Neuropsychiatric Symptoms Related to Cholinergic Deficits in

Parkinson's Disease

Santiago Perez-Lloret[1], María Cecilia Peralta[2], Francisco J. Barrantes[3]

[1]Institute of Cardiology Research, University of Buenos Aires, National Research Council (CONICET-ININCA), Marcelo T. de Alvear 2270, C1122AAJ Buenos Aires, Argentina.

[2]Parkinson's disease and Movement Disorders Clinic, Neurology Department, CEMIC University Hospital. Elias Galvan 4102, C1431. Buenos Aires, Argentina.

[3]Laboratory of Molecular Neurobiology, Institute for Biomedical Research, UCA-CONICET, Faculty of Medical Sciences, Av. Alicia Moreau de Justo 1600, C1107AFF Buenos Aires, Argentina.

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Address for correspondence:
Santiago Perez-Lloret MD PhD CPI,
Institute of Cardiology Research,
Marcelo T. de Alvear 2270
(C1122AAJ) Buenos Aires. Argentina
Telephone/Fax= +54 +11 4508-3880/1
Email= santiagopl@conicet.gov.ar

Abstract

Given its ability to explain the most frequent motor symptoms of Parkinson's disease (PD), degeneration of dopaminergic neurons has been considered one of the disease´s main pathophysiological features. Several studies have shown that neurodegeneration also affects noradrenergic, serotoninergic, cholinergic and other monoaminergic neuronal populations. In this work, the characteristic contribution of cholinergic deficits to cognitive dysfunction, psychosis and sleep disturbances in PD and their treatment will be explored. Important neurophysiological processes at the root of several motor and cognitive functions remit to cholinergic neurotransmission at the synaptic pathway and circuital levels. The bulk of evidence highlights the link between cholinergic alterations and the aforementioned symptoms. The pathophysiology of these symptoms is related to degeneration of cholinergic nuclei, most importantly the nucleus basalis magnocellularis and the pedunculo-pontine nucleus. 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. Evidence on the clinical effects of these drugs for psychosis and REM-sleep disturbances is still weak. Anticholinergic drugs should be used with caution in PD, as they may aggravate these cholinergic symptoms.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting about 1 person out of every 1,000 in their fifth decade and 19 out of every 1,000 in their eighth decade or older [1]. Its principal epiphenomenological clinical symptoms are abnormal involuntary movements, bradykinesia, rigidity and tremor. Patients also frequently display non-motor symptoms, including cognitive impairment, mood disorders, sleep alterations, dysautonomia and hallucinations, among other symptoms [2].

Histopathological changes are mainly, but not exclusively, characterized by the progressive loss of the nigrostriatal dopaminergic pathway and of the source 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 last 40 years [4].

At the cellular and molecular levels, neuronal death may be preceded by a series of dysfunctional states, including 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 pathologies are closely intertwined with one of the hallmarks of the disease, namely the abnormal accumulation of misfolded protein aggregates [5]. Lewy bodies constitute a characteristic pathological finding, second only to the neurofibrillary tangles in Alzheimer´s disease (AD). Early work identified the immunoreactivity of the Lewy bodies with antibodies against the presynaptic protein α-synuclein [6].One major target of α-synuclein is Rab1, a key

component of the ER-Golgi trafficking pathway [7]. ER stress has been invoked as a possible major disruptive mechanism, leading to an adaptive reaction known as the unfolded protein response [8].This response may be cytoprotective when activated to a moderate level, but is deleterious at a higher level, triggering in turn the apoptotic death of the damaged neuron [9, 10]. PD may also be considered a synaptopathy, i.e. abnormal synaptic connectivity compromising nigrostriatal pathways and intra-striatal interneuronal connections, presumably most apparent at the initial stages of the disease. Mutations in the α-synuclein gene cause familial forms of PD and dementia with Lewy bodies. Synaptic accumulation of α-synuclein is accompanied by the redistribution of the synaptic SNARE proteins SNAP-25, syntaxin-1 and synaptobrevin-2, as well as by an age-dependent reduction in dopamine release [11].

The striatum is the most important input nucleus of the basal ganglia. The principal source of afferents is layer 5 of the cerebral cortex, conveying glutamatergic (Glu) excitatory synapses. Motor areas (4 and 6 plus supplementary motor area) together with the primary somatosensory cortex follow, also with Glu neurotransmission. The second major striatal input is dopaminergic (DA), stemming from the substantia nigra A9 cell group. 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 [12]. In this regard, recent evidence suggests degeneration of adrenergic, serotoninergic and cholinergic neurons, among others [12].

The importance of cholinergic dysfunction in the physiopathology of many PD features cannot be overemphasized. For example, in a recent study in 137 PD patients, cholinergic denervation could be related to REM behavior disorder, fall history, gait disorders, psychosis and cognitive dysfunction [13, 14]. In this chapter we review the pathophysiology and treatment of neuropsychiatric symptoms originating from cholinergic degeneration, namely dementia, psychosis and sleep disturbances. A summary of cholinergic neurotransmission in health will precede the sections on cholinergic deficits in PD.

Bibliographical references were searched in Pubmed by the following string: (acetylcholine OR cholinergic) AND Parkinson's disease. Articles in English, Spanish or French were retrieved. Reference sections from retrieved papers were also explored for data-base enrichment.

2. Cholinergic neurotransmission in health

Acetylcholine (ACh) is an ubiquitous, small molecular weight neurotransmitter which plays a pivotal role in chemical neurotransmission in the central (CNS) and peripheral nervous system (PNS). In the brain, ACh mediates distant signaling through projection neurons and local signaling via interneurons. The type of message conveyed by ACh depends on a variety of factors, including site of release, the localization of the target neurons, the target receptor subtypes [15] 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 [16, 17]. In terms of gross anatomical

brain regions it is safe to state that ACh affects brain in its entirety. A recent review (ref.[18]) meticulously dissects current knowledge on the anatomy of cholinergic projections, summarized in two main tracks: i) the brainstem; and ii) the magnocellular basal forebrain- cholinergic systems. The former, as worked out by immunochemical techniques [19], involves neuronal soma located in the pedunculo-pontine tegmental nucleus (PPN) and the laterodorsal pontine tegmentum (LDT) and projecting to the thalamus, basal ganglia, the basal forebrain and to a much lesser extent, the cerebral cortex. The basal forebrain cholinergic system comprises neurons located in the medial septal nucleus (MS), 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. Cholinergic fibers in cortex appear not to be associated with postsynaptic densities, a fact that has been linked with the hypothesis that cholinergic transmission may not be synaptic but may involve modulation of target neurons via diffusion, so-called volume transmission [16].

From the standpoint of the target receptors, ACh neurotransmission is mediated through two entirely different types of receptor proteins and ensuing molecular mechanisms, i.e. the metabotropic 7-transmembrane domain (TM) muscarinic AChRs and the ionotropic pentameric nicotinic nAChRs (See Table 1 for a summary). The former are members of the G protein-coupled superfamily of receptors, 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), a collection of neurotransmitter receptors which also

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includes γ-amino butyric acid (GABA-A, GABA-C), glycine, serotonin (5-HT3) and bacterial homologs [20, 21].

The metabotropic mAChRs are coupled to different types of G proteins, e.g. $G_{i/o}$ type (M2 and M4 subtypes of mAChRs) of G proteins that negatively couple to adenylate cyclase or G_q proteins (M1, M3 and M5 subtypes of mAChRs), which convert the cholinergic signal into metabolic cascades [22]. Presynaptic mAChRs (M2, M4 subtypes) are largely inhibitory and perform this function partly as inhibitory autoreceptors on cholinergic terminals [23]. The M2 subtype is the predominant autoreceptor in the hippocampus and cerebral cortex, whereas M4 is the main subtype in the striatum [15, 22, 24]. Postsynaptic mAChRs can be either inhibitory (M2, M4) or excitatory (M1, M3, M5) [15, 24].

The ionotropic, fast-signaling nAChRs are composed of five polypeptide subunits organized pseudo-symmetrically around a central pore [25]. Each subunit contains an extracellular domain, four hydrophobic transmembrane segments arranged in the form of three concentric rings around the pore and a short extracellular carboxy-terminal domain. nAChRs are characteristically involved in the rapid "phasic" effects of ACh under conditions of brief release / high local concentration of the neurotransmitter, but they also operate under the low, tonic ACh release or mimicking systemically applied cholinergic drugs [16], a condition which may be particularly relevant to cholinergic neurotransmission –and/or its modulation- in the striatum.

Muscle-type nAChRs are expressed in the PNS and neuronal-type nAChRs in both PNS and the CNS as well as in other non-neural tissues such as immune cells, lymphocytes, lung epithelium and other tissues [26]. In the

CNS, the nAChR is present in various combinations of subunits (α4, α5, α6, α7, α9, α10 and β2)[27], the two most abundant ones being the hetero-pentameric receptor formed by α4 and β2 subunits and the homo-pentameric receptor formed exclusively by α7 subunits. The deficit of some of the nAChR subunits in PD has been explicitly explored [28]. The two predominant forms of the nAChR, the α4β2 and the α7 oligomers, are also strongly expressed in the striatum, accompanied by the α6β2 form[29]. It is not clear whether other subunits are present in the heteromeric nAChRs. The α4β2 and α6β2 nAChRs in the striatum are localized at the dopaminergic terminal, the predominant target undergoing degeneration in PD. The α4β2 nAChR is also found in striatal GABAergic inhibitory interneurons [30].

The α7nAChR exhibits certain functional properties that distinguish it from other nicotinic receptors: a) fast desensitization kinetics, b) unusually high Ca^{2+} permeability and c) high affinity for binding α-bungarotoxin [27, 31]. In most regions of brain the α7 nAChR is found presynaptically, where it modulates enhanced neurotransmitter release of various other neurotransmitters, including DA, 5-HT, glutamate and GABA; and postsynaptically, where it generates postsynaptic currents [32, 33]. In addition, the peri-synaptic presence of the receptor has also been demonstrated, where it modulates neuronal activity, presumably by an unconventional mechanism involving diffusion of the natural neurotransmitter and binding to non-synaptic sites [16]. In the striatum, the α7 nAChRs are found in cortical glutamatergic excitatory afferents [32].

Cholinergic mechanisms are intimately linked to cognitive functions associated with cortical and hippocampal brain anatomical regions. Working

memory, spatial and episodic memory acquisition, storage, maintenance and retrieval, attention and other neurophysiological processes at the root of neural information and cognitive functions remit to ACh neurotransmission at synaptic, pathway and circuital levels.

3. Neuropsychiatric symptoms resulting from cholinergic degeneration in PD

A summary of the brain cholinergic nuclei exhibiting signs of denervation in PD and their neuropsychiatric correlates is presented in Table 2. In this section the contributions of cholinergic degeneration to the physiopathology of cognitive impairment, psychosis and sleep disturbances in PD will be summarized.

3.1 Cognitive impairment and mood disorders

The physiopathology of PD Dementia (PDD) is complex and involves severe dopaminergic and cholinergic deficits, the main pathological drivers of cognitive decline being a synergistic effect between α-synuclein and AD's pathology [34]. Only cholinergic deficits will be reviewed in this section.

3.1.1 Alteration in cholinergic receptors expression or function in cognitive impairment in PD

Because of their distribution in brain anatomical regions associated with cognitive processes, various subtypes of nAChR have been invoked as being associated with abnormal cognitive processes. The $\alpha7$ nAChR is highly expressed in the hippocampus, a region particularly affected in cognitive

disorders [27, 35, 36, 37], as recently reviewed in ref. [38], whereas a massive loss in cerebral cortex of the other most abundant type of CNS nAChRs, the $\alpha4\beta2$-type, accompanies the cognitive decline observed in AD [39, 40]. Not surprisingly, alterations in memory and cognition associated with nAChRs have also been reported in pathological states other than AD, such as schizophrenia [41]. The various functions afflicted in PD have been associated with nAChR dysfunction of different brain nAChR oligomeric forms [42, 43, 44].$\alpha7$ nAChR ligands are a subject of intense research in diseases affecting cognitive functions, especially the subclass of ligands termed positive allosteric modulators (PAMs, see reviews in ref.[45]). It is a group of compounds that enhance recognition memory and cognitive improvement in animal models (e.g. ref. [46, 47]).

Muscarinic receptors are also implicated in cognitive disturbances. Antagonists such as scopolamine perturb the performance of cognitive tasks in animal models [48] and even lead to extreme cognitive disturbances with delirium at higher doses [49]. This condition has also been reported in children after application of postsurgical transdermal patches to ameliorate nausea and motion sickness [50] and in the elderly, who are particularly vulnerable to even modest levels of antimuscarinic drugs due to their cumulative effects [51].

Several lines of evidence link brain nicotinic nAChRs, the α7 in particular, with the development of neurodegenerative disease with cognitive impairments, like AD [45]. The greater the depletion of cholinergic neurons and associated cholinergic pathways in cognitive-associated brain areas such as the neocortex and hippocampus, the more severe the associated dementia, suggesting a relationship between the clinical manifestations and the level of cholinergic

decline [52, 53]. Cholinergic pathways are associated with the processes of learning and memory, and nicotinic agonists and cholinomimetics in general have been used as therapeutic agents providing symptomatic improvements in cognitive impairment [54, 55, 56, 57, 58].This constitutes the basis of therapeutic approaches aiming at α7 AChR activation with selective agonists.

3.1.2   Data from studies in PD patients

The involvement of ACh pathways in PD is further exemplified by the results of a recent trial by Park and colleagues [59]. White matter hyperintensities in the cholinergic pathways were assessed by means of the Cholinergic Pathways Hyperintensities Scale (CHIPS) using 3.0 Tesla magnetic resonance. Patients with AD (n=20), PDD (n=21) and

Dementia with Lewy Bodies (DLB, n=17) were compared with a group of 20 healthy controls. Results showed that the CHIPS score was correlated with MMSE, SOB scores of the Clinical Dementia Rating, and verbal and visuospatial memory domains in demented patients.

Degeneration of the NBM appears to be highly correlated with PDD [60]. A recent study showed that PD patients with mild cognitive impairments (PD-MCI) who would develop PDD during follow-up had greater degeneration of the substantia innominata, where the NBM is located [61]. In this study, 51 PD-MCI were followed for a minimum of 2 years, during which PDD was diagnosed in 15 cases. Greater grey matter loss in the prefrontal area was also observed in subjects developing PDD. Loss of neurons in the substantia innominata was observed in early stages of the disease, and was further accentuated in PDD.

Recent results in post-mortem analyses of brains from demented and non-demented PD patients confirmed these results. In the study by Hall and colleagues, stereological analyses of the A9 and A10 dopaminergic neurons and Ch1, Ch2 and Ch4 cholinergic neurons located in the basal forebrain, along with an assessment of α-synuclein pathology in these regions and in the hippocampus, were performed in six demented and five non-demented PD patients and five age-matched control individuals with no signs of neurological disease [62]. Choline acetyltransferase (ChAT) activity in the hippocampus and frontal cortex was also measured in a different set of eight demented and eight non-demented PD patients, as well as in the same areas of eight age-matched controls. Stereological analyses showed a significant 54% reduction in the NMB of PDD compared to controls and a non-significant reduction of 30% in non-demented PD. No differences were observed in other cholinergic regions. Furthermore, the density of ACh neurons in the NBM correlated inversely with the severity of dementia. ChAT activity, a measure of the presence of cholinergic terminals in a given brain region, was reduced in the hippocampus of PD with dementia compared to non-demented patients and controls. Interestingly, neocortical ChAT activity was reduced in the neocortex of both demented and non-demented PD compared to controls. 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.

The diminution in the density of the α4β2 nAChR in the CNS has been recently correlated with cognitive impairments in non-demented PD patients

[63]. Previous studies had revealed reduced binding to these receptors in PD brains, and some preliminary findings suggest that the lower density of these receptors might correlate with cognitive impairments. In this 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 [63]. 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.

An interesting question is whether the alteration of the NBM is the same as that found in AD. NBM degeneration is comparable or even more intense in PD compared to the latter, yet the clinical characteristics of the two dementias differ significantly. Some authors have suggested that the divergence may be connected to possible differences in the degree to which subsections of the NBM are affected [64], but this hypothesis remains to be studied.

Depression can precede dementia, or at least depressed patients are at greater risk of developing PDD [65]. In a recent study, neocortical cholinergic innervation was assessed in 12 non-demented PD patients, 6 PDD and 10 normal control patients [66] by means of dynamic PET scanning of previously injected [11C]methyl-4-piperidinyl propionate radioligand, a selective substrate for the enzyme AChE. Pooled analyses demonstrated a significant inverse

correlation between cortical AChE activity and Cornell Scale for Depression in Dementia scores (r=0.5, p=0.007). The correlation remained significant when only PD patients were assessed, in whom AChE activity also correlated with the MMSE score. 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 [67].

3.1.3 Cognitive dysfunction as a side-effect of cholinergic drugs

In the light of the evidence reviewed above, it is not surprising that drugs interfering with cholinergic function have profound effects on cognitive function in PD. Muscarinic receptor blockers can cause acute confusion, dementia and chronic intellectual impairment [68]. In a study with trihexyphenidyl, an oral anticholinergic agent, clinical disability, cognitive assessment and measurements of cerebral blood flow (rCBF) and oxygen metabolic rate (rCMRO) were performed in 6 PD before and after administration of the drug for 7 weeks at 6 mg/day [69]. Results showed improvements in motor symptoms without evident changes in cognitive function. Cortical and striatal rCBF and rCMRO2 were significantly decreased, a typical finding in PDD [70].

3.2 Psychosis and delirium

Visual hallucinations (VHs) are frequently reported by PD patients [2]. Besides the effect of dopaminergic medication, anticholinergics are associated with VHs even in patients without PD.

3.2.1 Data from studies in PD patients

In a recent study, inhibitory cholinergic activity in the CNS was measured by means of the short-latency afferent inhibition (SAI) technique in 10 non-demented PD patients with VHs, in 12 non-demented PD patients without VHs and in 11 age-matched healthy controls [71]. Results showed reduced SAI in patients with VHs, which was otherwise normal in patients without hallucinations. In addition, patients with VHs showed more frequent MCI and had reduced values in some cognitive function tests. The authors speculated that these results might be related to diminished neocortical cholinergic input from the NBM.

3.2.2 Delirium

Characterized by an acute and fluctuating disturbance in attention and awareness accompanied by an additional disturbance in cognition, delirium is more frequent in PD than in the general population [72]. Cholinergic deficiency is one of the most frequently found abnormalities in delirium. In a recent study, the association between exposure to anticholinergic drugs and delirium was studied in a database of more than 16.000 PD patients [73]. Results showed that 57.8% of PD patients were prescribed non-PD medications with moderate to very strong anticholinergic potential. Subjects exposed to anticholinergic polypharmacy had increased risk of delirium (adjusted OR: 1.61, 95% CI: 1.08–2.40).

3.3 Sleep disturbances

Sleep disturbances are common disabling non-motor features of PD that have a detrimental effect on health-related quality of life [2].Activation of the

PPN is capable of inducing REM sleep [74] and degeneration of cholinergic neurons in the basal forebrain and brainstem is one of the factors resulting in a reduction in REM sleep and REM-sleep Behavior Disorder (RBD) [75]. RBD is characterized by a loss of normal muscle atonia during REM sleep and dream-enacting behavior. RBD occurs in 0.5% of the general population, but is considered to be a risk factor for synucleinopathies and even as a pre-motor sign of PD [76].

3.3.1 Data from studies on animal models

The effects on REM sleep of drugs acting on different monoaminergic systems have been explored in the MPTP mouse model of PD [77]. The objective of the study was to assess the effects of these drugs on sleep/wakefulness patterns, measuring the amount of REM sleep (or paradoxical sleep -PS-). Arecoline, a muscarinic agonist, increased the amount of PS in the MPTP-treated mice but not in the controls, probably reflecting supersensitivity in the former.

3.3.2 Data from studies in PD patients

Cholinergic function has been recently evaluated in PD patients with or without RBD by means of short latency afferent inhibition (SAI), a transcranial magnetic stimulation protocol able to test an inhibitory cholinergic circuit in the human brain [78]. In this study, 10 PD patients with RBD diagnosis by polysomnography, 13 patients without the disorder and 10 healthy controls were enrolled. In addition to SAI, neuropsychological examination was also performed. SAI was reduced in PD patients with RBD compared to unaffected

PD and healthy controls. Interestingly, MCI was more frequent in the former, and cognitive parameters correlated with SAI. These findings indicate that cholinergic dysfunction may play an important role in RBD in PD.

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. Other non-cholinergic treatments will be (briefly) mentioned for the sake of completeness.

4.1 Cognitive impairment

A recent systematic review and meta-analysis suggested that inhibitors of cholinesterase are effective in the treatment of cognitive impairment in patients with PD [79].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 [80]. 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 [81]. 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 [82]. Results showed that these drugs significantly slowed MMSE decline (MD=−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 lower in treated patients than in those receiving a placebo (OR=0.295, 95% CI 0.108 to 0.806; p=0.017; I2=0%). Tremor and adverse drug reactions in general were more frequent with cholinesterase inhibitors. A summary of these studies is presented in Table 3.

Long-term safety of rivastigmine was studied in a 76-week, prospective, open-label, randomized study of 583 PD patients aged 50 to 85 years old [83]. Patients were randomly assigned rivastigmine 12 mg/d capsules or 9.5 mg/24 h patches. Primary outcomes included incidence of, and discontinuation due to, predefined adverse events (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 Parkinson´s disease. 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 [84]. Use of donepezil is considered "Investigational" [84].

The efficacy and safety of rivastigmine for the treatment of minimal cognitive impairment in PD (PD-MCI) have been explored in a recent study [85]. 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, patients with PDD or PD-MCI were compared to controls and studied before and after a 3-month therapy with rivastigmine patch [86]. 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 [68], which has been confirmed in PD by a study measuring cerebral blood flow and oxygen metabolic rate after treatment with trihexyphenidyl [69]. These parameters are markers for dementia in PD [70]. Therefore, antimuscarinic drugs should be avoided in patients with cognitive impairments.

Memantine, a channel blocker of the N-methyl-d-aspartate (NMDA) type of glutamate receptors, has been prescribed for Alzheimer´s disease patients, and could possibly be used for the treatment of PDD who cannot tolerate cholinesterase inhibitors, but its efficacy has been poorly documented [87].

4.2 Psychosis, delirium and sleep disturbances

The management of psychosis should start by withdrawal of potential offending drugs, anticholinergics and tricyclic antidepressant in particular [87]. Quetiapine in small doses might also be used if drug withdrawal fails [87]. Anecdotal evidence suggests interesting clinical effects with donepezil [88], and there is an ongoing randomized, double-blind, placebo-controlled trial with donepezil for this indication [89].

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 [90]; however, there are no studies in PD patients.

RBD symptoms were improved by rivastigmine in two small case series of patients with DLB [91]. Further results in PD are awaited. The most commonly used RBD treatments include low-dose clonazepam or high-dose melatonin taken orally at bedtime [92].

The potential effects of PPN DBS on sleep and somnolence were explored in a pilot study involving 2 PD subjects with intractable gait dysfunction [93]. 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.

Discussion

Cholinergic deficits are common in PD and contribute to motor disturbances including gait dysfunction and non-motor symptoms like cognitive impairment, dementia, mood abnormalities, psychosis and sleep disorders [14, 94]. 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 administering inhibitors of the enzyme cholinesterase and/or withdrawing drugs with cholinergic antagonizing effects, could be effective for treating cognitive impairment, psychosis and sleep disturbances in PD. Interestingly, cholinesterase inhibitors have also been found to be effective for gait impairment and falls [95, 96], which are also related to cholinergic degeneration [97, 98].

Several pieces of evidence suggest that rivastigmine may be considered pivotal for the treatment of PDD [79]. The evidence is weaker for PD patients with minimal cognitive impairment [85]. These patients might obtain some benefit from this type of drug, 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 [87]. If further treatment is needed, cholinesterase inhibitors might also offer some benefit in the former, as suggested by anecdotal evidence. A randomized, double-blind, placebo-controlled trial with donepezil 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 [91]. Trials in PD are still lacking.

There are, however, certain issues that will need to be addressed by future studies. Firstly, the safety of cholinesterase inhibitors should be more thoroughly explored. Theoretically, these drugs could worsen parkinsonian motor symptoms by further misbalancing ACh-DA tone in the striatum. Although short-term trials have not disclosed any such effects and one 1.5-year study showed results that could be considered in line with normal disease progression [83], further studies comparing disease progression in patients under these treatments with untreated controls are needed to dispel any doubts on the matter.

Psychosis and related sleep disturbances might also benefit from cholinesterase inhibitors, as suggested by low-quality evidence [87] or by evidence from other diseases [99]. Studies are urgently needed for these domains, as actual treatments either have low efficacy or are unsafe.

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

Pharmacol. type	Metabotropic		Ionotropic*		
Common denomination	Muscarinic		Nicotinic		
Subtype	M2,M4	M1 (50-60% of the total mAChRs), M3, M5	hetero-pentameric ($\alpha4$ and $\beta2$ subunits)	homo-pentameric receptor (only $\alpha7$ subunits)**	hetero-pentameric ($\alpha6$ and $\beta2$ 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 survivalis also modulated	Mesostriatal pathway, substantia nigra, ventral tegmental area, nucleus accumbens, caudate-putamen, visual pathways

AC= adenylate cyclase

* Only neuronal-type receptors present in the CNS are included.

Subtypes listed correspond to the most frequently found combination of subunits. **See the particular case of the heteromeric $\alpha7\beta2$ in the text.

For further reference see Refs. [15, 22, 24, 25, 32, 33].

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

PD feature	Pathological basis
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= Pedunculopontine nucleus.

Table 3. Studies with cholinesterase inhibitors for cognitive impairmentin PD.

Author & Year	Drug/ Procedure	Design	Sample	Main results
Emre 2004 [80]	Rivastigmine	Randomized, double-blind, placebo-controlled trial	541 demented PD patients	Improvement of 2.1 points in the ADAS-cog with rivastigmine vs 0.7-point worsening with placebo (p<0.001)
Ravina 2005 [82]	Donepezil	Randomized, double-blind, placebo-controlled trial	22 demented PD	There was a 1.9 point trend toward better scores on the ADAS-cog on donepezil vs placebo (p=NS)
Dubois 2012 [81]	Donepezil	Randomized, double-blind, placebo-controlled trial	355 demented PD	In a post-hoc analysis, donepezil was better than placebo
Mamikonyan 2015 [85]	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.