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REVIEW

Pharmacotherapies for Parkinson's disease symptoms related to cholinergic degeneration

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ABSTRACT

Introduction: Dopamine depletion is one of the most important features of Parkinson's Disease (PD). However, insufficient response to dopaminergic replacement therapy suggests the involvement of other neurotransmitter systems in the pathophysiology of PD. Cholinergic degeneration contributes to gait impairments, cognitive impairment, psychosis, and REM-sleep disturbances, among other symptoms.

Areas covered: In this review, we explore the idea that enhancing cholinergic tone by pharmacological or neurosurgical procedures could be a first-line therapeutic strategy for the treatment of symptoms derived from cholinergic degeneration in PD.

Expert opinion: Rivastigmine, a drug that increases cholinergic tone by inhibiting the enzyme cholinesterase, is effective for dementia, whereas the use of Donepezil is still in the realm of investigation. Interesting results suggest the efficacy of these drugs in the treatment of gait dysfunction. Evidence on the clinical effects of these drugs for psychosis and REM-sleep disturbances is still weak. Stimulation of the pedunculo-pontine tegmental nuclei (which provide cholinergic innervation to the brain stem and subcortical nuclei) has also been used with some success for the treatment of gait dysfunction. Anticholinergic drugs should be used with caution in PD, as they may aggravate cholinergic symptoms. Notwithstanding, in some patients they might help control parkinsonian motor symptoms.

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Parkinson's disease; acetylcholine; cholinergic dysfunction; neurodegeneration; treatment; pathophysiology

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting about 1 person out of every 1000 in their fifth decade and 19 out of every 1000 in their eighth decade or older [1]. Its principal epiphenomenological clinical symptoms are abnormal involuntary movements, bradykinesia, rigidity, and tremor. Patients also frequently present non-motor symptoms, including cognitive impairment, mood disorders, sleep alterations, dysautonomia and hallucinations, among others [2].

Histopathological changes are mainly, but not exclusively, characterized by the progressive loss of the nigrostriatal dopaminergic pathway because of degeneration of dopaminergic neurons in the substantia nigra pars compacta, which explain the most typical motor symptoms [3]. Administration of levodopa to parkinsonian patients has been considered the most effective symptomatic treatment for the past 40 years [4].

Nigrostriatal cell loss may be related to loss of redox control, alteration of lysosomal activity, abnormal protein control mechanisms in the endoplasmic reticulum (ER), and perturbation of the ER-Golgi trafficking mechanisms. These cellular abnormalities are the main factors leading to abnormal accumulation of misfolded protein aggregates [5]. Lewy bodies constitute a characteristic pathological finding resulting from protein aggregation, second only to the neurofibrillary tangles in Alzheimer´s disease (AD). Early work suggested that Lewy bodies were mainly constituted by α-synuclein [6]. One major target of α-synuclein is Rab1, a key component of the endoplasmic ER-Golgi trafficking pathway [7]. It has been suggested that dysfunction of the endoplasmic reticulum due to stress might lead to an adaptive reaction known as the unfolded protein response [8]. When activated to a supraphysiological level, this response might be deleterious, triggering the apoptotic death of the damaged neuron [9,10].

There are many features of PD that are unresponsive to levodopa, such as gait disorders and cognitive impairment or dementia, indicating the involvement of other neurotransmitter systems [11]; in this context, recent evidence suggests that degeneration of adrenergic, serotoninergic, glutamatergic and cholinergic neurons, among others, may play a role [11].

Cholinergic dysfunction is a major feature of PD. For example, antagonists of the muscarinic acetylcholine receptors, derived from *Atropa belladonna*, were used to treat akinetorigid disorders in the XIXth century [12], well before recognition of the role of dopaminergic degeneration in PD and the use of dopaminergic agents. Indeed, acetylcholine dysfunction is involved in a myriad of PD symptoms [13]. The possibility of

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Article highlights

- Cholinergic degeneration is widespread in Parkinson's Disease and may contribute to gait impairments, cognitive impairment, psychosis, or REM-sleep disturbances.
- Cholinesterase inhibitors, which enhance cholinergic tone, have shown some efficacy for the treatment of dementia and gait impairments. Evidence of their effect on psychosis and REM-sleep disturbances is weak. DBS of the PPN nuclei has also been used with some success for the treatment of gait dysfunction.
- Anticholinergic drugs should be used with caution in Parkinson's Disease, especially in patients with cognitive impairment and/or gait impairments. Nevertheless, in some patients they might help control parkinsonian motor symptoms.

This box summarizes key points contained in the article.

using pharmacological or neurosurgical procedures to enhance cholinergic neurotransmission as first-line strategies for these symptoms is appealing. This review will thus focus on cholinergic symptoms in PD and the usefulness of cholinergic drugs for their treatment.

Bibliographical references were searched in Pubmed by the following string: (acetylcholine or cholinergic or rivastigmine or donepezil) and PD. Articles in English, Spanish, or French were retrieved. Reference sections from retrieved papers were also explored for database enrichment.

2. Cholinergic neurotransmission in health and its role in motor control and cognitive function

Acetylcholine (ACh) is a small molecular weight neurotransmitter which plays a pivotal role in chemical neurotransmission in the central nervous system (CNS) and peripheral nervous system (PNS). In the CNS, ACh mediates distant signaling through projection neurons and local signaling via interneurons. The message conveyed by ACh depends on a variety of factors, including site of release, the localization of the target neurons, the target receptor subtypes [14] and the status of the target cells at the time of release. Furthermore, ACh signaling may be circumscribed to the synapse or result from the de-localized diffusion of the neurotransmitter in the extracellular milieu and binding to non-synaptic sites [15,16]. Cholinergic transmission reach spans subcortical as well as cortical domains. Pathways are organized into two main tracks: (i) the brainstem and (ii) the magnocellular basal forebrain-cholinergic systems [17]. The former involves neuronal soma located in the pedunculopontine tegmental nucleus (PPN) and the laterodorsal pontine tegmentum and projects to the thalamus, basal ganglia, the basal forebrain and to a much lesser extent, the cerebral cortex [18]. The basal forebrain cholinergic system comprises neurons located in the medial septal nucleus, the vertical and horizontal limbs of the diagonal band of Broca, and the nucleus basalis magnocellularis (NBM, the nucleus basalis of Meynert in humans), which send projections to neocortex, entorhinal cortex, limbic cortices, cingulate cortex, and hippocampus. In the cortex, cholinergic transmission appears to involve modulation of target neurons via diffusion (i.e. volume transmission) [15]. It has been recently described that the dorsomedial hypothalamus contains Ach-containing neurons, which might be involved in the regulation of body temperature [19].

Cholinergic neurotransmission is mediated through two entirely different types of receptor proteins and ensuing molecular mechanisms, that is, the metabotropic 7-transmembrane domain (TM) muscarinic AChRs (mAChRs) and the ionotropic pentameric nicotinic AChRs (nAChRs). The former are members of the superfamily of G protein-coupled of receptors (GPCR), which possess 7-transmembrane segments and mediate intracellular signals associated with metabolic cascades. The nAChRs, on the other hand, are members of the superfamily of pentameric ligand-gated ion channels (pLGIC) [20,21]. The characteristics of these receptors are summarized in Table 1. The mAChRs are ubiquitously distributed among all brain regions, and their phylogenetic kindredness, resulting in similar structures and particularly similar ligand-recognition sites, makes it difficult to produce subtype-specific ligands. It is generally accepted that native homomeric α7 nAChRs, expressed in neurons but also in astrocytes and microglia, are involved in classic excitatory neurotransmission in some brain regions, and also modulate the release and activity of other neurotransmitters, neurite outgrowth, and neuronal survival and as such are obligatory partners in the pathophysiology of several neurodegenerative diseases, including Alzheimer's disease, PD, and some forms of schizophrenia [22,23]. Activation of this receptor might reduce neuro-inflammation by activating the Jak2/STAT3 and Nrf2/HO-1 in the microglia [24]. The heteromeric α7β2 nAChRs is expressed in brain regions associated with learning and memory, such as basal forebrain and hippocampus, suggesting that this form of the nAChRs may constitute an important target for cholinergic modulation of cognitive functions. Pharmacological agents selective for this heteromeric nAChRs and without effects on the classical homomeric α7 nAChR are not as yet available. α4β2 nAChR appears to have a role in cognitive function [25]. Previous studies have revealed reduced binding to these receptors in PD brains, and some preliminary findings suggest that the density of these receptors might correlate with cognitive impairments. In one study, 25 non-demented PD patients underwent a 5-[123I]iodo-3-[2(S)-2-azetidinylmethoxy]pyridine (5-I-A-85380) SPECT to visualize α4β2 nAChRs and cognitive testing with the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) battery to identify domains of cognitive dysfunction [25]. Results showed significant correlations between performance of the CERAD subtests Boston Naming Test (a specific test for visual perception and for detection of word-finding difficulties) and Word List Intrusions (a specific test for learning capacity and memory for language information) with the density of α4β2 nAChRs at the right superior parietal lobe cortex and the left thalamus, and left and right posterior subcortical regions.

The cholinergic neurotransmitter system is deeply involved in motor control. Indeed, the striatum contains some of the highest levels of ACh and dopamine in the brain. The two neurotransmitter systems interact extensively in a bi-

Table 1. Most abundant acetylcholine receptors expressed in the CNS.

Pharmacology type	Metabotropic		Ionotropic[a]		
Common denomination	Muscarinic		Nicotinic		
Subtype	M2, M4	M1 (50–60% of the total mAChRs), M3, M5	Hetero-pentameric (α4 and β2 subunits)	Homo-pentameric receptor (only α7 subunits)[b]	Hetero-pentameric (α6 and β2 subunits)
Second messengers	$G_{i/o}$ protein, inhibition of AC	G_q protein, metabolic cascades	Increased Na^+ and K^+ permeability	Increased Ca^{2+}, Na^+ and K^+ permeability	Increased Na^+ and K^+ permeability
Localization	Presynaptic (M2/4). hippocampus and cerebral cortex, pedunculopontine and laterodorsal tegmental nuclei of the mesopontine tegmentum (M2), striatum (M4), co-localized with dopamine receptors	Predominantly extrasynaptic in forebrain, hippocampus, cerebral cortex, striatum, thalamus (M1) Hypothalamus and various other brain regions (M3). Pars compacta of the substantia nigra, ventral tegmental area (M5)	90% of the high-affinity nAChR in brain: localized in cortex, hippocampus, striatum, thalamus, superior colliculus and mesencephalon	Involved in classic excitatory neurotransmission in some brain regions where the release of neurotransmitters, neurite outgrowth and neuronal survival is also modulated	Mesostriatal pathway, substantia nigra, ventral tegmental area, nucleus accumbens, caudate-putamen, visual pathways

AC: adenylate cyclase.
[a]Only neuronal-type receptors present in the CNS are included.
Subtypes listed correspond to the most frequently found combination of subunits.
[b]See the particular case of the heteromeric α7β2 in the text.
For further details, see Refs. [14,22,23,26–28].

directional manner, both at the presynaptic and postsynaptic levels, affecting cognitive mechanisms, and the selection of motor responses and reward [29,30]. This interaction is mediated by cholinergic interneurons, which send projections widely throughout the striatum, establishing synaptic contacts over a vast territory [31]. ACh is released in a pulsatile manner under resting conditions [32], which does not produce receptor desensitization, probably due to the counteracting high acetylcholinesterase activity in the striatum. It has been observed that changes in this cholinergic tone may contribute to associative learning, particularly the relationship between environmental cues and outcomes. Input to these interneurons include glutamate (coming from the thalamic caudal intralaminar nuclei), GABA, substance P and enkephalin (stemming from striatal medium spiny neurons), among others. A full review of their physiological role can be found elsewhere [33–36]. Both nicotinic and muscarinic AChRs are found in the striatum. Several pieces of evidence suggest that ACh release can trigger or inhibit dopamine release depending on the type of receptor activated. Dopamine appears to inhibit cholinergic interneurons, which in turn causes inhibition of dopamine release by muscarinic activation, thus creating a vicious cycle. These interneurons also regulate the activity of medium spiny neurons, modifying excitability to cortical or nigral inputs. It has been suggested that these effects offer strong integrative opportunities based on networks of interneurons that participate not only in movement but also in attention and reinforcement-related mechanisms [37].

3. Consequences of cholinergic deficits in PD

Several studies reveal important deficits in cholinergic tone in PD patients [13,38]. For example, in a study in 125 non-demented PD patients and 32 controls, employing neuroimaging of cholinergic neurotransmission by 1-[^{11}C]methylpiperidin-4-yl propionate ([^{11}C]PMP) position emission tomography (PET), 38 PD patients (30.4%) exhibited cortical AChE activity below normal range while the PPN-thalamic AChE activity was below normal range in 21 subjects (16.8%) [39]. In this section, the symptomatic consequences of such deficits will be revisited. A summary of these symptoms and their pathophysiological correlates are shown in Table 2.

Table 2. Sources of cholinergic dysfunction in PD and its main clinical correlates.

PD feature	Pathological basis
PD motor symptoms	Altered cholinergic striatal tone
Gait impairment and falls	Degeneration of the NBM and/or the PPN nuclei
Cognitive impairment	Degeneration of the NBM
REM sleep behavior disorder	Degeneration of the PPN
Psychosis	Reduced cholinergic tone (maybe PPN)

NBM: nucleus basalis magnocellularis (Meynert's nucleus); PPN: pedunculo-pontine tegmental nucleus.

3.1. Motor symptoms and gait impairments

As reviewed in preceding sections, ACh plays a significant role in motor control by modulating striatal output. Striatal cholinergic interneurons fire tonically at a rate of 3–10 Hz, resulting in a pulsatile release of ACh under resting conditions [32]. Several pieces of evidence suggest that ACh release can trigger dopamine release from the nigrostriatal varicosities by acting on nicotinic cholinergic receptors, whereas activation of the muscarinic ones can produce the opposite effect. Furthermore, dopamine inhibits cholinergic interneurons, which are therefore overactive in PD. In turn, cholinergic hyperactivity, related to dopaminergic hypofunction, further potentiates the reduction in dopaminergic activity.

Gait impairment significantly affects quality of life and increase mortality among PD patients [40,41]. The cholinergic PPN nuclei appear to be key players in motor coordination [42]. Gait impairment and falls have been linked to PPN dysfunction in PD [43]. For example, in MPTP-treated young or aged monkeys, PPN lesions worsened postural parameters

[44]. Similar results were observed after PPN stimulation in 6-OHDA (oxidopamine, 6-hydroxydopamine or 2,4,5-trihydroxyphenethylamine)-lesioned rats [45].

Other studies suggested that lesions of cholinergic basal forebrain nuclei might also affect gait [46]. In PD patients, neuroimaging of cholinergic neurotransmission by [^{11}C] PMP PET revealed deficits in patients reporting falls versus non-fallers [47]. Interestingly, there were no differences between these groups in markers of dopaminergic dysfunction. Furthermore, PD patients with freezing of gait (FoG) showed more frequent deficits in neocortical cholinergic tone (as measured by the same neuroimaging technique) compared to PD without FoG [48]. These results have been confirmed in a recent study, in which brain cholinergic function was studied by short latency afferent inhibition (SAI) in older adults with or without falls and in PD fallers [49]. SAI is a transcranial magnetic stimulation technique that assesses an inhibitory circuit in the sensorimotor cortex and is regarded as a global marker of cholinergic function in the brain. SAI was reduced in older adults with falls as compared to non-fallers and in PD fallers compared with older adults (fallers and non-fallers).

3.2. Cognitive impairment and mood disorders

Recent long-term follow-up studies have shown that the development of dementia in PD is likely in as many as 80% of patients when considering 15–20 years of survival after diagnosis [50,51]. Cognitive impairment may precede the onset of motor symptoms [2,52] and has been identified as a prognostic factor for more severe onset of motor impairment and disability during the first five years following initial PD diagnosis [53]. The physiopathology of PD Dementia (PDD) is complex and involves both dopaminergic and cholinergic deficits [54]. Deposition of α-synuclein, β-amyloid and neurofibrillary tangles as in Alzheimer's disease contribute to PDD [54]. The involvement of ACh pathways in PD is exemplified by the results of a recent trial in which white matter hyperintensities in the cholinergic pathways were assessed by means of the Cholinergic Pathways Hyperintensities Scale (CHIPS) after 3.0 T magnetic resonance [55]. CHIPS score was correlated with Mini Mental-state examination score and Sum of Boxes scores of the Clinical Dementia Rating, and verbal and visuospatial memory domains in demented patients with PDD, Alzheimer or Lewy body dementia. In another study, PD patients with minimal cognitive impairment were followed for a minimum of 2 years, during which PDD was diagnosed in 15 cases. Loss of neurons in the substantia innominata was observed in early stages of the disease, and was further accentuated in PDD [56]. Neuropathological studies have also shown a 54% reduction in the NBM of PDD compared to controls, versus a non-significant reduction in non-demented PD and without differences in other cholinergic regions [57]. Furthermore, the density of ACh neurons in this nucleus correlated inversely with the severity of dementia. Finally, α-synuclein pathology and Lewy-body deposition in the basal forebrain of patients with PDD were more severe than in non-demented patients, thus suggesting the possible role of α-synuclein aggregation in the development of cortical and hippocampal cholinergic dysfunction.

Mood disorders have also been correlated with cholinergic deficits. Indeed, a significant inverse correlation between cortical cholinergic activity (as measured by [^{11}C]PMP-PET) and Cornell Scale for Depression in Dementia scores in PD with or without dementia was observed [58]. Recent evidence suggests that the early involvement of the posterior neocortex and visuoperceptual impairment may be risk factors for the rapid symptomatic progression and dementia in PD [59].

3.3. Psychosis and delirium

Visual hallucinations (VHs) are frequently reported by PD patients [2]. They are usual adverse reactions to dopaminergic or anticholinergic drugs. In a recent study, inhibitory cholinergic activity in the CNS as measured by the short-latency afferent inhibition (SAI) technique was shown to be reduced in non-demented PD patients with VHs, compared to PD without VHs or controls [60]. Patients with VHs showed impaired cognitive functioning.

Delirium is more frequent in PD than in the general population and is related to cholinergic deficiency [61]. This condition remains largely unstudied in PD. One recent study showed that anticholinergic drug burden was significantly related to delirium in PD patients [62].

3.4. Sleep disturbances

Sleep disturbances are a frequent and disturbing feature of PD [2]. Rapid eye movement (REM) sleep is in part regulated by cholinergic pathways originating at the PPN and basal forebrain [63]. Interestingly, degeneration of these structures leads to reduction in REM sleep and REM-sleep behavior disorder (RBD) [64]. Cholinergic function in PD patients with RBD as assessed by the SAI technique was reduced to those without RBD [65]. In addition, MCI was more frequent in patients with RBD and cognitive parameters correlated with SAI.

4. Symptomatic treatment of cholinergic deficits in PD

The idea that enhancing cholinergic tone might be a first-line therapeutic strategy for cholinergic symptoms is logical and appealing. In this section, clinical use of cholinergic tone manipulation at the brain level by pharmacological or neurosurgical approaches will be explored. A summary of the most relevant studies is presented in Table 3. Non-cholinergic treatments will not be mentioned.

4.1. PD motor symptoms

Anticholinergics were the first drugs available for the symptomatic treatment of PD and they are still widely used today, both as monotherapy and as part of combination regimes. Their efficacy has been assessed by some randomized controlled trials, and their results were summarized in a systematic review and meta-analysis in the early 2000s [12]. Nine

Table 3. Most relevant studies with drugs or neurosurgical procedures enhancing cholinergic tone for the treatment of PD symptoms connected with cholinergic degeneration.

Author and year	Drug/procedure	Design	Sample	Main results
Katzenschlager et al. (2003) [12]	Benzhexol, orphenadrine, benztropine, bornaprine, benapryzine	Meta-analysis of randomized, double-blind, controlled trials	221 PD patients in 9 studies	Mild-to-moderate efficacy for motor symptoms
Moro et al. (2010) [66]	PPN DBS	Double-blind, randomized (stimulation ON vs. OFF)	6 PD with severe gait disturbances	No effects in motor or gait parameters Reduction in the rate of falling
Ferraye et al. (2010) [67]	PPN DBS	Double-blind, randomized (stimulation ON vs. OFF)	9 PD with severe gait disturbances	Reduced duration of freezing episodes and related falls
Chung et al. [68]	Donepezil	Randomized, placebo-controlled, crossover trial,	23 PD patients with falls	Reduction in the frequency of falls
Henderson et al. (2016) [69]	Rivastigmine	Randomized, double-blind, placebo-controlled trial	130 PD with falls	Reduced step time variability and less falls
Li et al. (2015) [70]	Rivastigmine	Randomized, double-blind, placebo-controlled trial	82 PD with cognitive decline	Reduced frequency of falls
Pagano et al. (2016) [71]	Rivastigmine, donepezil	Meta-analysis of randomized, double-blind, controlled trials	918 demented PD patients	Slower MMSE and ADAS-Cog decline
Mamikonyan et al. (2015) [72]	Rivastigmine	Randomized, double-blind, placebo-controlled trial	28 PD patients with minimal cognitive impairment	Non-significant benefits with rivastigmine

PPN DBS: Deep brain stimulation of the pedunculo-pontine tegmental nuclei.

double-blind crossover placebo-controlled studies including 221 patients were identified, in which the effects of benzhexol, orphenadrine, benztropine, bornaprine, benapryzine, and methixine were assessed. All of these studies were conducted in the seventies and early eighties. The follow-up period in general did not exceed 4 weeks. Sample size was usually about 10–20 patients. Outcomes were varied, however, the *Unified PD Rating Scale (UPDRS)*, which is the current standard scale for the assessment of motor symptoms, was not included in any of these studies. The quality of some of these studies was low. Significant improvements from baseline in at least one outcome measure were observed with all anticholinergic drugs except for methixine. Efficacy was mild-to-moderate and appeared similar for motor symptoms, that is, rigidity, bradykinesia, gait disturbances and tremor. Neuropsychiatric and cognitive adverse events (AEs), such as confusion, hallucination, and sedation, were a frequent cause of drop-out.

Anticholinergics have been considered as 'clinically useful' drugs in monotherapy or in combination with levodopa for the treatment of motor symptoms in PD by the most recent Movement Disorder Society Evidence-Based Medicine Review [73].

4.2. Gait impairment

The efficacy and safety of unilateral PPN deep brain stimulation (PPN DBS) in PD was studied in a double-blinded fashion with intraoperative neurophysiological and post-operative imaging characterization of the surgical target [66]. This study included six PD patients with severe gait and balance impairment and freezing with falls, causing severe limitations to their ability to carry out the normal activities of their daily life, despite optimization of medical treatment. Trials with the stimulator turned ON or OFF, assigned double-blindly were performed 3 and 12 months after surgery. The study failed to show differences in motor or gait parameters between stimulator-ON and -OFF after surgery. However, patients reported less falls under both ON and OFF conditions after surgery (UPDRS Item 13 -falling- at baseline: 2.0 ± 09, at month 3: 0.5 ± 0.5, and at month 12: 0.5 ± 0.5, both $p < 0.05$ vs. baseline). In another double-blind study, PPN DBS was applied to 6 PD patients with severe gait and freezing unresponsive to levodopa and subthalamic nucleus stimulation [67]. The primary outcome measures were a composite gait score, freezing of gait questionnaire score and duration of freezing episodes occurring during a walking protocol at baseline and one-year after surgery. At the end of follow-up, the duration of freezing episodes under the off-drug condition improved, as did falls related to freezing. No serious AEs occurred. In a third double-blind, randomized crossover study, effects of low-frequency (10–25 Hz) versus higher (60–80 Hz) frequency stimulation of the PPN were explored in nine PD patients with severe gait disturbances [74]. Results on akinesia and gait difficulties were better for low-frequency stimulation.

Significant and interesting clinical effects for PPN DBS have also been observed in other open-label studies [75]. These data suggest that surgical targeting of the PPN is feasible and shows promise for addressing axial symptoms in PD but may require further refinements in targeting, improved imaging, and better lead design to fully support benefits [75].

The efficacy and safety of donepezil, which increases cholinergic tone by inhibiting the ACh-catabolizing enzyme cholinesterase, was studied in 23 PD patients who reported falling or nearly falling more than two times per week [68]. It was a randomized, placebo-controlled, crossover trial, with treatment phases of 6 weeks and a 3-week wash-out period in between. At the end of the follow-up, fall frequency per day on placebo was 0.25 ± 0.08 as compared with 0.13 ± 0.03 in patients taking donepezil ($p < 0.05$). No differences were observed in other motor parameters.

The ReSPonD trial aimed at assessing the efficacy of the acetylcholinesterase inhibitor rivastigmine to reduce gait variability [69]. The primary outcome of this randomized, double-blind, placebo-controlled, phase 2 trial was the difference

in step time variability between the two groups at 32 weeks, adjusted for baseline age, cognition, step time variability, and the number of falls in the previous year. One-hundred thirty patients received either rivastigmine up to 12 mg or placebo in a 1:1 ratio. Results showed reduced step time variability in rivastigmine-treated patients. These patients also had a lower monthly rate of falls. Nausea and vomiting were more frequent in patients in the active group. In a randomized, double-blind, placebo controlled study, 82 PD patients with cognitive impairment received rivastigmine (n = 41) or placebo (n = 40) for 12 months [70]. During this period, 31.7% of rivastigmine-treated patients and 60% of placebo-treated patients suffered from falls (OR [95% CI] = 0.31 [0.12–0.77] $p < 0.01$).

Other studies suggest that avoiding antagonists of the mAChR may also help reduce gait impairments. For example, FoG was assessed by the UPDRS in 672 unselected non-demented PD patients [41]. Exposure to antimuscarinic drugs was not only significantly associated with more frequent FoG in ON-state but also with decreased dopaminergic efficacy on this parameter.

4.3. Cognitive impairment and mood disorders

A recent systematic review and meta-analysis suggested that inhibitors of cholinesterase are effective in the treatment of cognitive impairment in patients with PD [71]. The systematic search yielded three studies involving donepezil and one involving rivastigmine. The EXPRESS study included 541 patients with PDD who were randomly administered 12 mg rivastigmine or placebo and followed up for a mean of 24 weeks [76]. The study by Dubois et al. included 355 patients with PDD receiving 5 mg donepezil10 mg donepezil, or placebo, followed up for a mean duration of 24 weeks [77]. The study by Ravina et al. was a crossover study in which 22 patients with PDD were randomized to receive either 10 mg/day donepezil followed by placebo, or placebo followed by 10 mg/day donepezil for a mean follow-up of 10 weeks [78]. Results showed that these drugs significantly slowed MMSE decline (standardized mean difference [SMD] = − 1.123, 95% CI = −1.638 to −0.608; p = 0.001; I2 = 44.6%), and ADAS-cog (SMD = −0.266, 95% CI −0.399 to −0.133; $p < 0.0001$; I2 = 0%). Interestingly, the death rate was reduced in treated patients as compared to those receiving a placebo (OR = 0.295, 95% CI 0.108 to 0.806; p = 0.017; I2 = 0%). Similar results were also observed in another meta-analysis [79]. Rivastigmine is considered to be 'clinically useful' for the treatment of dementia in PD according to the latest review of the Movement Disorder Society Evidence-Based Medicine Task Force [80]. Use of donepezil is considered 'investigational' [80].

The efficacy and safety of rivastigmine for the treatment of minimal cognitive impairment in PD (PD-MCI) have been explored in a recent study [72]. Patients with PD-MCI (n = 28) were enrolled in a 24-week, randomized, double-blind, placebo-controlled, crossover, single-site study of the rivastigmine transdermal patch. The primary outcome measure was the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). Twenty-six participants (92.9%) completed both study phase assessments, and 23 (82.1%) completed both phases on study medication. The CGIC response rate demonstrated a non-significant difference favoring rivastigmine.

In a recent study, spontaneous brain activity in patients with PDD or PD-MCI was compared to controls before and after a 3-month therapy with rivastigmine patch [81]. Spontaneous brain activity was measured by using the fractional amplitude of low-frequency fluctuations after task-free functional magnetic resonance. At baseline, patients showed reduced spontaneous brain activity in regions important for motor control (e.g. caudate, supplementary motor area, precentral gyrus, thalamus), attention and executive functions (e.g. lateral prefrontal cortex), and episodic memory (e.g. precuneus, angular gyrus, hippocampus). Spontaneous brain activity deficits in the left premotor cortex, inferior frontal gyrus, and supplementary motor area were restored such that the activity was increased post-treatment compared with baseline and was no longer different from controls. These results are in line with a potential restoration of cortical cholinergic tone from the NBM induced by the drug.

Antimuscarinic drugs have a well-known deleterious effect on cognitive function [82], which has been confirmed in PD by a study measuring cerebral blood flow and oxygen metabolic rate after treatment with trihexyphenidyl [83]. These parameters are markers for dementia in PD [84]. Therefore, antimuscarinic drugs should be avoided in patients with cognitive impairments.

4.4. Other cholinergic symptoms

The management of psychosis should start by withdrawal of potential offending drugs, anticholinergics and tricyclic antidepressant in particular [85]. Anecdotal evidence suggests interesting clinical effects with donepezil [86], and there is an ongoing randomized, double-blind, placebo-controlled trial with donepezil for this indication [87]. In an open label study involving 23 patients in whom cognitive impairment occurred at least 1 year after a diagnosis of PD were treated by rivastigmine transdermal patch for 6 months [88]. The Neuropsychiatric Inventory (NPI) was used to assess neuropsychiatric symptoms. At month 6, NPI scores for hallucinations, depression, and appetite were reduced significantly.

Withdrawal of anticholinergic drugs is also the first therapeutic measure for delirium. Cholinesterase inhibitors do not appear to be effective for delirium in older adults [89], however, there are no studies in PD patients.

RBD symptoms were improved by rivastigmine in two small case series of patients with DLB [90]. Further results in PD are awaited.

The potential effects of PPN DBS on sleep and somnolence were explored in a pilot study involving two PD subjects with intractable gait dysfunction [91]. Low-frequency stimulation of the PPN area increased alertness, whereas high-frequency stimulation induced non-REM sleep. In addition, the sudden

withdrawal of the low-frequency stimulation was consistently followed by REM sleep episodes in one of the patients.

5. Safety of treatments for cholinergic symptoms

The side-effect profile of cholinesterase inhibiting drugs in PDD is similar to that reported in the AD population [92]. They are generally well tolerated at the usual dose range with drop-out rates reported in 10–31% of patients [92]. In the trials with donepezil, nausea, insomnia, vomiting, back pain, constipation, and hallucinations were more frequent with the drug compared to placebo [77]. Other common AEs were worsening of motor symptoms, tremor and dizziness [68,77,78]. In the trials with rivastigmine, AEs were more common with the drug compared to placebo, specially nausea, vomiting, and tremor [76]. Other frequent AEs were anorexia, falls, hypotension, and constipation [69,72,76].

The potential of rivastigmine to affect tremor and other motor symptoms in patients with PDD was assessed in a retrospective analysis of the EXPRESS study and its open-label extension [93]. During the double-blind trial, the AE of emerging or worsening tremor was reported in 10.2% of patients in the rivastigmine group, compared with 3.9% in the placebo group (p = 0.012), but only six patients (1.7%) were experiencing this AE at the end of this phase. In the open-label extension in which all patients received rivastigmine, tremor was reported by 6.9% of patients: 3.8% and 12.2% of whom had previously received double-blind rivastigmine and placebo, respectively (p = 0.006), suggesting that first exposure to rivastigmine leads to a transient increase in tremor. There was no evidence connecting rivastigmine to worsening of any other parkinsonian symptom.

Long-term safety of rivastigmine was studied in a 76-week, prospective, open-label, randomized study of 583 PD patients aged 50–85 years old [94]. Patients were randomly assigned rivastigmine 12 mg/day capsules or 9.5 mg/24 h patches. Primary outcomes included incidence of, and discontinuation due to, predefined AEs potentially arising from worsening of PD. Incidence of predefined AEs was 36.1% for capsules vs. 31.9% for patch. Discontinuation due to worsening of motor symptoms was observed in 4.4% and 2.4% for capsule/patch, respectively; tremor in 24.5% vs. 9.7%. Authors argued that these figures were in the range expected due to the natural progression of PD.

The effects of abrupt withdrawal of donepezil in patients with PDD or with probable dementia with Lewy bodies were studied in an open label study [95]. Eight patients with DLB and 11 with PDD were treated with up to 10 mg of donepezil daily for 20 weeks followed by a 6-week withdrawal period. Sudden withdrawal was found to be detrimental, producing acute cognitive and behavioral decline. Therefore, long-term treatment might be advisable.

The experience with PPN DBS is still limited and adverse events have not been reported [96] or where reported to be absent [66,74]. In one study, one patient subjected to this procedure developed worsening parkinsonism and other one seizures, which resolved spontaneously [67]. Stimulation frequency appears to be a key parameter for safety [67]. Reversible positive and negative myoclonus of the limbs with frequencies below 5 Hz, ipsilateral oscillopsia with frequencies between 5 and 35 Hz, and contralateral paresthesias with frequencies above 60 Hz [67].

6. Conclusions

Cholinergic deficits are common in PD and contribute to motor disturbances including gait dysfunction and non-motor symptoms such as cognitive impairment, dementia, mood abnormalities, psychosis, and sleep disorders [33,97]. It is therefore logical to hypothesize that increasing cholinergic tone might be a first-line strategy for the treatment of these symptoms. The bulk of evidence suggests that enhancing cholinergic tone by neurosurgical manipulation of the PPN, by administering inhibitors of the enzyme cholinesterase, or by withdrawing drugs with cholinergic antagonizing effects, could be effective for these symptoms. The only PD feature not falling into this category would be the parkinsonian core motor symptoms resulting from striatal dysfunction, which are ameliorated by anticholinergic drugs.

Experimental observations showing the key role of PPN for the generation of gait patterns, together with evidence that its function is significantly diminished in PD [48], led to the suggestion that DBS might be effective for gait disturbances in PD. Results are promising, but still inconclusive and thus further research is warranted [75]. In the meantime, it might represent an option for patients with severe gait disturbances who are unresponsive to other treatments. On the other hand, evidence on the efficacy of cholinesterase inhibitors for this symptom is stronger [68,69], and suggest that these drugs could be tried initially in patients with gait impairment and/or falls unresponsive to dopaminergic therapy. The use of anticholinesterase drugs has another advantage over stimulation of PPN. As suggested by some studies, reduced cortical tone is also involved in gait abnormalities in PD [49], which could be restored by cholinesterase inhibitors, but not by PPN stimulation.

Cognitive disturbances and dementia also have a significant cholinergic correlate [33]. Several pieces of evidence suggest that rivastigmine is effective and safe, while the use of donepezil still remains a matter of research. Therefore, rivastigmine may be considered pivotal for the treatment of PDD [71]. The evidence is weaker for PD patients with minimal cognitive impairment [72]. These patients might obtain some benefit from these drugs, but further evidence is needed before any concrete claims can be made in this connection.

Withdrawing anticholinergic drugs is the first step in the management of psychosis and delirium in PD [85]. Some evidence suggests that rivastigmine might also be effective for this symptom, but further research is needed. A randomized, double-blind, placebo-controlled trial with donepezil for this indication is underway. Delirium might not respond to these drugs, but no study on PD is available. Case reports also suggest that these drugs might be beneficial for RBD, at least in patients with Lewy body dementia [90]. Trials in PD are still lacking.

On the other extreme of the spectrum, reducing cholinergic tone by administering anticholinergic drugs has shown some efficacy for the control of parkinsonian motor symptoms [12]. Anticholinergics have been used since the XIX century for the

treatment of parkinsonian symptoms. Not surprisingly, such efficacy comes at the expense of aggravating cognitive and/or gait deficits.

7. Expert opinion

Cholinergic deficits in PD might be as widespread and deleterious as dopaminergic degeneration, both conditions affecting an array of domains ranging from motor to cognitive functions. The idea of using pharmacological and/or neurosurgical approaches to enhance cholinergic tone for the treatment of symptoms related to cholinergic dysfunction is thus appealing. It is seldom the case that a class of drugs is effective in such a large number of relevant clinical domains, as is the case of cholinesterase inhibitors in PD. They are first-line drugs for PDD and probably the agents with the best documented efficacy for gait impairment. Given the degree of disability resulting from cholinergic symptoms, cholinesterase inhibitors might have a true 'disease-modifying effect' in the sense that they might have a long-lasting impact on this parameter [98].

There are, however, certain issues that will need to be addressed by future studies. First, it has been shown that the inhibition of the acetylcholinesterase enzyme is only partial with the currently available drugs [99] and thus, efficacy would be very much improved if more potent cholinesterase inhibitors were developed. In addition, the safety of cholinesterase inhibitors should be better explored. Theoretically, these drugs may worsen parkinsonian motor symptoms by further misbalancing ACh-Dopamine tone in the striatum. Short-term trials have not disclosed such effects, and one 1.5-year study showed results that might be in line with normal disease progression [94]. Further studies comparing disease progression in patients under these treatments or not are needed to support this claim. It is also possible that the risk/benefit ratio for pro- or anti-cholinergic drugs depends on the stage of the disease and/or the particular patient. For example, patients with intact cholinergic function might benefit from the use of anticholinergic drugs for the treatment of parkinsonian symptoms. In contrast, in the case of patients with advanced cholinergic degeneration, cholinesterase inhibitors might be administered if gait disturbances, cognitive impairment or psychosis are present. Furthermore, in these patients, attention should be paid to the use of drugs with anticholinergic effects. In PD, 'anticholinergic burden' has been shown to result from the association of several drugs with mild-to-moderate effects, such as antimuscarinic agents for urinary incontinence, some antidepressants, or opioids, among others [62,100]. Another issue is how to assess effectively cholinergic neurodegeneration in the clinical practice, and if this could be achieved in a cost-effective way. This issue requires further research.

Psychosis and related sleep disturbances are related to cholinergic degeneration [60,65] and thus might benefit from cholinesterase inhibitors, at least theoretically. Notwithstanding, evidence about efficacy is weak [85] or comes from other diseases [101]. Studies are urgently needed for these domains, as actual treatments either have low efficacy or are unsafe.

PPN DBS can offer some benefits for gait dysfunction without the potential parkinsonian effects of pro-cholinergic drugs. Results from small trials are encouraging, but there are still many questions that need to be answered. In the first place, localization of the PPN in humans has been extrapolated for studies in non-human primates. This may lead to errors in placing electrodes, which would lead to stimulating surrounding non-PPN neurons or fibers. Furthermore, it is not clear which portions of the PPN are being stimulated (i.e. the cholinergic, glutamatergic or GABAergic ones). In addition, the best parameters for stimulation are still not fully understood. It is also not clear whether unilateral or bilateral stimulation should be performed. PPN DBS has been used so far for treating gait dysfunction in PD. Interesting effects on sleep parameters were also noticed in one pilot study, indicating that PPN DBS might also be effective in patients with insomnia and/or diurnal somnolence. Further studies are required.

Anticholinergic drugs have been recognized as clinically useful for the treatment of motor symptoms such as monotherapy or in conjunction with levodopa [73]. Clinical efficacy is mild-to-moderate and some neurologists have suggested that it might have a greater effect on tremor, which is not supported by current evidence. Generally speaking, studies conducted during the seventies and eighties, long before current standards for clinical trials were set in place, have been small with a relatively short follow-up. Larger clinical trials, using modern rating scales, might help to better appraise the place of anticholinergic drugs in the therapeutic arsenal for PD. As mentioned earlier, these effects have to be weighed against the possibility of adverse reactions.

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