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Nicotine and Parkinson's Disease: Implications for Therapy

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Abstract: Accumulating evidence suggests that nicotine, a drug that stimulates nicotinic acetylcholine receptors, may be of therapeutic value in Parkinson's disease. Beneficial effects may be several-fold. One of these is a protective action against nigrostriatal damage. This possibility stems from the results of epidemiological studies that consistently demonstrate an inverse correlation between tobacco use and Parkinson's disease. This reduced incidence of Parkinson's disease has been attributed to the nicotine in tobacco products, at least in part, based on experimental work showing a protective effect of nicotine against toxic insults. Second, several studies suggest a symptomatic effect of nicotine in Parkinson's disease, although effects are small and somewhat variable. Third, recent data in nonhuman primates show that nicotine attenuates levodopa-induced dyskinesias, a debilitating side effect that develops in the majority of patients on levodopa therapy. Collectively, these observations suggest that nicotine or CNS selective nicotinic receptor ligands hold promise for Parkinson's disease therapy to reduce disease progression, improve symptoms, and/or decrease levodopa-induced dyskinesias. © 2007 Movement Disorder Society

Key words: dyskinesias; L-dopa; neuroprotection; nicotinic receptors; striatum; smoking.

Although dopamine replacement therapy has proved very effective in Parkinson's disease management, side effects develop and efficacy declines due to disease progression.[1-5] There is therefore a continual search for better treatment strategies. This article will review accumulating evidence that nicotine or nicotinic receptor agonists may be useful in the therapeutic management of Parkinson's disease. We initially describe anatomical and functional work that provides a rationale for a relationship between the nicotinic cholinergic and dopaminergic systems. This is followed by studies showing that there are several nicotinic receptor populations in the striatum that regulate dopamine release under physiological conditions and with nigrostriatal damage. These studies provide a cellular basis for behavioral studies demonstrating a functional interaction between the dopamine and nicotinic cholinergic system. Lastly, we discuss a role for nicotine and nicotinic agonists in neuroprotection against nigrostriatal damage, in the treatment of Parkinson's disease symptoms, and in the reduction of side effects (dyskinesias) associated with levodopa (L-dopa) treatment.

LINK BETWEEN THE STRIATAL NICOTINIC CHOLINERGIC AND DOPAMINERGIC SYSTEMS

Anatomical studies clearly demonstrate a close association between the cholinergic and dopaminergic systems in the striatum.[6] Striatal dopamine, tyrosine hydroxylase, dopamine receptors, and other catecholaminergic markers[7-9] extensively colocalize with acetylcholine,

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Potential conflict of interest: Maryka Quik is named on a provisional patent for the use of nicotine for the treatment of L-dopa dyskinesias.

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choline acetyltransferase, acetylcholinesterase, and cholinergic receptors across species. All these cholinergic measures are associated with large cholinergic interneurons that comprise ~2% of the striatal neuronal population.[6] Although their number is limited, cholinergic neurons have extensive axonal arbors yielding a dense local innervation in the striatum that overlaps with dopaminergic terminals from the substantia nigra. Striatal cholinergic neurons are tonically active and continually secrete acetylcholine, which interacts with acetylcholine receptors present throughout the striatum.[10,11] The two major acetylcholine receptor types in striatum include muscarinic receptors, which are activated by acetylcholine and muscarine, and nicotinic receptors, so-named because these are stimulated by acetylcholine and nicotine, but not muscarine.[12-14]

Muscarinic receptors, which are G-protein linked, reside on striatal GABAergic neurons and cholinergic interneurons. Their stimulation modulates motor function. In fact, muscarinic receptor blockers were extensively used to ameliorate Parkinson's disease symptoms before the advent of L-dopa. Their use is currently limited to the treatment of early Parkinson's disease and/or as an adjunct therapy to L-dopa because improvement is modest and associated with significant side effects.[3,4,15]

Nicotinic receptors are ligand gated ion channels that are also extensively present in the striatum.[10,16-19] These receptors are localized to striatal GABAergic and cholinergic neurons and, in addition, are present at presynaptic sites including nigrostriatal dopaminergic terminals and cortical glutamatergic afferents.[10,11,20,21] Extensive studies in experimental models show that the role of these presynaptic nicotinic receptors is to regulate dopamine release.[10,11,22] These findings underlie the cellular basis for the functional interaction between the striatal nicotinic and dopaminergic systems, which is the current focus. Behavioral studies in rodent models further support this relationship as dopamine receptor antagonists can block nicotine-evoked changes in locomotor activity.[23] These latter findings also support the idea that the nigrostriatal pathway is key in regulating motor functions. As well, administration of nicotine and nicotinic agonists influence motor function in animals with nigrostriatal damage,[18] providing the basis for the idea that they may be useful in Parkinson's disease management.

NICOTINIC RECEPTORS IN THE NIGROSTRIATAL SYSTEM

The nicotinic receptors controlling striatal dopamine function are composed of different combinations of α and β subunits, or only select α subunits.[16,19,22] The α subunits are critical as they express the acetylcholine recognition sites, while the β subunits modulate binding of acetylcholine to the α subunit. Multiple α and β subunits have been identified including α2 through α7, and β2 through β4. This multiplicity of subunits allows for expression of numerous nicotinic receptor subtypes, as five subunits are required for formation of functional receptors. Combined evidence from in situ hybridization, receptor binding experiments and immunoprecipitation studies using receptor subunit-directed antibodies show that several major nicotinic receptor subtypes are present in rodent and nonhuman primate striatum.[24-33] These include homomeric α7 nicotinic receptors, and heteromeric receptors containing the α4β2 and the α6β2 subunits (Table 1). The latter two receptor populations will subsequently be designated as α4β2* and α6β2* nicotinic receptor, with the asterisks signifying the possible presence of other subunits in the receptor complex. Interestingly, the α6β2* nicotinic receptors are restricted to the striatum and only a few other brain regions.[34-36] Studies to further elucidate the subunits comprising these receptors demonstrate the presence of at least two populations of α6β2* nicotinic receptor, including those composed of the α6α4β2β3 and α6β2β3 subunits.[20,37] There also appear to be multiple populations of α4β2* receptors, with the primary one composed solely of α4β2 subunits.[20,25,26,32] The α6α4β2β3, α6β2β3, and α4β2 nicotinic receptor populations form the major striatal subtypes, and appear fairly consistent across species, including mice, rats, monkeys (Table 1).[37] Importantly, for drug development, data suggest that these same nicotinic receptor subtypes are present in human striatum.[17,37-39]

TABLE 1. *Putative subunit composition of nicotinic receptor subtypes in rodent, monkey, and human striatum*

Species	Nicotinic receptor subtypes
Rodents, monkeys, humans	α4β2, α6α4β2β3, α6β2β3, α7
Rodents only	α4α5β2, α6β2[a]
Monkeys only	α4α2β, α3β2[a]

[a]The possible presence of additional subunits in the receptor complex.

Current evidence suggests that both the α6β2* and α4β2* nicotinic receptors are present on dopaminergic terminals, and are important for controlling dopamine release in striatum.[22] The magnitude of the involvement of these two subtypes appears to vary with species. In nonhuman primates, the α6β2* nicotinic receptors are responsible for about 75% of nicotinic receptor-evoked striatal dopamine release and the α4β2* the remaining 25%, with these percentages reversed in rodent striatum.[20,28,40] Dopamine release is also indirectly mediated

by a smaller population of α7 receptors present on striatal glutamatergic afferents from the cortex.[21,39]

NEURONAL NICOTINIC RECEPTORS ARE DECREASED WITH NIGROSTRIATAL DAMAGE

Since the α4β2* and α6β2* subtypes are the primary nicotinic receptors that regulate dopamine release from nigrostriatal terminals, it is important to know how nigrostriatal damage impacts their expression. Such information is critical for the design of suitable nicotinic receptor drugs for Parkinson's disease. To address this, studies have been done in several parkinsonian animal models, including 6-hydroxydopamine-lesioned rats, MPTP-treated mice, and MPTP-lesioned nonhuman primates. The α6β2* nicotinic receptors generally appear to be the most susceptible to nigrostriatal damage across species, an observation suggesting they are primarily localized to striatal dopaminergic terminals.[25,26,31,35,41] The α4β2* nicotinic receptors are decreased only with a severe nigrostriatal lesion, a finding suggesting they are localized to nigrostriatal afferents more resistant to nigrostriatal damage and other striatal neurons.[25,26,41,42] By contrast, α7 nicotinic receptors are unaffected by lesioning, further confirming that they are not present on dopamine terminals.[25,26,32,43,44]

Since nicotinic receptors are present on neuronal elements that are lost in Parkinson's disease,[17,45] the question arises whether there are corresponding changes in striatal nicotinic receptors in this disorder. Receptor studies done using radiolabeled nicotine, methylcarbachol, and epibatidine, demonstrate 30 to 75% declines in nicotinic receptors in the caudate, putamen, and substantia nigra that appear to correlate with nigrostriatal damage.[17,46-48] Subsequent studies to elucidate the receptor subtypes that are affected suggest that the more severe losses are in the α6β2* receptor population, with somewhat smaller declines in the α4β2* subtype, in agreement with results in animal models.[17,37,38,45,49] α7 nicotinic receptors were generally unaffected by nigrostriatal damage, also consistent with experimental studies. The observed reductions in α6β2* nicotinic receptors generally paralleled decreases in other indices of nigrostriatal degeneration, such as dopamine and/or dopamine transporter levels.[37,38,45,49]

These combined findings suggest that α6β2* and α4β2* nicotinic receptors may represent promising pharmacological targets for Parkinson's disease for neuroprotection and/or symptomatic improvement. Since α6β2* subtypes are localized primarily on dopaminergic terminals and regulate dopamine release, they may be particularly relevant for the development of Parkinson's disease therapies, which could provide optimal therapeutic benefits with minimal side effects. However, another important consideration is that certain receptor subtypes are more vulnerable to nigrostriatal damage and preferentially lost with a mild lesion.[37] These findings raise the question whether the more susceptible subtypes may be more relevant targets for drug development in the initial stages of Parkinson's disease whereas others may be more important targets with disease progression.

NICOTINE AND PARKINSON'S DISEASE MANAGEMENT

The studies described in the preceding sections show that (1) there is extensive overlap between the striatal nicotinic and dopaminergic system, (2) that nicotinic receptors are expressed in striatum with several subtypes present on striatal dopaminergic terminals, and (3) that nicotinic receptor activation elicits dopamine release. (4) In addition, nicotine treatment enhances expression of some nicotinic receptor subtypes decreased with nigrostriatal damage,[50] which may suggest that function mediated through these receptors is restored closer to control levels with nicotine treatment.

These combined data provide a rational basis for the suggestion that nicotine or nicotinic receptor agonists may enhance dopamine function. Since Parkinson's disease is characterized by a loss of nigrostriatal dopaminergic function, stimulation of the nicotinic cholinergic system offers therapeutic potential. This is important because dopamine replacement therapy with L-dopa and dopamine agonists, the mainstay of Parkinson's disease management, is associated with serious side effects including on-off phenomena and dyskinesias. Moreover, there is a diminished efficacy with time because of continued disease progression. There is therefore an urgent need for alternate and/or complementary therapeutic approaches. Below we describe a role for nicotine and/or nicotinic agonists in Parkinson's disease management for (1) protection against nigrostriatal damage, (2) symptomatic relief of motor symptoms, and (3) attenuation of L-dopa-induced side effects (dyskinesias).

Nicotine and Neuroprotection for Parkinson's Disease

The ultimate mode of treatment for any neurological disorder is one that halts disease progression and reverses existing damage. Such a strategy for Parkinson's disease offers the advantage that it may not only alter the development of the disease process but, in addition, delay or minimize motor and/or nonmotor symptoms, as well as complications associated with treatment. An understanding of the etiology of Parkinson's disease would

greatly facilitate the identification of suitable candidate agents. However, the origin of Parkinson's disease is currently uncertain although it is most likely due to a complex interaction between genetic and environmental factors. These result in the activation of diverse neurodegenerative mechanisms, including oxidative stress, free radical generation, mitochondrial deficits, glutamate excitotoxicity, inflammation, neurotrophic factor deprivation, and dysfunction of the ubiquitin-proteasome system.[1-5,51] There is currently an ongoing search for drugs that delay Parkinson's disease progression by targeting the molecular mechanisms that underlie the neurodegenerative process. These include agents that increase mitochondrial function (coenzyme Q10, creatine), enhance trophic activity (GDNF), inhibit monoamine oxidase (selegiline, rasagiline), modulate inflammatory processes (minocycline), block protein aggregation, and inhibit apoptosis.[15,52-54] Nicotine has been proposed as a putative neuroprotective agent against nigrostriatal damage based on several lines of evidence. These include a large and compelling literature showing that (1) cigarette smoke, in which nicotine is a major component, is a robust negative risk factor for Parkinson's disease, and (2) nicotine acts as a neuroprotectant in in vitro and in vivo experimental models, as described in greater detail in the following sections.

Epidemiological Studies Demonstrate a Reduced Incidence of Parkinson's Disease With Tobacco Use.

An extensive and compelling epidemiological literature shows that smoking is inversely associated with Parkinson's disease. This concept initially appears counterintuitive based on the generally detrimental health-related consequences of smoking. However, over 50 prospective cohort and case-control studies over the last half century indicate that smoking and other forms of tobacco use appear protective against Parkinson's disease in both males and females.[55-61] There was a dose-response relationship between the number of pack-years smoked, such that the incidence of Parkinson's disease was lower with increased length of time of smoking and the number of cigarettes smoked per day. Moreover, the decline in risk, or apparent protective effect, was diminished in former smokers. These inverse trends between smoking incidence and Parkinson's disease were observed in every age group except the very elderly (>75 years), suggesting that smoking delays the onset of Parkinson's disease.[55,62] An inverse association has also been identified with the use of cigars, pipes, chewing tobacco, and snuff.[55,63] Alternative interpretations for this association have been proposed. These include a higher mortality in smokers with Parkinson's disease,[64] a genetically conferred decreased propensity to smoke, a premorbid personality, and a reduced dopaminergic tone that results in a lower reward of smoking and thus nonsmoking behavior in people fated to develop Parkinson's disease.[65] Evidence against these theories derive from a study in twin pairs discordant for Parkinson's disease, in which twins without Parkinson's disease had smoked more than their brothers.[66] This difference was most evident in the monozygotic pairs, known to be remarkably similar in personality. Other studies of twins[67] and siblings[68] discordant for Parkinson's disease replicate this finding, suggesting that the inverse trend between smoking and Parkinson's disease is unlikely to result from a genetic factor determining both smoking and Parkinson's disease risk.

In summary, the inverse relationship between Parkinson's disease and smoking appears consistent with a true biological protective effect of tobacco use, based on findings that: (1) it is observed in large prospective cohort studies; (2) is stronger in current compared to former smokers; (3) is correlated with smoking duration and intensity; (4) is seen with other forms of tobacco use; and (5) is observed in monozygotic twins discordant for Parkinson's disease. However, because tobacco products contain thousands of compounds, the question arises as to which of these confers the apparent protection against Parkinson's disease. A large body of evidence derived from experimental animal models suggests that nicotine, the primary psychoactive component in tobacco, plays a key role in the observed protection from nigrostriatal damage as discussed below.

Nicotine Treatment Protects Against Nigrostriatal Damage.

Numerous studies using culture models have shown that nicotine reduces toxicity in striatal, nigral, cortical, hippocampal, cerebellar, and spinal cord neurons, as well as in neuroblastoma and phaeochromocytoma (PC12) cell lines. Protection was observed against glutamate excitotoxicity, ischemic damage, ethanol-induced toxicity, nerve growth factor deprivation, MPTP exposure, and other forms of insult.[18,69-71]

Importantly, in vivo studies also show that nicotine pretreatment attenuates damage induced by dopaminergic neurotoxins such as MPTP, 6-hydroxydopamine, methamphetamine, and paraquat (Table 2). Nicotine administered prior to lesioning consistently reduced nigrostriatal degeneration in 6-hydroxydopamine lesioned rats with the extent of protection dependent on the dose of nicotine and severity of nigrostriatal damage.[72-77] Nicotine pretreatment also protected against MPTP-induced dopaminergic loss in the mouse nigrostriatal sys-

TABLE 2. *Nicotine treatment protects against nigrostriatal damage in parkinsonian animal models*

Animal model	Protection	Type of lesion	Treatment	References
Rat	Striatum and substantia nigra	Hemitransection	Nicotine injection and minipump	Janson et al.[72]
	Striatum	6-OHDA	Nicotine minipump	Ryan et al.[73]
			Nicotine injection	Costa et al.,[74] Abin-Carriquiry et al.,[75] Soto-Otero et al.,[76] Visanji et al.[77]
Monkey	Striatum	MPTP	Nicotine in drinking water	Quik et al.[78,79]
Mouse	Striatum and substantia nigra	MPTP	Nicotine injection and minipump	Janson et al.[80]
			Nicotine injection	Janson et al.[81]
		Paraquat	Nicotine in drinking water	Khwaja et al.[82]
	Striatum	MPTP	Smoke	Carr and Rowell,[83] Shahi et al.[84]
			Nicotine injection	Gao et al.[85]
		Methamphetamine	Nicotine injection	Ryan et al.[73]
	Substantia nigra	MPTP	Smoke or nicotine injection	Parain et al.[86,87]
	No protection in striatum and/or substantia nigra	MPTP	Smoke	Perry et al.[88]
			Nicotine in drinking water	Sershen et al.[89]
			Nicotine minipumps	Behmand and Harik,[90] Janson et al.[81]
			Nicotine injection	Hadjiconstantinou et al.,[91] Ferger et al.[92]

All reported studies using either the rat or monkey model indicate that nicotine treatment protects against nigrostriatal damage. However, it should be noted that level of protection was dependent on the lesioning condition (severity) and nicotine treatment (timing and dose). Protection was observed with both intermittent and continuous nicotine dosing. In mice, however, nicotine attenuated nigrostriatal damage in some but not all studies. Moreover, protection was inconsistent with no clear relationship between protective effects and the nicotine and/or MPTP-lesioning protocols. In most of the studies nicotine was given a few hours or days prior to lesioning, and in one study at the time of lesioning. The outcome measures used to evaluate protection in the striatum include tyrosine hydroxylase, dopamine and/or dopamine transporter levels, while tyrosine hydroxylase positive cells were counted as a measure of protection in the substantia nigra.

tem.[73,80-87] However, results have proved somewhat inconsistent in this model possibly because of the large, acute lesions that develop in mice administered MPTP or because nicotine is very rapidly metabolized in this species.[72,88-92] By contrast, chronic nicotine treatment did protect against a slow MPTP-induced neurodegenerative lesion in monkeys. There were enhanced levels of tyrosine hydroxylase, the dopamine transporter, vesicular monoamine transporter, and dopamine in striatum of lesioned animals receiving nicotine compared to nontreated lesioned monkeys.[78,93] Nicotine exposure not only improved morphological measures related to the dopaminergic system but also normalized lesion-induced overactivity of the nigrostriatal pathway in monkeys and preserved synaptic plasticity lost with nigrostriatal damage.[79] Continued studies in rat and nonhuman primate models should help identify the nicotinic receptor subtypes through which this effect occurs, as well as the mechanisms of nicotine-mediated neuroprotection. It will also be important to test whether nicotine protects against nigrostriatal damage when administered after the lesion, as this would more closely resemble the clinical situation.

A variety of different experimental approaches suggests that nicotine exerts its protective effect by acting at nicotinic receptors. The use of nicotinic receptor knockout mice and/or selective nicotinic receptor antagonists indicate that the $\alpha6\beta2^*$ and $\alpha4\beta2^*$ subtypes are most likely involved.[73,74] Stimulation of these receptors may lead to a protective activation via an increase in trophic factors and/or immune modulators.[94-96] There is also some evidence that nicotine may act through nonreceptor mediated mechanisms by reducing oxidative stress and/or enhancing mitochondrial function.[92,97]

Collectively, these data in culture systems and parkinsonian animal models have yielded a better understanding of the role of nicotine in neuroprotection against nigrostriatal damage. These results provide a firm basis for the suggestion that nicotine contributes to the lower incidence of Parkinson's disease with tobacco use. Work remains to be done to determine whether nicotine is also protective when administered during nigrostriatal damage.

Nicotine and Symptomatic Improvement of Parkinson's Disease

Since nicotine can stimulate dopamine release in the striatum, an important question that arises is whether it can also improve motor symptoms associated with Parkinson's disease. There is precedence for this possibility from rodent and nonhuman primate studies, which demonstrate that nicotinic receptor activation modulates motor function under normal physiological conditions.[23] In addition, nicotine or nicotinic agonists given to parkinsonian rats or monkeys improved parkinsonian behaviors.[98-100]

Several small studies have also evaluated the effect of nicotine on motor symptoms in Parkinson's disease patients (Table 3). One of the first reports investigated the effect of smoking combined with the nicotine gum in six

TABLE 3. *Summary of the effectiveness of nicotine or a nicotinic agonist in Parkinson's disease patients*

Study	Test agent	Type of study	No. of patients	Outcome measure relating to movement	Duration		Final dose/ day	Antiparkinsonian effect
					Dose titration	Dose maintenance		
Ishikawa and Miyatake[101]	Smoking and nicotine gum	Open-label	6	Tremor, rigidity, bradykinesia, posture	Chronic smoker		NA	Yes
Fagerstrom et al.[102]	Nicotine gum and patch	Double-blinded	2	Tremor, rigidity	≥ 7 mo	15 mg patch + 4 × 4 mg gum	Yes	
Clemens et al.[103]	Nicotine gum	Double-blinded placebo-controlled	48	UPDRS	ND	1 day	3 × 2 mg	No
Ebersbach et al.[104]	Nicotine patch	Double-blinded crossover	16	UPDRS	ND	12 hr	7 mg	No
Kelton et al.[105]	Nicotine iv and patch	Open-label	15	Pronation/supination, finger dexterity, stand/ walk/sit	2 wk	1-2 wk	14 mg	Yes
Vieregge et al.[106]	Nicotine patch	Double-blinded placebo-controlled	32	Columbia Univ rating scale, Schwab-England Fine motor testing	1 wk	2 wk	14 mg	No
Mitsuoka et al.[107]	Nicotine gum	Open-label	8	UPDRS	ND	1 day	NA	Yes
Lemay et al.[108]	Nicotine patch	Open-label	22	UPDRS	22 days	3 days	21 mg	No
Shoulson[109]	SIB-1508Y	Double-blinded placebo controlled	77	UPDRS	2 wk	2 wk	10 mg	No
Hanagasi et al.[110]	Smoking	Open-label	1	UPDRS, Hoehn and Yahr	Chronic smoker		NA	Yes
Villafane et al.[111]	Nicotine patch	Open-label	6	UPDRS	14 wk	4 wk	Up to 105 mg	Yes

This table (in modified form) is reproduced from Biochemical Pharmacology, Volume 74, Quik M, Burdia T, and O'Leary K, Nicotinic receptors as CNS targets for Parkinson's disease, pages 1224–1234, 2007, with permission from Elsevier. In some of the above studies nicotine treatment appeared well tolerated with no side effects noted,[101,102,105] whereas in others side effects were noted although similar side effects were often also observed with placebo.[103,104,106] Reported side effects in the nicotine-treated groups include, itchiness at the site of the patch, dizziness, lightheadedness, headache, vivid dreaming, deterioration of tremor and balance, akinesia, sleep disturbances, nausea, vomiting, hypersalivation, dry mouth, hypertension, palpitations, and intestinal cramps.[103,104,106,112] Side effects in the placebo groups were similar and include itchiness at the site of the patch, dizziness, lightheadedness, fatigue, headache, vivid dreaming, deterioration of balance, tremor and gait, sleep disturbances, nausea, dry mouth, and orthostatis.[103,104,106] Since tolerance develops with continued nicotine use as readily evident with smoking, a more gradual dose escalation may circumvent the development of side effects.

NA, not available; ND, not determined.

individuals with Parkinson's disease; a transient beneficial response was observed on motor function.[101] A single more recent case report also indicated that smoking transiently reduced symptoms in a patient with juvenile Parkinson's disease.[110] Attenuation of symptoms was also observed in two Parkinson's disease patients receiving the nicotine gum and patch for variable periods over several months.[102] These reports were followed by several studies that investigated the effect of acute nicotine exposure (1 day) with the nicotine patch or gum. Results were conflicting, with a worsening of motor performance in two of the studies,[103,104] and improvement in one.[107] Small-scale clinical trials have also yielded variable outcomes. Improvements in cognitive measures and motor performance were obtained in a group of 15 Parkinson's disease patients after treatment with intravenous nicotine and the nicotine patch, with beneficial effects persisting up to 1 month after nicotine was stopped.[105] However in another trial involving 32 patients, positive effects were not observed with 3 weeks of patch application.[106] It should be noted however that symptoms were only evaluated 3 weeks after patch cessation, at which time any improvements may have dissipated. In line with these results, however, is the study by Lemay et al. in which there were no improvements in motor or cognitive deficits with immediate testing of Parkinson's disease symptoms after 3 to 4 weeks of treatment.[108] A possible explanation for the lack of effect of nicotine in these studies may relate to inadequate dosing as Villafane et al. recently showed that high dose nicotine resulted in a dramatic improvement in parkinsonism in a small open label study.[111] An $\alpha4\beta2^*$ CNS selective nicotinic agonist (SIB-1508Y) was also tested in one study; however, there was no observable effect on parkinsonism after 4 weeks of treatment.[109] These latter data may suggest that other nicotinic receptor subtypes ($\alpha6\beta2^*$ and $\alpha7$) mediate effects against parkinsonism, that stimulation of multiple subtypes are required for an enhancement of motor function and/or may relate to pharmacokinetic issues with this specific drug. Further work with additional subtype selective nicotinic receptor drugs are required to understand the subtypes through which nicotine mediates its effects on motor control.

In summary, beneficial effects of nicotine treatment were reported in about half the clinical studies (Table 3). These results may suggest that nicotine has the potential to ameliorate symptoms but that the conditions required for improvement remain to be clarified. One notable

observation is that almost all of the double-blinded trials yielded negative results, while the open-label studies were positive, suggesting a placebo effect. However, it is also possible that the mode of administration of nicotine (patch versus gum), nicotine dose, the dosing regime, or duration of nicotine treatment require optimization. The role of nicotine to reduce Parkinson's disease symptoms thus currently remains unclear.

Nicotine Reduces L-Dopa-Induced Dyskinesias

As mentioned earlier, L-dopa often has a dramatic impact on motor deficits that arise with Parkinson's disease and is one of the most effective therapies. However, chronic treatment is associated with significant side effects including on-off phenomena, neuropsychiatric problems, and the development of abnormal involuntary movements or dyskinesias that may be very disabling. The development of dyskinesias may counterbalance L-dopa's beneficial effects and adversely affect the quality of life of Parkinson's disease patients[15,54,113-122] Current preventive strategies involve initial use of dopamine agonists, which induce dyskinesias much less readily. However, almost all patients require eventual use of L-dopa, which is then followed by dyskinesias in the majority of cases. Once present, dyskinesias are not easily eliminated. For most, pharmacological and surgical interventions result in only a partial decrease in dyskinesias, often at the expense of increased parkinsonian symptoms or other side effects. Better treatment is therefore urgently needed.

Novel drugs targeted to neurotransmitter and/or neuromodulatory systems linked to basal ganglia function are currently being tested for their ability to attenuate L-dopa-induced dyskinesias.[119-121,123-127] This includes nicotine, which was recently shown to reduce dyskinesias in parkinsonian nonhuman primates (see Fig. 1).[128] This effect of nicotine was most pronounced (50% decrease) in monkeys that were given nicotine before L-dopa treatment was initiated (L-dopa naïve). Dyskinesias were decreased to a somewhat lesser extent (~35%) in monkeys which first received L-dopa (L-dopa-primed animals) and then received nicotine together with L-dopa.[128] This difference in effectiveness is consistent with findings that dyskinesias are generally more readily suppressed in L-dopa naïve versus L-dopa-primed animals.[119,120] Importantly, nicotine treatment did not worsen Parkinsonism either on or off L-dopa. Continued studies should help determine whether nicotine treatment may be useful for alleviating this debilitating consequence of L-dopa therapy in Parkinson's disease patients. Subsequent work with selective nicotinic receptor ago-

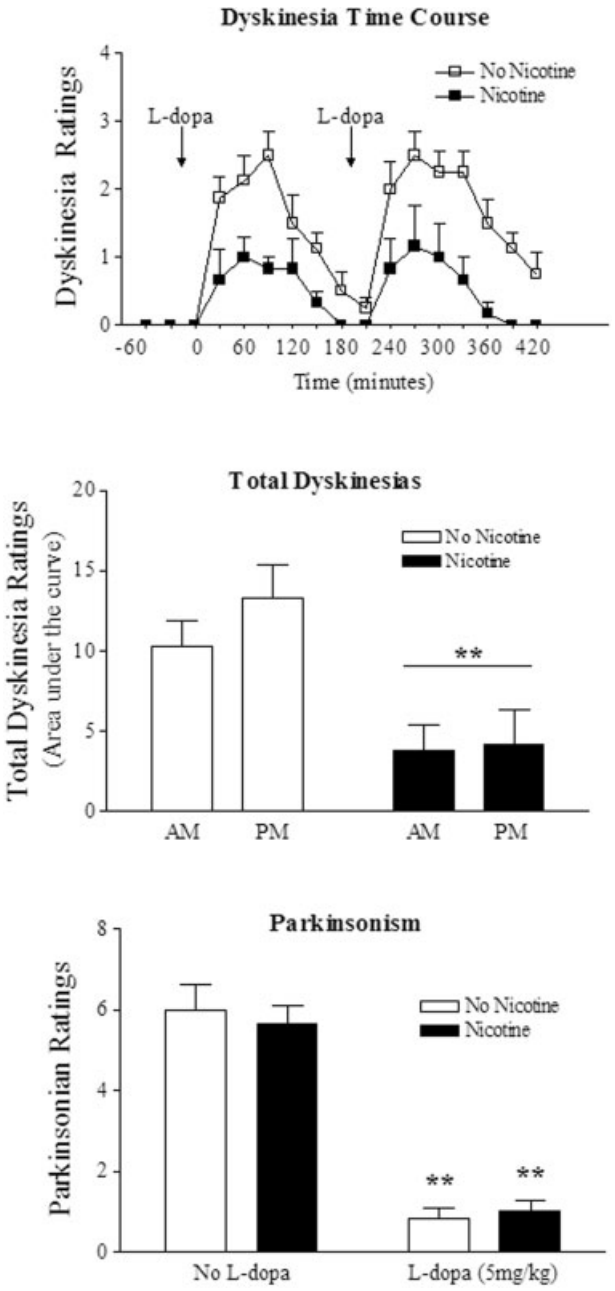

FIG. 1. Nicotine treatment reduces L-dopa-induced dyskinesias in nonhuman primates.[128] Time course of the nicotine-induced decline in levodopa-induced dyskinesias (top panel). MPTP-lesioned monkeys were given either nicotine or vehicle for several weeks and then gavaged with levodopa (L-dopa, 5 mg/kg) twice daily. Each symbol is the mean ± SE of 3 to 4 monkeys. Dyskinesias were significantly reduced in nicotine-treated animals compared to monkeys not receiving nicotine ($P < 0.01$) using a Mann-Whitney test. Total dyskinesias were significantly decreased by nicotine treatment after both the morning and afternoon dose of L-dopa (middle panel). $^{**}P < 0.01$ depicts a main effect of nicotine by two-way ANOVA. Nicotine treatment did not affect parkinsonism either on or off L-dopa (lower panel). $^{**}P < 0.01$ as compared to the same group with no levodopa treatment by a Mann-Whitney test.

nists could then be initiated to determine which receptor subtypes are involved.

NICOTINE TREATMENT REGIMENS

The preceding discussion suggests that nicotine or nicotine receptor ligands may be of therapeutic use in the management of Parkinson's disease, as neuroprotectants against continued nigrostriatal degeneration, for the treatment of Parkinson's disease symptoms or to attenuate L-dopa-induced side effects. An important question that now arises is what is the optimal nicotinic treatment regimen with respect to dosing, mode of delivery, and duration of administration. Numerous approaches are currently used in animal models including intermittent exposure via injection or self-administration, as well as continuous treatments via minipump or infusion.[129] This distinction is important because continuous and intermittent administration may have significantly different impacts on nicotinic receptor function. Continuous administration yields steady nicotine plasma levels and most likely results in receptor desensitization. By contrast, intermittent or pulsatile treatment leads to a cycle of receptor activation, desensitization, and resensitization, with a potentially different repertoire of functional effects.[50,130-132] A multitude of nicotine formulations are currently available for use in humans as therapy for smoking cessation,[129] which could potentially be used for Parkinson's disease treatment. These include continuous dosing via the nicotine patch, or intermittent administration using nicotine gum, lozenge, sublingual pill, inhalant, and spray. The specific manner in which nicotine is administered (pulsatile versus constant), the duration of treatment, and the dose of nicotine are very important questions for appropriate management of Parkinson's disease. Both preclinical studies and double-blinded placebo-controlled or crossover clinical trials will be required to address these issues. Parameters may differ for its use for neuroprotection or symptomatic treatment. Administration of nicotine via smoking would, of course, not be recommended because of the multitude of detrimental health-related effects associated with smoking.

Another very important point for consideration is that nicotine stimulates all nicotinic receptors in both the peripheral and central nervous systems. Its use may therefore be associated with side effects, in addition to its desired action. These may include alterations in cardiovascular measures (blood pressure, heart rate), the gastrointestinal system (cramping, nausea, vomiting), exocrine glands (dry mouth), as well as CNS effects including dizziness, headache, and lightheadedness. On the other hand, tolerance is well known to develop to systemic effects of nicotine, as evidenced by chronic smoking. However, the use of agonists that selectively target CNS nicotinic receptors, or better still the nigrostriatal system, such as the $\alpha6\beta2^*$ and $\alpha4\beta2^*$ receptor populations, would most likely be more beneficial from a therapeutic standpoint, with fewer peripherally mediated side effects and greater specificity of central action. The use of selective nicotinic agonists that target the nicotinic receptor subtypes involved in motor control may also obviate potential problems with addiction.[133-136] On the other hand, the detrimental effects of smoking do not appear to relate to the presence of nicotine but rather to the effects of a multitude of other toxic components in tobacco products.

Another important therapeutic consideration relates to the fact that most Parkinson's disease patients are already treated with numerous medications anyone of which may interact with nicotine or nicotinic agonists and affect metabolism, metabolic pathways, the cardiovascular, and other systems. However, as mentioned earlier, there is a large literature showing that Parkinson's disease incidence is reduced with smoking, a behavior associated with a substantial nicotine intake. In addition, clinical trials have been done in Parkinson's disease patients receiving nicotine (see Table 3). These observations suggest that nicotine treatment is most likely compatible with current Parkinson's disease therapies.

CONCLUSION

These combined data indicate that nicotine or nicotinic agonists may be useful for Parkinson's disease therapy from several perspectives, including neuroprotection against nigrostriatal damage, alleviation of symptoms, and reduction of drug-induced side effects (L-dopa-induced dyskinesias). The use of such agents, in combination with existing treatments, may represent a new disease modifying approach for Parkinson's disease.

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