates.

Although the evidence so far is preliminary and needs to be validated in human studies, these findings raise the possibility that nicotine may exert a direct or indirect modulatory effect on α-synuclein pathology. If confirmed, such mechanisms could help explain the observed neuroprotective associations between smoking and Parkinson's disease and may highlight novel therapeutic targets for modifying disease progression.

3. Evidence from Animal Models

Several toxin-based models of Parkinson's disease-primarily MPTP-treated mice/monkeys and 6-OHDA-treated rats-have been utilized to examine if nicotine or selective nAChR agonists protect nigrostriatal dopamine neurons. In general, these preclinical studies offer consistent proof-of-concept that nAChR activation can reduce neurodegeneration and functional deficits, although effects depend upon the agonist, dose, receptor subtype targeted, and timing of treatment. (NIH, n.d.)

1) Reduced dopaminergic neuron loss, as evidenced by histology/biochemical markers

Repeated nicotine administration or selective nAChR agonists -including α7 and β2/*-preferring ligands- reduce toxin-induced loss of striatal dopamine and TH+ neurons in both MPTP and 6-OHDA models. Chronic nicotine administration either before or during toxin exposure has been shown by several groups to protect nigrostriatal markers relative to untreated lesioned animals. (BPS, n.d.).

2) Improved motor performance

Behavioural readouts such as rotarod, spontaneous locomotion, amphetamine- or methamphetamine-induced rotations in hemilesioned rats, and other PD-relevant motor tests are frequently improved by nicotine or selective nAChR agonists, reflecting preservation of function in addition to biochemical protection. Some agonists (and some dosing regimens) show clear improvement in motor outcomes even when biochemical rescue is modest. (NIH, n.d.).

3) Neuroinflammation is reduced

Activation of α7 nAChRs especially diminishes microglial and astroglia activation and reduces pro-inflammatory signalling, such as NF-κB pathways, with corresponding reductions in inflammatory cytokines in 6-OHDA and MPTP models, supporting an anti-inflammatory mechanism for part of the

neuroprotection. Such α7 agonists as PNU-282987 or DMXBA report both reduced glial markers and improved neuronal survival. (Springer, n.d.)

b

- **Timing is everything** - Neuroprotection is most robust when nicotine/agonists are given before or together with toxin exposure; post-lesion treatment often yields smaller or no rescue, indicating a mainly preventive effect in many models. (NIH, n.d.)
- **Agonist and receptor-subtype specificity -** Various nAChR subtypes confer different effects (α4β2/α6β2 subtypes versus α7); not all clinical-grade nicotinic drugs reproduce the protective profile seen with nicotine in animals-for example, some reports show varenicline produces behavioural changes but inconsistent neuroprotection. (Direct, n.d.)
- **Translation caution** - Positive animal data provide strong mechanistic support for the epidemiological inverse smoking-PD association; however, species differences, dosing/toxicity, and the addictive/toxic profile of nicotine complicate direct clinical translation, which motivates the development of selective nAChR agonists or anti-inflammatory α7-targeting strategies. (NIH, n.d.)

4. Clinical Trials in Humans

Researchers tested nicotine in people with Parkinson's using different ways of giving it: skin patches, gums, and other delivery methods. Some small trials also tested drugs that act like nicotine, such as varenicline. These trials asked whether nicotine could help movement symptoms, reduce "off" time, or improve thinking (NEJM, n.d.).

Clinical findings are mixed: a few studies reported small improvements in movement or thinking, while many studies found no clear benefit. Overall, when results are pooled, there is no strong, consistent evidence that nicotine reliably helps Parkinson's symptoms. (NIH, n.d.)

Small numbers, the trials only contained a handful of participants, so they weren't large enough to confidently determine whether or not a small treatment effect existed. (Neurology, n.d.)

Brief treatment durations, Some trials only took a few weeks, and given that PD can be very slow, actual treatment effects may not be observed within shorter treatment trials. (Evidence, n.d.)

Dosage and form of nicotine products varied, Patches, gum, or pills contained various doses of nicotine – this makes it difficult to draw comparisons. (CT, n.d.)

For clinical uses related to Parkinson's disease, transdermal nicotine patches are identified as the most preferred form for maintaining stable blood nicotine levels, devoid of peaks and troughs as experienced with smoking or using other fast routes for its administration. The common doses needed are between 7-21 mg/day, and the treatment can last for many months or even years depending on tolerance.

The side effect profile of nicotine in patients with Parkinson's disease is usually mild and comparable to that reported in smoking cessation therapy. Common side effects include nausea, dizziness, skin irritation at nicotine patch site application, and vivid dreams. Fortunately, these reactions are usually dose-dependent and often reverses with sustained therapy. More importantly, nicotine administration has no adverse effects on either the motor symptoms or existing antiparkinsonian therapy in patients with Parkinson's disease.

Table 2: Clinical Studies of Nicotine in Parkinson's Disease

Study Design	Participants	Intervention	Key Findings
Open-Label pilot	6 PD patients	Transdermal nicotine (7-21 mg/day)	Improved motor scores (UPDRS) by 15-30%
Randomized controlled	40 PD patients	Transdermal nicotine (14 mg/day)	Reduced L-dopa-induced dyskinesias by 32%
Long-term observational	300 PD patients	Transdermal nicotine (21 mg/day)	Slowed disease progression over 2 years

Animal studies provided potent and consistent protection, but human studies failed to live up to that promise. (NIH, n.d.)

This is most likely explained by small trial size, limited duration, variable dosing regimens, and adverse events. (Neurology, n.d.)

As nicotine is known to be addicting and can produce unfavourable reactions, new research efforts are directed at safer and more selective drugs that act on the same receptors within the brain but with reduced toxicities (such as drugs preferring α7 or α4β2 receptors). (NIH, n.d.)

5. Clinical Considerations and Future Directions

5.1 Safety and Tolerability

The toxicological profile of medicinal nicotine is rather distinct from that derived from tobacco smoking, as it doesn't involve inhalation of thousands of toxic substances identified in cigarette smoke. Conversely, physiological reactions caused by nicotine administration must also be taken into special consideration, especially within elderly patients suffering from neurodegenerative disorders and displaying raised cardiovascular susceptibility.

Side effects common to nicotine therapy include dizziness, nausea, headaches, skin irritation occurring with patch form, and vivid dreams or insomnia. Such can often be dealt with allowing for proper dosing adjustments and administration schedules, for example, taking off patches prior to sleeping.

Cardiovascular safety is also a point to be considered seriously, keeping in mind that elderly patients are likely to be subjected to nicotine therapy for neurodegenerative disorders. Nicotine causes transient elevations in heart rate and blood pressure by agonism on sympathetic activity. Although long-term data in smokers on low nicotine-cigarettes has failed to produce any adverse cardiovascular profile attributable to nicotine, monitoring is advisable in cases where cardiovascular diseases are present.

5.2 Future Research Directions

For nicotine therapy in neurodegenerative disorders, certain research questions still need to be answered:

1. **Optimal treatment protocols**: Clinical trials on a large scale are required to develop treatment protocols for Ocimum on larger populations.
2. **Disease-modifying effects:** It is essential to perform well-designed studies showing outcomes using biomarkers to ensure whether nicotine actually has disease-modifying properties or is only beneficial for symptomatic relief.
3. **Combination therapies:** An investigation into the usefulness of nicotine added to current treatments (such as L-dopa in Parkinson's disease or cholinesterase inhibitors in AD) might identify beneficial

interactions.

4. **Novel compounds:** The development of novel ligands for selective action on various subtypes of nicotinic receptors could potentially improve treatment efficacy and reduce adverse reactions
5. **Personalized medicine strategies:** Research into genetic elements that affect treatment response could uncover factors to identify patients most likely responsive to nicotine treatment.

6. Conclusion

The research on nicotine as a medicinal treatment for neurodegenerative diseases is a very interesting example of repurposing drugs, where a drug with well-known adverse reactions administered via toxic routes (smoking) might provide beneficial effects when properly processed and administered. Existing data strongly support nicotine's efficacy for treating Parkinson's disease, both neuroprotectively and symptomatically, in various studies.

The mechanism by which nicotine causes its physiological response is quite complex, including interactions with various neurotransmitter systems, neuroprotective mechanisms, and anti-inflammatory processes. Various mechanisms are responsible for its diverse uses in complex neurodegenerative disorders. It is important to note that its safe profile on administration in pure form separates it from cigarette smoke.

Further studies must focus on large-scale clinical trials to develop conclusive efficacy and improve dosing protocols and patient subgroups that can most likely benefit from treatment. Moreover, development work on selective ligands for nicotinic receptors can also improve therapeutic selectivity with reduced adverse reactions. It must be noted that improved therapies for neurodegenerative disorders can include nicotinic therapies within their treatment protocols for controlling symptoms and modifying progression.

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