We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Possible Treatments of Atypical Parkinsonism

Moretti Davide Vito

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/63948>

Abstract

Success in treating patients with atypical parkinsonism remains exceedingly low. It is particularly important for both neurologists and general practitioners to have a guideline in the actual possible cure options. This study reviews the limited available literature reporting treatment trials about treatment in parkinsonism. Various therapeutical approaches have been tried with rasagiline, immunoglobulin, autologous mesenchymal stem cells, davunetide, lithium, and tideglusib. Recently, transdermal rotigotine (RTG) has been proposed for the treatment of atypical parkinsonism, as well as deep brain stimulation (DBS) of the pedunculopontine nucleus (PPN) alone or combined with globus pallidus internus (Gpi) stimulation. The outcomes reviewed here highlight the need for the development of randomized, placebo-controlled trials to validate outcomes about rotigotine, DBS, and all other new therapies directed at altering the underlying biological mechanisms involved in the disease process.

Keywords: atypical parkinsonism, treatment options, pharmacological intervention, deep brain stimulation, diagnosis

1. Introduction

Progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), Parkinson's disease with dementia (PDD), and dementia with Lewy bodies (DLB) are usually indicated as atypical parkinsonian syndromes (APS). Anyway, each of that syndrome is characterized by peculiar anatomo-pathological picture [1–5]. Up to date, the amount of pathophysiological data available regarding APS has progressively grown in the past two decades. Nonetheless, the etiology of APS is still under investigation and effective treatments are lacking [6,7]. Various therapeutical approaches have been tried with rasagiline, immunoglobulin, autologous mesenchymal stem cells, davunetide, lithium, and tideglu-

sib [8]. Recently, the transdermal rotigotine (RTG) has been proposed for the treatment of atypical parkinsonism [9–11], as well as deep brain stimulation of the pedunculopontine nucleus (PPN) alone or combined with globus pallidus internus (Gpi) stimulation [12]. This study reviews the limited available literature reporting treatment trials. The outcomes reviewed here highlight the need for the development of novel therapies directed at altering the underlying biological mechanisms involved in the disease process.

2. Materials and methods

This study reviews all the limited available literature reporting treatment trials about treatment in atypical parkinsonism.

3. Clinical features

Diagnosis of AP has been performed in accordance with the primary diffuse tips and medical criteria [13–20]. PSP is characterized by vertical gaze abnormalities, early falls, postural instability, and presenile cognitive impairment. PSP has two principal clinical forms: classical PSP (or Richardson's syndrome) and PSP-parkinsonism (PSP-P). Respect to the classical form, PSP-P is characterized by the presence of tremor and an inconstant clinical response to levodopa. The classical CBD phenotype includes apraxia, cortical sensory loss, alien limb, as well as dystonia and myoclonus. MSA patients usually show a mix of cerebellar and pyramidal signs, parkinsonism, and autonomic dysfunction. The predominant phenotype at onset of MSA allows the classification into MSA-parkinsonism or MSA-cerebellar form. The diagnosis of PD was made following previously published criteria [21]. Only subjects with idiopathic PD were enclosed within the present study in order to get a homogeneous sample study population [22]. So, patients had unilateral onset and development of parkinsonian signs, two of the three cardinal signs among akinesia, rigidity, and postural abnormalities and resting tremor. A superb response to a dopaminoagonist treatment was a strong criterion. In the Parkinson-dementia group, patients with idiopathic PD, who developed cognitive decline after a year of the onset of parkinsonism, were included. On the contrary, in Lewy Body Dementia (LBD) group, patients with cognitive impairment appeared within 1 year after the onset of movement disorders were included. Moreover, in this group patients with Rapid Eye Movements (REM) sleep behavior disorders, vivid dreams, hallucinations and postural instability have been enclosed [22].

4. Results

4.1. Current pharmacological chances in APS

Table 1 summarizes the most important clinical trials aiming to find a drug therapy for APS.

Authors	Disease	Treatment	Duration	Outcomes
Poewe et al. [23]	MSA	Rasagiline	48 weeks	No improvement
Novak et al. [24]	MSA	Intravenous immunoglobulin	6 months	Improvement
Lee et al. [25]	MSA-cerebellar type	Autologous mesenchymal stem cells	12 months	Improvement
Hoglinger et al. [35]	PSP	Tideglusib	12 months	Improvement
www.allontherapeutics.com, 2012	PSP	Davunetide	52 weeks	No improvement
Stamelou et al. [40]	PSP	CoQ10	6 weeks	Improvement
Moretti et al. [9–11]	MSA-PSP-CBD-LBD	Transdermal rotigotine	24 months	Improvement
Servello et al. [12]	PSP	DBS of PPN	12 months	Improvement

Table 1. Synopsis of the main clinical trials for the treatment of atypical parkinsonism.

The monoamine oxidase-B inhibitor rasagiline with the dosage of 1 mg/day has been assessed in a randomized, placebo-controlled clinical trial for 48 weeks in 174 patients with possible or probable MSA-parkinsonism type. The total Unified Multiple System Atrophy Rating Scale (UMSARS) score did not found significant improvements in the treated when compared to placebo groups [23].

A monthly infusions of 0.4 g/kg intravenous immunoglobulin for 6 months in seven patients with MSA found significantly improved UMSARS part I (activities of daily living) and II (motor functions) score. A verification study has been programmed [24] to validate the anti-inflammatory approach.

Injections of autologous mesenchymal stem cells (MSCs) in 33 patients with probable MSA-cerebellar compared with placebo demonstrated a smaller increase in total and part II UMSARS scores in the MSC group. Anyway, a careful evaluation of the exact efficacy of the staminal cells is under investigation [25].

Due to the dangers of postural instability in MSA from orthostatic hypotension, considerable attention has been directed toward blood pressure control. A synthetic norepinephrine precursor was tested in 10 patients with MSA in a randomized, double-blind, placebo-controlled study, resulting in an increase in supine and upright blood pressure [26,27]. Moreover, the droxidopa has been evaluated in a phase III clinical trial in order to assess the efficacy in orthostatic hypotension, and recently FDA approved its clinical use (<http://www.medscape.com/viewarticle/820786>). As about other autonomic symptoms, oxybutynin or tolterodine can be helpful for neurogenic bladder and desmopressin can be helpful for nocturnal polyuria, whereas sildenafil may be efficacious in erectile dysfunction, but can dramatically worsen postural hypotension (Stamelou and Bathia). Recent large controlled studies with rasagiline and rifampicin have shown no neuroprotective effect [23,28].

In regard to PSP and CBD, in clinical practice, treatment options are limited to a levodopa trial (up to 1 g/d) and amantadine for parkinsonism and gait disturbance as well as valproate or levetiracetam for myoclonus [29]. Although not sufficiently studied, botulinum toxin injections can be helpful to relieve dystonic spasms of the hand or to treat levator inhibition [30]. Early clinical trials in PSP employed drug treatment to correct alterations in the dopaminergic, cholinergic, and gamma-amino butyric acid (GABA)ergic pathways and produced limited evidence of benefit. Trials with both physostigmine and donepezil were employed with a poor response in memory as well as motor function [31,32]. As about GABAergic agonists, trials with zolpidem [33] and gabapentin [34] found, respectively, transient improvement in eye movements and inhibitory frontal function. Anyway, these trials were limited by small sample size and little evidence of a long-term benefit of the treatment.

Progressive Supranuclear Palsy Rating Scale (PSPRS) and the Schwab and England Activities of Daily Living (SEADL) did not show significant outcomes in a multinational randomized, double-blind, placebo-controlled trial in which 313 patient with PSP received davunetide 30 mg twice daily or placebo (press release December 18, 2012 by Allon Therapeutics, www.allontherapeutics.com).

The inhibitors of glycogen synthase kinase-3 (GSK-3) such as lithium or tideglusib have been administered in PSP or CBD patients in two distinct trials. The lithium trial (ClinicalTrials.gov; identifier NCT00703677) a patient with PSP ended before the natural time because the drug was not tolerated. The tideglusib trial did not show significant improvement between the high-dose, low-dose, and placebo groups in the final clinical evaluation [35].

Methylene blue derivatives are inhibitors of tau protein aggregation. These agents could be a rational treatment for PSP and CBD. Anyway, the most advanced strategies for reducing tau protein are immunologic approaches targeting different tau epitopes [36]. Moreover, passive immunization approaches, which act through anti-tau monoclonal antibody directed against various tau epitopes, were shown to block seeding activity and improve cognitive deficits in transgenic mice [37].

Microtubule-stabilizing agents are also explored as potential therapies compensating the loss of tau protein function in PSP and CBD. In particular, taxanes, a class of cancer drugs and a related class of compounds called epothilones, are now being investigated as tau-related neurodegeneration. The epothilone D was found to improve axonal microtubule density and improved spatial learning in treated mice [38,39]. It has been suggested that mitochondrial dysfunction may contribute to pathogenesis of atypical parkinsonisms. This evidence has led to an interest in replacing the coenzyme Q10 (CoQ10), a component of the complex I of the mitochondrial chain. A small, double-blind, placebo-controlled, randomized trial involving 21 PSP patients treated with CoQ10 for 6 weeks has shown improvement in PSPRS scores, frontal assessment battery scores, and occipital energy when compared with placebo [40]. Currently, a large phase III trial with CoQ10 in PSP patients for 12 months is underway.

As about the LBD, the cholinergic deficit that affects in an important way these patients could benefit from the cholinesterase inhibitors; hallucinations, neuropsychiatric symptoms, and psychosis are all reduced in LBD [41].

In a large, randomized, double-blind controlled trial with 120 LBD patients over 20 weeks, rivastigmine treatment resulted in reduction of apathy, delusions, anxiety, and hallucinations, as well as improvements in cognitive assessment [42]. Furthermore, a 3-week post-treatment follow-up has also shown better Neuropsychiatric Inventory (NPI) scores [43]. A recent multicenter trial in Japan has administered donepezil to 140 patients with LBD showing clinical, cognitive, and behavioral improvement when compared to placebo [44].

Recently, the effect of memantine, an NMDA-receptor antagonist, has been evaluated in two clinical trials [45,46] in patients with both LBD and PDD. Although some clinical benefits have been reached, the effect of memantine remains inconclusive.

Atypical antipsychotic agents such as quetiapine are recommended because of the risk of extrapyramidal side effects in patients with LBD. Clonazepam at low dosage could be used in REM sleep behavior disorder. As about parkinsonian disorders, levodopa should be administered instead of dopaminergic agents with a particular care to the aggravation of psychotic symptoms.

4.2. Transdermal RTG as treatment option for atypical parkinsonian syndrome

Transdermal RTG seems to be effective and well tolerated in patients with APS. Recent studies [9–11] show significant improvement in UDPRS-III scores, maintained along the course of the 248 months follow-up. Only seven patients were dropped out, and 15 patients were affected by adverse events. In this study, behavioral or psychiatric adverse events and ICDs were not found. Moreover, results also show a reduction in NPI scores that became significant at the last follow-up evaluation (T18). Finally, during the study the patients did not suffer from congestive heart failure. These results confirm previous evidences obtained in patients with idiopathic Parkinson's disease showing positive effect on motor control and behavioral disturbances [47–55] as well as a good safety of RTG [56]. On the whole, these outcomes highlight that transdermal RTG should be considered as a therapeutic option for the treatment of atypical parkinsonism.

4.3. Deep brain stimulation in PSP

In a recent study [12], three patients with PSP were submitted to the deep brain stimulation of the pedunculopontine nucleus (PPN). A reduction of falls and an amelioration of postural balance were observed. The patients required less assistance for daily living activities. The clinical improvement was, however, not fully reflected in the evaluating scales. The mean PSPRS percentage decrease was of 26.3% (SD = 8.3) at the 12-month follow-up visit for the three patients. The diversity between the reported improvement and the PSPRS might be due to the phenomenological diversity of PSP, not fully captured by the PSPRS, and repeated scheduled postoperative evaluations are necessary to capture objectively the overall clinical improvement. That the greatest PSPRS percentage decrease (35.7%) was seen in the double-implanted GPi-PPN patient is possibly due to the improvement of the concomitant amelioration of his or her dystonic state. It remains of course speculative in light of a single case if this better clinical outcome seen in the GPi-PPN patient is reflection of an increased synergic effect

of PPN and GPi secondary to stimulation, bearing in mind the strong connectivity between the basal ganglia and the PPN. An interesting observation was related to the stimulation parameters; we started with low-frequency stimulation, which was increased progressively to 130 Hz without noticing a significant change in clinical presentation.

4.4. Supportive therapies

The palliative therapies are highly recommended in APS patients. An assortment of physical, occupational, and language therapies should be considered, paying attention to the most invalidating symptom, that is, apraxia. If the risk of falls and postural instability become prevailing symptoms, a wheelchair has to be suggested and should be advised to patient and family. This acknowledgment can be shockingly testing and troublesome. Numerous families see the utilization of a wheelchair as a marker of the last loss of the capacity to ambulate and stay free. They should be persuaded that in addition to the fact that this is vital for the well-being of the patient, the wheelchair can give a more prominent level of flexibility than the constrained portability given by the patient's attempts to try to deambulate. At long last, it is vital to screen and support the prosperity of the caregivers. The especially troublesome mix of serious motor inability with cognitive and behavioral aggravations increases the risk of an overwhelming burnout.

4.5. Future treatment options

Different approaches such as "regenerative" or "restorative" (e.g., stem cells and trophic factors) are desirable to provide advance in the field of disease-modifying therapy. Trials of "neuroprotective" therapies are actively being planned or have been implemented (e.g., a trial of riluzole for PSP and multiple system atrophy has been initiated in Europe). Further discussion and evaluation of the best endpoints for clinical trials in these disorders are an important priority. One of the major obstacles to the design of the necessary clinical trials is the accuracy of clinical diagnosis. This finding emphasizes the need for developing biological markers for these neurodegenerative disorders. The similarities in the underlying neuropathology and molecular biology of these disorders suggest that critical advances in this field will equally impact on the treatment outcomes [1].

5. Conclusions

Up to date, the possibilities of the APS care are without no doubt very low. Two main goals are to achieve: the better understanding of the pathogenic mechanisms and the improvement of both symptomatic and disease-modifying treatments through controlled clinical trials. In the near future, every effort should be made to give hope to patients and caregivers whose number will not decrease.

Acknowledgements

Author contributions: Moretti DV was responsible for the conception and design of the study, acquisition, analysis, and interpretation of data, as well as for the drafting and revising of the article.

Author details

Moretti Davide Vito

Address all correspondence to: davide.moretti@afar.it

IRCCS S. Giovanni di Dio Fatebenefratelli, Brescia, Italy

References

- [1] Litvan I, Bhatia KP, Burn DJ, et al. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Mov Disord* 2003;18:467–486.
- [2] Williams DR, de Silva R, Paviour DC, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. *Brain* 2005;128(Pt 6):1247–1258.
- [3] Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* 2008;71:670–676.
- [4] Stamelou M, Quinn N, Bhatia K. 'Atypical' parkinsonism: new genetic disorders presenting with features of PSP, MSA or CBD. *Mov Disord* 2013 (Epub ahead of print).
- [5] Wenning GK, Geser F, Krismer F, et al. The natural history of multiple system atrophy: a prospective European cohort study. *Lancet Neurol* 2013;12:264–274.
- [6] Antonini A, Cilia R. Behavioural adverse effects of dopaminergic treatments in Parkinson's disease: incidence, neurobiological basis, management and prevention. *Drug Saf* 2009;32(6):475–488.
- [7] Vilas D, Pont-Sunyer C, Tolosa E. Impulse control disorders in Parkinson's disease. *Parkinsonism Relat Disord* 2012;18 Suppl 1:S80–S84.
- [8] Lang AE. Treatment of progressive supranuclear palsy and corticobasal degeneration. *Mov Disord* 2005;20(Suppl 12):S83–S91.

- [9] Moretti DV, Binetti G, Zanetti O, Frisoni GB. Rotigotine is safe and efficacious in Atypical Parkinsonism Syndromes induced by both α -synucleinopathy and tauopathy. *Neuropsychiatr Dis Treat* 2014;10:1003–1009. doi: 10.2147/NDT.S64015 (eCollection 2014a).
- [10] Moretti DV, Binetti G, Zanetti O, Frisoni GB. Behavioral and neurophysiological effects of transdermal rotigotine in atypical parkinsonism. *Front Neurol* 2014;5:85. doi: 10.3389/fneur.2014.00085 (eCollection 2014b).
- [11] Moretti DV, Binetti G, Zanetti O, Frisoni GB. Non-ergot dopamine agonist rotigotine as a promising therapeutic tool in atypical parkinsonism syndromes: a 24 months pilot observational open-label study. *Neuropharmacology* 2014;85:284–289. doi: 10.1016/j.neuropharm.2014.05.028 (Epub 2014 Jun 7).
- [12] Servello D, Zekaj E, Saleh C, Menghetti C, Porta M. Long-term follow-up of deep brain stimulation of pedunculopontine nucleus in progressive supranuclear palsy: report of three cases. *Surg Neurol Int* 2014;5(Suppl 8):S416–S420. doi: 10.4103/2152-7806.140208 (eCollection 2014).
- [13] Litvan I, Mangone CA, McKee A, et al. Natural history of progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome) and clinical predictors of survival: a clinicopathological study. *J Neurol Neurosurg Psychiatry* 1996;60:615–620.
- [14] Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology* 1996;47:1–9.
- [15] Wenning GK, Ben-Shlomo Y, Magalhaes M, Daniel SE, Quinn NP. Clinicopathological study of 35 cases of multiple system atrophy. *J Neurol Neurosurg Psychiatry* 1995;58:160–166.
- [16] Wenning GK, Tison F, Ben Shlomo Y, Daniel SE, Quinn NP. Multiple system atrophy: a review of 203 pathologically proven cases. *Mov Disord* 1997;12:133–147.
- [17] Wenning GK, Scherfler C, Granata R, et al. Time course of symptomatic orthostatic hypotension and urinary incontinence in patients with postmortem confirmed parkinsonian syndromes: a clinicopathological study. *J Neurol Neurosurg Psychiatry* 1999;67:620–623.
- [18] Wenning GK, Stefanova N, Jellinger KA, Poewe W, Schlossmacher MG. Multiple system atrophy: a primary oligodendrogliopathy. *Ann Neurol* 2008;64:239–246.
- [19] Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. *Lancet Neurol* 2009;8:270–279.
- [20] Ling H, O'Sullivan SS, Holton JL, et al. Does corticobasal degeneration exist? A clinicopathological re-evaluation. *Brain* 2010;133(Pt 7):2045–2057.
- [21] Berardelli A, Wenning GK, Antonini A, Berg D, Bloem BR, Bonifati V, Brooks D, Burn DJ, Colosimo C, Fanciulli A, Ferreira J, Gasser T, Grandas F, Kanovsky P, Kostic V,

- Kulisevsky J, Oertel W, Poewe W, Reese JP, Relja M, Ruzicka E, Schrag A, Seppi K, Taba P, Vidailhet M. EFNS/MDS-ES/ENS [corrected] recommendations for the diagnosis of Parkinson's disease. *Eur J Neurol*. 2013;20(1):16–34. doi: 10.1111/ene.12022. Review. Erratum in: *Eur J Neurol* 2013;20(2):406.
- [22] McKeith I, Dickson D, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005;65:1863–1872.
 - [23] Poewe W, Barone P, Gliadi N, et al. A randomized, placebo-controlled clinical trial to assess the effects of rasagiline in patients with multiple system atrophy of the parkinsonian subtype. *Mov Disord* 2012; 27(Suppl 1):1182.
 - [24] Novak P, Williams A, Ravin P, et al. Treatment of multiple system atrophy using intravenous immunoglobulin. *BMC Neurol* 2012; 12:131.
 - [25] Lee PH, Lee JE, Kim HS, et al. A randomized trial of mesenchymal stem cells in multiple system atrophy. *Ann Neurol* 2012; 72:32–40.
 - [26] Freeman R, Landsberg L, Young J. The treatment of neurogenic orthostatic hypotension with 3,4-dl-threo-dihydroxyphenylserine: a randomized, placebo-controlled, crossover trial. *Neurology* 1999;53(9):2151–2157.
 - [27] Tsai RM, Boxer AL. Clinical trials: past, current, and future for atypical parkinsonian syndromes. *Semin Neurol* 2014;34(2):225–234. doi: 10.1055/s-0034-1381739.
 - [28] Low PA, Robertson D, Gilman S, et al. Efficacy and safety of rifampicin for multiple system atrophy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2014;13:268–275.
 - [29] Stamelou M, Hoeglinger GU. Atypical parkinsonism: an update. *Curr Opin Neurol* 2013;26:401–405.
 - [30] Stamelou M, Alonso-Canovas A, Bhatia KP. Dystonia in corticobasal degeneration: a review of the literature on 404 pathologically proven cases. *Mov Disord* 2012;27:696–702.
 - [31] Fabbrini G, Barbanti P, Bonifati V, Colosimo C, Gasparini M, Vanacore N, Meco G. Donepezil in the treatment of progressive supranuclear palsy. *Acta Neurol Scand* 2001;103(2):123–125.
 - [32] Litvan I, Phipps M, Pharr VL, Hallett M, Grafman J, Salazar A. Randomized placebo-controlled trial of donepezil in patients with progressive supranuclear palsy. *Neurology* 2001;57(3):467–473
 - [33] Daniele A, Moro E, Bentivoglio AR. Zolpidem in progressive supranuclear palsy. *N Engl J Med* 1999;341(7):543–544. No abstract available. Erratum in: *N Engl J Med* 1999;341(21):1632.

- [34] Poujois A, Vidailhet M, Trocello JM, Bourdain F, Gaymard B, Rivaud-Péchoux S. Effect of gabapentin on oculomotor control and parkinsonism in patients with progressive supranuclear palsy. *Eur J Neurol* 2007;14(9):1060–1062.
- [35] Hoeglinger GU, Huppertz HJ, Wagenpfeil FS, et al. Tideglusib reduces progression of brain atrophy in progressive supranuclear palsy in a randomized trial. In: Alzheimer's Association International Conference, Vancouver, British Columbia, Canada, 2012, proposal number: 34102.
- [36] Yanamandra K, Kfoury N, Jiang H, Mahan TE, Ma S, Maloney SE, Wozniak DF, Diamond MI, Holtzman DM. Anti-tau antibodies that block tau aggregate seeding in vitro markedly decrease pathology and improve cognition in vivo. *Neuron* 2013;80(2):402–414. doi: 10.1016/j.neuron.2013.07.046.
- [37] Brunden KR, Ballatore C, Lee VM, Smith AB 3rd, Trojanowski JQ. Brain-penetrant microtubule-stabilizing compounds as potential therapeutic agents for tauopathies. *Biochem Soc Trans* 2012;40(4):661–666. doi: 10.1042/BST20120010 (review).
- [38] Barten DM, Fanara P, Andorfer C, Hoque N, Wong PY, Husted KH, Cadelina GW, Decarr LB, Yang L, Liu V, Fessler C, Protassio J, Riff T, Turner H, Janus CG, Sankaranarayanan S, Polson C, Meredith JE, Gray G, Hanna A, Olson RE, Kim SH, Vite GD, Lee FY, Albright CF. Hyperdynamic microtubules, cognitive deficits, and pathology are improved in tau transgenic mice with low doses of the microtubule-stabilizing agent BMS-241027. *J Neurosci* 2012;32(21):7137–7145.
- [39] Stamelou M, Pilatus U, Reuss A, Magerkurth J, Eggert KM, Knake S, Ruberg M, Schade-Brittinger C, Oertel WH, Höglinger GU. In vivo evidence for cerebral depletion in high-energy phosphates in progressive supranuclear palsy. *J Cereb Blood Flow Metab* 2009;29(4):861–870. doi: 10.1038/jcbfm.2009.
- [40] Stamelou M, Reuss A, Pilatus U, Magerkurth J, Niklowitz P, Eggert KM, Krisp A, Menke T, Schade-Brittinger C, Oertel WH, Höglinger GU. Short-term effects of coenzyme Q10 in progressive supranuclear palsy: a randomized, placebo-controlled trial. *Mov Disord* 2008;23(7):942–949. doi: 10.1002/mds.22023.
- [41] McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, Cicin-Sain A, Ferrara R, Spiegel R. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 2000;356(9247):2031–2036.
- [42] Wesnes KA, McKeith IG, Ferrara R, Emre M, Del Ser T, Spano PF, Cicin-Sain A, Anand R, Spiegel R. Effects of rivastigmine on cognitive function in dementia with Lewy bodies: a randomised placebo-controlled international study using the cognitive drug research computerised assessment system. *Dement Geriatr Cogn Disord* 2002;13(3):183–192.
- [43] Mori E, Ikeda M, Kosaka K, Donepezil-DLB Study Investigators. Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. *Ann Neurol* 2012;72(1):41–52. doi: 10.1002/ana.23557.

- [44] Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, Kossakowski K, Leroi I, Pozo-Rodriguez F, Minthon L, Londos E. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multi-centre trial. *Lancet Neurol* 2009;8(7):613–618. doi: 10.1016/S1474-4422(09)70146-2.
- [45] Fernandez HH, Wu CK, Ott BR. Pharmacotherapy of dementia with Lewy bodies. *Expert Opin Pharmacother* 2003;4(11):2027–2037.
- [46] Emre M, Tsolaki M, Bonuccelli U, Destée A, Tolosa E, Kutzelnigg A, Ceballos-Baumann A, Zdravkovic S, Bladström A, Jones R, 11018 Study Investigators. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2010;9(10):969–977. doi: 10.1016/S1474-4422(10)70194-0.
- [47] LeWitt PA, Boroojerdi B, Surmann E, Poewe W, SP716 Study Group, SP715 Study Group. Rotigotine transdermal system for long-term treatment of patients with advanced Parkinson's disease: results of two open-label extension studies, CLEOPA-TRA-PD and PREFER. *J Neural Transm* 2013;120(7):1069–1081. doi: 10.1007/s00702-012-0925-5 (Epub 2012 Dec 4).
- [48] LeWitt PA, Lyons KE, Pahwa R, SP 650 Study Group. Advanced Parkinson disease treated with rotigotine transdermal system: PREFER study. *Neurology* 2007;68:1262–1267.
- [49] Poewe WH, Rascol O, Quinn N, Tolosa E, Oertel WH, Martignoni E, Rupp M, Boroojerdi B, SP 515 Investigators. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. *Lancet Neurol* 2007;6:513–520.
- [50] Scheller D, Ullmer C, Berkels R, Gwarek M, Lübbert H. The in vitro receptor profile of rotigotine: a new agent for the treatment of Parkinson's disease. *Naunyn Schmiedeberts Arch Pharmacol* 2009;379(1):73–86.
- [51] Scheller D, Stichel-Gunkel C, Lübbert H, Porras G, Ravenscroft P, Hill M, Bezard E. Neuroprotective effects of rotigotine in the acute MPTP-lesioned mouse model of Parkinson's disease. *Neurosci Lett* 2008;432(1):30–34 (Epub 2007 Dec 8).
- [52] Georgiev D, Danieli A, Ocepek L, Novak D, Zupancic-Kriznar N, Trost M, Pirtosek Z. Othello syndrome in patients with Parkinson's disease. *Psychiatr Danub* 2010;22(1):94–98.
- [53] Sanford M, Scott LJ. Rotigotine transdermal patch: a review of its use in the treatment of Parkinson's disease. *CNS Drugs* 2011;25(8):699–719.
- [54] Ray Chaudhuri K, Martinez-Martin P, Antonini A, Brown RG, Friedman JH, Onofrj M, Surmann E, Ghys L, Trenkwalder C. Rotigotine and specific non-motor symptoms of Parkinson's disease: post hoc analysis of RECOVER. *Parkinsonism Relat Disord* 2013;19(7):660–665. doi: 10.1016/j.parkreldis.2013.02.018 (Epub 2013 Apr 1).

- [55] Zhou CQ, Li SS, Chen ZM, Li FQ, Lei P, Peng GG. Rotigotine transdermal patch in Parkinson's disease: a systematic review and meta-analysis. PLoS One 2013;8(7):e69738. doi: 10.1371/journal.pone.0069738; 1–9.

IntechOpen

IntechOpen