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# Progress in the treatment of Parkinson-Plus syndromes

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ABSTRACT

Progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB) are the four major proteinopathic neurodegenerative disorders. Currently, there are no disease modifying therapies for these disorders. However, better understanding of the etiopathogenic mechanisms of these disorders has allowed the development of novel therapeutic approaches. These mainly include strategies directed to the pathologic conformational shift, seeding and aggregation, as well as transcellular spread of the proteins that aggregate in the brain which are α-synuclein and tau. Modulation of inflammatory responses and neuroprotection are also targets of interest. A number of clinical trials have been performed and others are ongoing or are planned to address the authentic need for disease modifying treatments. However, challenges exist in terms of accurate early clinical diagnostic criteria and robust outcome measures, and preclinical animal models that would best recapitulate human disease.

## 1. Introduction

The term atypical parkinsonian disorders (APDs) or Parkinson plus syndromes is used mainly to denote the four major neurodegenerative clinicopathological entities including progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB). These disorders can present with a parkinsonian syndrome that is atypical in terms of rapid progression rate, symmetric distribution, poor response to levodopa or other dopaminergic medications, and presentation of atypical clinical features in addition to parkinsonism, such as supranuclear gaze palsy, early postural instability, early dementia, asymmetrical apraxia, and autonomic dysfunction [1,2]. APDs can present with various clinical phenotypes, as a consequence of different brain distribution patterns of the distinct underlying pathologies. Based on the underlying proteinopathic process, APDs are classified as tauopathies, (PSP and CBD), or α-synucleinopathies (MSA and DLB) [3].

Currently, there are no disease modifying therapies for these disorders and treatment is largely symptomatic [4]. Better understanding of the etiopathogenic mechanisms has led to the development of novel disease-modifying therapeutic approaches. This article reviews current disease modifying trials and summarize the future targets being evaluated in preclinical studies and current symptomatic trials.

## 2. Parkinsonian synucleinopathies (MSA and DLB)

MSA main phenotypes are a cerebellar-dominant (MSA-C) and a parkinsonism-dominant (MSA-P) syndrome. Both have autonomic features characterized by neurogenic bladder, erectile dysfunction, orthostatic hypotension (OH), pseudobulbar symptoms, pyramidal signs, rapid eye movement sleep behavior disorder (RBD) and frontal disturbances [5,6]. On the other hand, DLB main features are dementia, visual hallucinations unrelated to medication, fluctuating cognition and alertness, parkinsonism, and RBD [7]. While in MSA the widespread accumulation of α-synuclein is in the glia forming glial cytoplasmic inclusions (GCIs), in DLB α-synuclein is aggregated in cortical neurons forming Lewy bodies (LBs) [8]. Since α-synuclein is not physiologically expressed in oligodendroglia, its uptake from neurons and/or possibly its abnormal expression in oligodendroglia have been proposed as explanations for formation of GCIs [9,10]. In its membrane-unbound state in cytoplasm, α-synuclein is found as unstructured monomers or possibly as soluble tetramers [11,12]. However, a pathological conformational change to β-sheet structure promotes aggregation [12]. Two alpha helices at the N-terminal lipid-binding domain and a regulatory, unstructured C-terminal tail consist α-synuclein structure [12]. The lipid-binding region also contains the NAC (non-amyloid component) domain which is believed to be responsible for α-synuclein aggregation [13,14].

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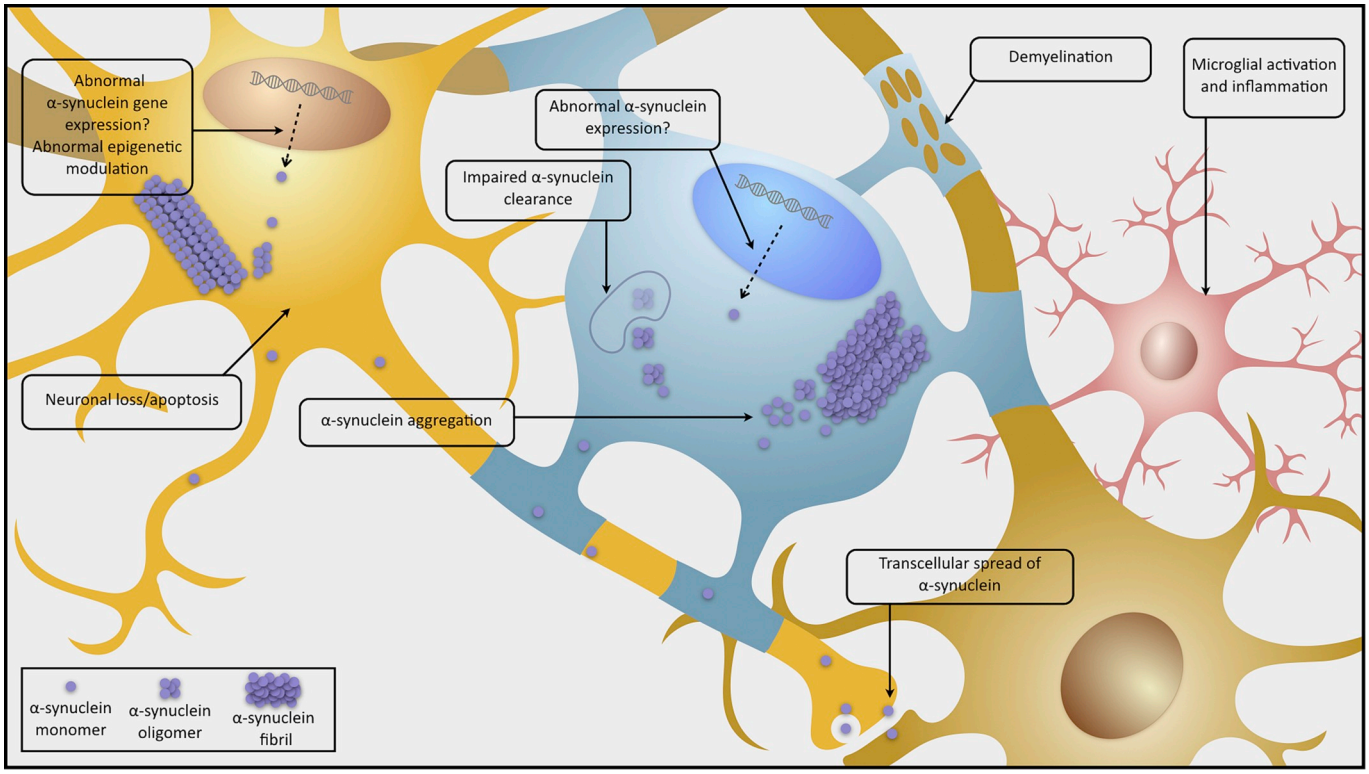


**Fig. 1.** Etiopathogenic mechanisms of multiple system atrophy.

### 2.1. *Disease modifying treatments for MSA*

The various mechanisms α-synuclein targeted for disease modifying therapy include: α-synuclein inhibition of aggregation, degradation enhancement, anti-α-synuclein immunotherapy, neuroinflammation, neural growth enhancement, and reduction of α-synuclein expression (Fig. 1).

#### 2.1.1. *α-synuclein aggregation inhibitors*

Correlation of GCI and LB pathology burden with disease severity and neuronal loss in MSA and DLB brains [15–17] has been observed. The role of *rifampicin* on α-synuclein aggregation was investigated because treated patients had reduced β-amyloid aggregation [18,19]. Preclinical and MSA mouse model studies confirmed its effectiveness in disaggregation of α-synuclein fibrils [20] and in neuroprotection [21]. However, a large double-blind trial of rifampicin in MSA patients was terminated after an interim analysis showed that the futility criteria was met [22].

*Epigallocatechin-gallate (EGCG),* a polyphenol found in green tea, reduced aggregation and toxicity of α-synuclein oligomers and remodeled formed amyloid fibrils in vitro [23,24]. A phase III randomized double blind trial assessed its effects on 92 MSA patients (clinicaltrials.gov, NCT02008721) [25] with preliminary results indicative of general safety (except for liver enzyme elevation) [26].

#### 2.1.2. *α-synuclein degradation enhancers*

Pathologic studies of MSA brains show involvement of macroautophagy in the pathogenesis of MSA [27] and dysfunctional intracellular clearance of α-synuclein in synucleinopathies including MSA [27–31].

*Lithium* was first tested as a potential autophagy inducer [28,32] in multiple neurodegenerative disorders including MSA and all were terminated because of poor tolerability [33,34] (clinicaltrials.gov, NCT00703677) [35]. Recently, *sirolimus (rapamycin),* a non-selective autophagy enhancer, entered a phase II double blind futility trial in MSA patients (clinicaltrials.gov, NCT03589976).

#### 2.1.3. *α-synuclein immunotherapy*

Studies on various synucleinopathy animal models (including MSA and PD models) have shown that anti-α-synuclein immunotherapy can act through different mechanisms including prevention of cell-to-cell spread [36], enhancing autophagy-mediated clearance [37], increasing microglial-mediated clearance [38], or reducing pathological truncation of α-synuclein at the C-terminus tail [39]. Finding the relevant target epitope could be a major challenge in developing MSA-specific immunotherapeutic agents considering that MSA-specific disease-causing α-synuclein strains and seeds are not yet fully characterized [40,41].

Two α-synuclein vaccines (PD03A, PD01A) [38,39] were recently evaluated in MSA. After successful preclinical studies in MSA, DLB and PD mouse models [38,42] a phase I study included 30 early MSA and 36 early PD patients. Results suggested good safety and tolerability of both products [43,44]. Interestingly, significant immunogenicity was found with PD01A but not with PD03A injections in MSA patients while in PD both showed immunogenicity [43,44].

#### 2.1.4. *Reducing neuroinflammation and microglial activation*

Pathological evaluation of MSA brains and PET studies of MSA patients showed distribution of α-synuclein pathology, GCI burden, and neurodegeneration with pattern of microglial activation [45,46]. This might be partly mediated by pathological dominance of the M1 (proinflammatory) microglia phenotype [47] that subsequently leads to reduced clearance of pathologic α-synuclein species by these cells. Reduction of microglial activation, eg. via myeloperoxidase (MPO) inhibition [48], decreased α-synuclein pathology and improved motor deficits in MSA mouse models [49] and led to evaluation of two MPO inhibitors (Minocycline and BHV3241) in MSA. However, a double blind, *Minocycline* controlled trial in 63 MSA patients [50] did not find significant changes on the Unified MSA Rating Scale (UMSARS) and Unified PD Rating Scale (UPDRS) scores. Preliminary results of a phase

IIa double blind trial of the oral MPO inhibitor, BHV3241(AZD3241) in 58 MSA patients (clinicaltrials.gov, NCT02388295) posted on the Biohaven company website show a favorable safety profile and satisfactory efficacy to allow advancing the agent into a phase III study [51].

*Intravenous Immunoglobulins (IVIg)* in an open-label trial of 9 MSA patients claimed some success measuring UMSARS [52]. However results are inconclusive considering the lack of a control group. Moreover, the investigators did not report if the subjects had anti-ganglionic autoantibodies which could have in part explain the results.

#### 2.1.5. Neuroprotective agents, neural growth enhancers, antioxidants

Trophic effects of *growth hormone* on neurons and glia and induction of myelination have been shown in animal studies [53–55]. In a double blind, placebo controlled study, its general safety and tolerability was acceptable, however, compared to 21 placebo-treated patients, no significant clinical effect was observed in active arm (n = 22). This study had a high dropout rate (37%) [56].

*Riluzole* was neuroprotective in multiple neurologic disorders [57,58] and mouse models of MSA [59,60]. In the large randomized double blind phase III trial 398 MSA and 362 PSP patients received a mean 180 mg daily riluzole or placebo. However results were negative after 3 years of follow-up [61]. Similarly, *rasagiline,* also with preclinical evidence of anti-apoptotic [62,63] and neuroprotective effects [64], failed in a large phase II double blind, placebo controlled trial on 174 MSA patients [65]. However, it should be noted that the dose used in this study was 10–15 time lower than the doses showed neuroprotection in animal models [65].

Studies in MSA mouse models claimed that fluoxetine has neuroprotective [66], and anti-inflammatory properties [67]. However, results of its double blind, placebo-controlled phase II study on 87 MSA patients did not justify advancement into phase III (clinicaltrials.gov, NCT01146548) [68].

*Intra-arterial mesenchymal stem cell (MSC) treatment* was first evaluated in an open label controlled trial in 11 MSA patients despite lack of preclinical studies. Surprisingly, it showed improvement on the UMSARS scores [69]. Results were confirmed in a double blind placebo-controlled trial on 33 MSA-C patients [70]. Unfortunately, 6 patients in the MSC arm had small subclinical infarcts. Another open-label trial of intrathecal MSC in 24 MSA patients (clinicaltrials.gov, NCT02315027) found a significant reduction of disease progression (based on UMSARS scores) [71] accompanied with increased brain- and glial-derived growth factors in CSF [72]. Before this approach could be translated to the clinic, it will be necessary to conduct an appropriately powered, randomized placebo controlled study using objective biomarkers.

Uric acid is a potent anti-oxidant. Observational studies showed an association between lower levels of serum uric acid with occurrence or severity of MSA [73–77] and led to conduct an ongoing double blind, placebo-controlled phase II clinical trial of *inosine 5′-monophosphate (uric acid precursor)* in 80 MSA patients (clinicaltrials.gov, NCT03403309).

#### 2.1.6. Future disease-modification targets and candidates

As α-synuclein aggregation inhibitors, Anle138b, (a small molecule), CLR01, (a molecular tweezer), and VX-765 (a caspase-1 inhibitor) are currently in preclinical development and were successful in MSA mouse model studies [78–81]. Based on studies showing that C-terminally cleaved α-synuclein is aggregation-prone [82–84], caspase-1 was targeted as an enzyme that cleaves α-synuclein at the C-terminus tail [85]. More animal studies are needed to evaluate the feasibility of using these agents in future human trials of MSA.

Modulation of autophagy-regulating microRNAs (microRNA-101) and the Abelson tyrosine kinase inhibitor, nilotinib, are under evaluation as autophagy-enhancing options. Micro-RNA-101 is overexpressed in MSA brains and its inhibition has reduced oligodendroglial α-synuclein pathology in transgenic mouse models of MSA [86]. Nilotinib has mainly been assessed in preclinical [87] and open-label clinical studies of PD [88]. There is a case report of a patient with MSA treated with nilotinib [89], but randomized, placebo controlled trials are lacking.

A study [90] comparing the immunoreactivity of MSA cerebellar samples to glial-derived neurotrophic factor (GDNF) to those in controls showed similar patterns in both groups. The immunostaining of the MSA Purkinje dendrites was more pronounced possibly due to their functional impairment. Another study showed reduction of GDNF in MSA brains and GCI-bearing MSA mouse models [91] and suggested that infusion of GDNF reduces neurodegeneration in these transgenic mice. Hence, GDNF was proposed as a future neuroprotective candidate for MSA treatment.

The role of genetic factors is not yet well established in MSA pathogenesis [92], however, there are compelling evidence that epigenetic modifications of DNA, histones, and micro RNA dysregulation could probably have role [93–95]. Pan histone deacetylase inhibitor, sodium phenylbutyrate (NaPB), in aged overexpression mouse model of MSA improved motor function, neuronal survival, and α-synuclein pathology [96]. Further studies are still needed to elucidate the specific epigenetic changes associated with MSA and their therapeutic significance.

### 2.2. Disease modifying treatments for DLB

Considering the lack of robust clinical outcome measures in view of the fluctuating nature of the disease [7], currently there are as yet no disease-modifying candidates in clinical development for DLB. A number of preclinical studies in DLB or PD animal models (considering shared LB pathology [97]), mainly targeting α-synuclein as stated above in MSA, are providing possible future targets for treatment of DLB. Reduction of α-synuclein expression is a potential future therapeutic strategy for DLB targeting α-synuclein.

Immunotherapeutic strategies also might be considered as future possibilities, including PRX002, a humanized IgG1 antibody against a C-terminal α-synuclein epitope [98]; BIIB-054, which binds to α-synuclein aggregates on PD and DLB tissues; and BAN0805, a monoclonal antibody recognizing toxic oligomeric and protofibrils of α-synuclein in PD and DLB brains [99,100]. PRX002 and BIIB-054 are in clinical development phase II in PD patients (clinicaltrials.gov, NCT03100149 and NCT03318523) and BAN0805 showed successful results in preclinical animal studies [101,102]. Phase I studies of PRX002 [103] and BIIB-054 [104] were indicative of their general safety and tolerability, however a case of subclinical parietal infarct was reported in one healthy subject receiving the highest dose of BIIB-054 [105].

Although the pathologic hallmark of DLB is neuronal α-synuclein aggregations in cortical and brainstem areas, the contribution of other pathologies, especially β-amyloid and tau, is prominent in DLB [106,107]. In fact, studies have shown that in DLB, the total amyloid pathology burden and the H1 haplotype of tau gene were correlated with the severity of α-synuclein pathology [106–108]. However, the interaction of these co-occurrent proteinopathies and their effect on DLB pathogenesis as well as their significance as therapeutic targets for DLB are yet to be known and there is currently no therapeutic trials or preclinical studies targeting amyloid or tau pathologies in DLB.

## 3. Parkinsonian tauopathies (PSP and CBD)

Progressive supranuclear palsy (PSP) is the most common APD with prevalence of 5–6 per 100,000 [109,110], typically presenting with postural instability causing frequent unprovoked falls, vertical supranuclear gaze palsy, akineto-rigid parkinsonism not benefitting from dopaminergic agents, and frontal cognitive deficits [111]. In addition to this typical presentation currently classified as PSP-Richardson (PSP-R), PSP presents with a wide range of clinical syndromes including parkinsonism-dominant PSP (PSP−P), progressive gait freezing (PSP-PGF), corticobasal syndrome (PSP-CBS), behavioral variant of frontal lobe syndrome (PSP-bvFTD), nonfluent primary progressive aphasia (PSP-

SL), and other rare variants [112].

In PSP there is a relative over-expression and accumulation of tau isoforms containing four microtubule-binding repeat domains, namely 4R-tau [113,114]. Another typical but less frequent 4-Repeat tauopathy is corticobasal degeneration (CBD). The corticobasal syndrome (CBS) is the typical CBD presentation that includes a progressive lateralized ideomotor limb apraxia, asymmetric parkinsonism, myoclonus and limb dystonia [115]. CBD also presents with a variety of other clinical syndromes including the typical PSP syndrome, a frontotemporal syndrome, and a nonfluent primary progressive aphasia [116].

Until recently the treatment of both PSP and CBD has largely been based on symptomatic management and rehabilitation that improves quality of life but has no benefit on disease duration [117]. Since APDs generally progress rapidly leading to death in less than 10 years [116,118], disease-modifying treatments are in urgent need. Although some important etiopathologic features such as distribution of tau aggregates, pathological hallmarks, ultrastructural features of tau fibrils, and post-translational modifications are reported to be different in PSP compared to CBD [119–121], disease-modifying treatment targets are not yet disease-specific. Both disorders share targets that could slow disease progression and include tau gene expression, tau protein post-translational modifications (PTMs), aggregation, transcellular spread and degradation. Neuroprotection and microtubule stabilization, addressing mitochondrial dysfunction and neuroinflammation are also under exploration [122]. Etiopathogenic bases of the emerging disease-modifying treatment targets are shown in Fig. 2.

### 3.1. Reduction of abnormal PTMs

Tau undergoes numerous regulatory PTMs mainly phosphorylation, acetylation, O-GlcNAcylation, and truncation [123]. Tau hyperphosphorylation, acetylation, and loss of O-GlcNAc moieties have been implicated in the pathogenesis of PSP and CBD [124–128]. Glycogen synthase kinase 3β (GSK3β) is tau's main kinase and its association with pathologic tau hyperphosphorylation has been shown in various tauopathies [129]. *Tideglusib* is an irreversible GSK3β inhibitor that was tested clinically in 146 PSP patients in a phase II double-blind, placebo controlled clinical trial, however, no significant benefit was observed on clinical measures [130]. Other GSK3β inhibitors, *lithium* and *sodium valproate* also failed in smaller clinical trials [131] (clinicaltrials.gov, NCT00703677).

Acetylation mainly occurs on lysine residues and prevents proteasomal tau degradation [132]. *Salsalate* is a salicylic acid dimer that can reduce tau acetylation and also has anti-inflammatory effects [133]. An open-label phase I futility trial is currently ongoing in 10 PSP patients (clinicaltrials.gov, NCT02422485).

There is evidence showing that removal of O-GlcNAc moieties (catalyzed by the enzyme O-linked N-acetylglucosaminidase (OGA)) from tau protein can lead to tau hyperphosphorylation [134]. Two OGA inhibitors, ASN120290 and MK-8719 are currently in phase I clinical development for PSP [135,136].

### 3.2. Blocking transcellular tau spread

Prion-like spread of tau has been suggested and supported by multiple lines of evidence [137–140]. Extracellular tau could be targeted by anti-tau antibodies or vaccines during cell-to-cell transfer [141,142]. *ABBV-8E12 and BIIB092 (Gosuranemab)* recently completed their phase I trials and started double blind, placebo-controlled phase II trials with an enrollment of 330 and 396 PSP patients respectively (clinicaltrials.gov, NCT02985879 and NCT03068468). New 4R-specific anti-tau antibodies are also under development [143].

### 3.3. Stabilizing microtubules and neuroprotection

Tau normally localizes in axons, where it binds to and regulates assembly of microtubules and also contributes to fast axonal transport [144]. Tau aggregation leads to its detachment from MTs and its loss of function is probably partly accountable for the neurodegeneration in tauopathies [123,145]. *Davunetide* is an oligopeptide that was the first

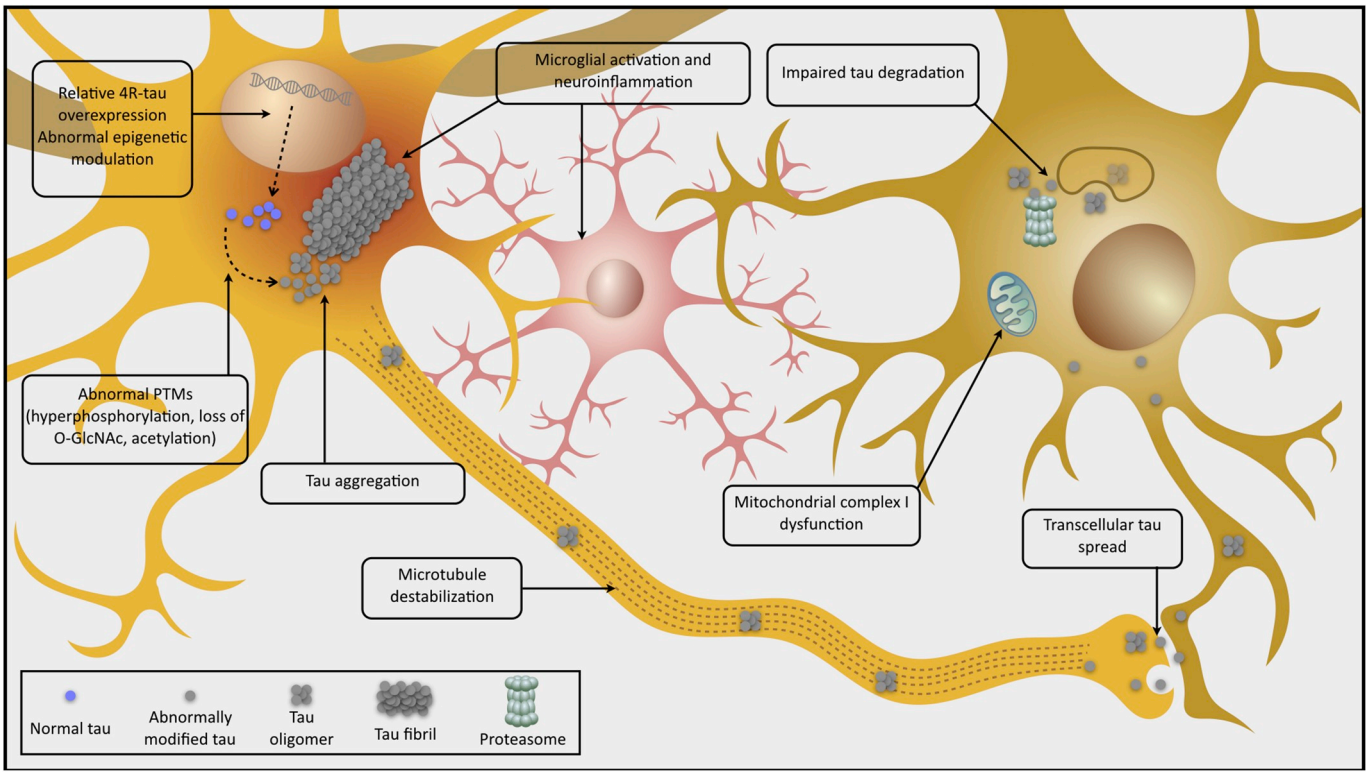


**Fig. 2.** Etiopathogenic mechanisms of tauopathic atypical parkinsonian disorders.

clinically tested MT stabilizer in PSP. Preclinical studies on Davunetide were indicative of a wide range of neuroprotective effects against various toxic insults as well as MT stabilization properties [146]. Reduction of hyperphosphorylated tau and improved motor and cognitive function was reported by Davunetide in tauopathy mouse models [147]. However, its double blind, placebo-controlled phase II/III trial on 313 PSP patients showed no clinical or radiologic improvement [148]. *Abeotaxane* (TPI-287) is a microtubule stabilizer that recently completed a 12-week phase Ib trial in 14 PSP and in 30 corticobasal syndrome (CBS) patients [149]. Although a significant decrease in a marker of inflammation (CSF YKL-40 level) was reported in this study, there was no clinical improvement in terms of cognitive function and daily living scales in exploratory analysis.

### 3.4. Enhancing tau degradation

Dysfunction of proteasomal and autophagy systems have also been shown in both PSP and CBD [150,151]. AZP2006 is a tau autophagy enhancing agent which is considered as a potential clinical therapeutic option for PSP [152].

### 3.5. Other therapeutic targets

The role of mitochondrial, especially complex I, dysfunction has been shown in 4R tauopathies in multiple in vitro and in vivo studies [153–155]. Two mitochondrial enhancing nutrient combinations (α-lipolic acid with L-acetyl carnitine, clinicaltrials.gov, NCT01537549 and pyruvate with creatine and niacinamide, NCT00605930) and also coenzyme Q10 (CoQ10) [156,157] were administered to PSP patients in separate phase I clinical trials. Results were inconclusive for CoQ10. The nutrient trial was discontinued due to manufacturer' bankruptcy.

A trial of young plasma transfusion was recently completed on 6 PSP patients, but results have not yet been reported (clinicaltrials.gov, NCT02460731).

### 3.6. Other future disease-modification targets and candidates

RNA interference silencing and new direct inhibitors of other tau kinases such as CDK5 and Rho-associated protein kinase are other potential targets [158–162].

It has been hypothesized that small molecules with capability of binding to tau monomers can prevent their assembly and formation of toxic oligomers and fibrils. Thereby these anti-aggregation agents can prevent the depressing effect of molecular crowding caused by tau aggregates on neuronal energy metabolism [163]. Further elucidation of the PSP− and CBD-specific tau strain structures would hopefully lead to development of strain-specific 4R-tau aggregation inhibitors [164].

Reduction of tau expression or correction of tau isoform imbalance using antisense oligonucleotides [165,166] and small RNA interference silencing of tau mRNA [167] are proposed as future treatment modalities. As a microtubule (MT) binding protein, tau stabilizes MTs and engages in axonal transport and probably has role in development of the fetus [144]. However, despite these major roles, tau knockout mice did not show any severe abnormality [168,169] indicating that a reduction of tau expression could be attainable safely [170].

The role of neuroinflammation in the pathogenesis of PSP and CBD is still debatable. However, its role has been shown in recent in vitro, in vivo, and genome-wide studies [171–174]. These studies underline inclusion of anti-inflammatory targets as a stand-alone or adjuvant therapeutic option.

## 4. Symptomatic management of atypical parkinsonian disorders

Pharmacologic symptomatic therapy and rehabilitation are the mainstays of treatment [4]. There are scarce large double blind randomized clinical trials focusing on symptomatic therapy in patients suffering from atypical parkinsonisms and most available therapeutic recommendations are based on expert opinions, small clinical trials, or open label use of medications which have been approved for other disorders with similar symptoms [4,117]. In this section, we will briefly review the main therapeutic options for parkinsonism as the prominent symptom of most APDs. Recent advances in symptomatic management of the other common APDs symptoms are summarized in the table but not discussed below.

Parkinsonism, the core feature of the APDs, is defined as a combination of bradykinesia with resting tremor, rigidity and/or postural instability [175]. Although the response to levodopa is usually minimal and less persistent in the tauopathies compared to idiopathic PD, a trial of levodopa with the maximum tolerated dose (usually 750–1000 mg/day) for at least one month is recommended for patients with prominent parkinsonism [4,7,117,176]. Patients with parkinsonism phenotype of PSP (PSP−P variant) show more dramatic response to levodopa at beginning of disease before more typical features of Richardson syndrome become evident [177]. Although mild response to levodopa has been reported in 0–24% of CBD patients in various studies [178–180], it can worsen dystonia and lead to choreiform movement disorders [178]. On the other hand, if tolerated in view of orthostatic hypotension, approximately one third of MSA-P patients may benefit from levodopa started at low doses [181,182]. Similarly, if tolerated in view of dementia and psychotic features, DLB patients usually benefit from levodopa. Levodopa may worsen psychiatric symptoms and orthostatic hypotension and the dose should be increased gradually to minimal required dose [183]. Facial dyskinesia (sometimes painful) maybe a side effect of levodopa in MSA patients (especially in MSA-P phenotype) [184,185]. Of note, side effects of levodopa such as orthostatic hypotension, dystonia, psychiatric symptoms, and impulse control disorders are more common in patients with APDs compared to PD patients and patients should be monitored closely for these side effects during treatment with levodopa [4,186].

Dopamine agonists and MAO inhibitors are less effective than levodopa and they have a greater risk for side effects [117,185,187–189]. Some researchers recommend not to use these groups of medications in treatment of APDs [190], but in our experience they can be beneficial if well managed. Amantadine may ameliorate rigidity and imbalance in some patients [117,185,187,189] but more clinical trials are needed to verify its positive effects [117]. It can also worsen orthostatic hypotension [186] and cognitive disturbances. Deep brain stimulation and other neurosurgical procedures are not effective in treatment of patients with atypical parkinsonisms [189,191]. Table 1 shows recent studies and ongoing trials in symptomatic treatment of APDs.

## 5. Conclusion

Despite that current management of patients with APDs remains symptomatic, there are exciting novel approaches that are being tried. We have moved away from the times in which there was no hope for slowing of these devastating disorders. Advances in disentangling the etiopathogenesis of these diseases briefly reviewed has allowed the conduction of several large therapeutic trials. These therapeutic trials so far have failed similarly to what has occurred in other more common neurodegenerative diseases such as PD. However, they have taught us many lessons. We learned that large therapeutic trials are feasible in these rare APDs. Current disease-modifying studies use appropriate methodological designs including sample size, randomization, placebo-control and use of robust biomarkers such as structural MRI. The tauopathies and MSA mainly have one main aggregated protein to be targeted, therefore are disorders in which therapeutic neuroprotective trials could be more effective, could use less resources because they progress much faster than more common neurodegenerative disorders such as Alzheimer's disease and PD. Moreover, the development of tau PET ligands that could measure target engagement is promising. However, much more work needs to be done. While new diagnostic

**Table 1**
Recent evidence and ongoing trials on symptomatic management of atypical parkinsonian disorders.

| Intervention | Patients | Target symptom | Study design | Results/Outcome measures | Reference |
|---|---|---|---|---|---|
| **Multiple System Atrophy** | | | | | |
| Droxidopa 100–600 mg for 3 months vs placebo | Estimated 108 MSA | nOH | Phase II/III, double blind, randomized withdrawal | Change in score of Orthostatic Hypotension Symptom Assessment (OHSA) | NCT02071459 Recruiting |
| Droxidopa 100–600 mg for 3 months vs placebo | Estimated 482 nOH including MSA | nOH | **Phase IV, double blind, randomized** | Time to intervention based on change in score of Orthostatic Hypotension Symptom Assessment (OHSA) | NCT02586623 Recruiting |
| TD-9855 (norepinephrine and serotonin reuptake inhibitor) daily for 5 months | 34 nOH including MSA | nOH | Phase II, single blind, randomized | Seated SBP 6–8 h after administration<br>Primary results (4 weeks) indicative of significant increase in SBP (Theravance Biopharma report) compared to placebo | NCT02705755 Active, not recruiting |
| Atomexetine 10 or 19 mg twice a day vs placebo | Estimated 40 nOH | nOH | **Phase II, double blind, randomized crossover, 1 week washout** | Change from baseline of Orthostatic Hypotension Questionnaire (OHQ) score | NCT02796209 |
| Pseudoephedrine + 480 or 50 ml water | Estimated 35 PAF and MSA | nOH | **Early phase I, open label, 4-way crossover** | Peak increase in SBP after pseudoephedrine or placebo from baseline measured between 60 and 120 min after pseudoephedrine or placebo | NCT02149901 |
| Droxidopa 100–600 mg for 3 months vs placebo | Estimated 32 PD/MSA/PSP | Fatigue | **Phase II, double blind, open label extension** | Changes in score of Visual Analogue Fatigue Scale measured at baseline and weeks 18, 28 and 29 | NCT03446807 |
| Intranasal Insulin, 40 IU daily for 4 weeks | 16 PD/MSA | Cognitive impairment | **Phase II, double blind, randomized** | Change from baseline of Brief Visuospatial Memory Test-Revised score | NCT02064166 |
| **Dementia with Lewy Bodies** | | | | | |
| Intepirdine (RVT-101) 35/75 mg daily | 38 DLB/AD/PDD<br>269 DLB<br>Estimated 240 DLB | Cognitive impairment, gait, motor function | **Phase II, double blind, randomized, placebo controlled** | Intepirdine was not effective in lead-in study and extension study terminated | NCT02910102<br>NCT02669433<br>NCT02928445 |
| Nelotanserin (APD-125) 40–80 mg daily for 4 weeks | 20 DLB/PDD | Visual hallucination | **Phase II, double blind, randomized, placebo controlled, crossover** | No significant effect on clinical scales (UPDRS II, III) | Wen et al. [192] |
| Nelotanserin (APD-125) 20 mg daily for 4 weeks | 29 DLB/PDD | RBD | **Phase II, double blind, randomized, placebo controlled** | Change in the frequency of REM sleep behaviors from baseline | NCT02708186 Active, not recruiting |
| Nelotanserin (APD-125) 20–80 mg daily for 24 weeks | Estimated 80 DLB | Visual hallucination or RBD | Phase II, open label, extension study | Safety and tolerability<br>Clinical assessment of frequency and severity of visual hallucinations and RBD | NCT02871427 Enrolling by invitation |
| Traneurocin (NA-831) 10–40 mg daily for 24 weeks | Estimated 146 MCI including DLB | Mild cognitive impairment | **Phase II, double blind, randomized, placebo controlled** | Change from baseline in Clinical Dementia Rating Scale- Sum of Boxes score | NCT03538522 Not yet recruiting |
| HTL0018318 (Muscarinic M1 receptor agonist) daily for 12 weeks | Estimated 172 DLB | Cognitive impairment, psychosis | **Phase II, double blind, randomized, placebo controlled** | Safety and tolerability, efficacy (secondary outcome) based on change in measures of cognition impairment and psychosis | NCT03592862 Not yet recruiting |
| E2027 50 mg daily (Phosphodiesterase 9 inhibitor) for 12 weeks | Estimated 182 DLB | Cognitive impairment | **Phase II, double blind, randomized, placebo controlled** | Mean change from baseline in the Montreal Cognitive Assessment (MoCA) and Clinician's Interview Based Impression of Change Plus Caregiver Input scores | NCT03467152 Recruiting |
| Donepezil 3–10 mg daily for 60 weeks | 160 DLB | Cognitive impairment | **Phase IV, double blind, randomized, placebo controlled** | Change in Clinician's Interview-Based Impression of Change, Plus Caregiver Input Version | NCT02345213 Active, not recruiting |
| Zonisamide 25 or 50 mg daily for 12 weeks | 158 DLB | Parkinsonism | **Phase II, double blind, add-on, randomized, placebo controlled** | Significant (2 points) improvement in UPDRS III | Murata et al. [193] |
| **4-Repeat Tauopathies, Progressive Supranuclear Palsy and Corticobasal Degeneration** | | | | | |
| Pimavanserin 20 or 34 mg daily for 26 weeks | 356 dementia including DLB/PSP/CBD | Dementia-related psychosis | **Phase III, double blind, randomized, placebo controlled** | Time from randomization to relapse in the double-blind period | NCT03325556 Recruiting |
| Rivastigmine twice daily for 24 weeks | Estimated 106 PSP-RS | Cognitive/behavioral/motor impairments | **Phase III, double blind, randomized, placebo controlled** | Change from baseline in the number of falls and near falls over the past 2 week | NCT02839642 Recruiting |

Abbreviations: nOH: neurogenic orthostatic hypotension; PAF: pure autonomic failure; MCI: mild cognitive impairment; PDD: Parkinson's disease dementia

criteria are allowing the inclusion of other tauopathy phenotypical presentations, the PSP and CBD criteria, studies that determine their reliability and accuracy need to be appropriately designed. We also need better biological outcome measures. For example, the need for PET ligands exclusively binding to tau and the development of α-synuclein PET ligands remain a priority. The lack of biological markers does not allow an early and accurate diagnosis of these disorders, which in turn may explain the frequent failure of clinical trials in finding significant therapeutic effects. The low prevalence of APDs limits the possibility of having multiple concomitant trials. In addition, there are no perfect APD models, and more importantly, it is unclear if the benefit observed in therapeutic trials in animal models could be translated to humans. Moreover, the lack of robust outcome measures limits the possibility of conducting disease modifying trials DLB because its fluctuating features. We wait with anticipation the results of studies that are addressing these issues. It is hoped that an NIH funded DLB consortium searching for robust biologic outcome measures in patients with DLB followed prospectively for two years and the layman associations funding research may help tackle this issue. We look forward to the success in finding novel tau PET ligands and the development of PET synuclein ligands as a consequence of a Michael J Fox Foundation million dollar award.

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## Declarations of interest

None.

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