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## Clinical Trials: past, current and future for atypical parkinsonian syndromes

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### Abstract

There are currently no effective, Food and Drug Administration (FDA) approved treatments for atypical parkinsonian disorders such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), dementia with lewy bodies (DLB) or multiple system atrophy (MSA). Previous treatment trials for these disorders were focused on symptomatic support and did not affect disease progression. Recent breakthroughs in neuropathology and pathophysiology have allowed a new understanding of these disorders and investigation into potentially disease modifying therapies. Randomized, placebo-controlled clinical trials of these disorders will be reviewed here. Suggestions for future therapeutic targets, clinical trial design, with a focus on PSP will also be provided.

### Keywords

Clinical trials; progressive supranuclear palsy; corticobasal degeneration; dementia lewy bodies; multiple system atrophy; treatment

### Introduction

Neurodegenerative diseases' prevalence and impact on cost, quality of life are increasingly recognized by not only healthcare providers but public health policy advocates as well. Amongst the various neurodegenerative diseases, a subset of disorders are typically labeled as atypical parkinsonian disorders (APD), defined by symptoms of progressive parkinsonism, atypical features and lack of response to levodopa therapy.<sup>1</sup> Disorders typically included under APD include syndromes associated with underlying tau neuropathology, the tauopathies, in particular progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and the neuropathologically defined synucleinopathies

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which are associated with underlying  $\alpha$ -synuclein pathology, dementia with Lewy bodies (DLB) and multiple system atrophy (MSA).

There are currently no effective, Food and Drug Administration (FDA) approved treatments that alter the natural history of disease or affect survival for APD, and contemporary therapeutic strategies mostly focus on symptom management. Historically, clinical trials in APD have focused on neurotransmitter modulation and symptomatic support. In addition, due to the complexities of APD diagnosis, longitudinal evaluation and relatively low prevalence, past clinical trials have been limited by small size, funding and lack of appropriate biomarkers. Recently, remarkable progress in understanding APD and related neurodegenerative disorders has contributed to breakthroughs in genetics, molecular biology and neuroimaging. Efforts to develop targeted therapeutic agents with disease modifying properties have begun. Cooperation between academic and industry partners, as well as novel clinical trial strategies utilizing appropriate outcomes, markers will likely accelerate this process.

This article reviews past and current treatment trials for the APDs, with a focus on randomized, controlled clinical trials. It also provides suggestions for conducting future clinical trials in these progressive, relentless neurodegenerative disorders, with a focus on the primary tauopathies, PSP and CBD, since a number of new tau-directed therapies will soon enter human clinical trials.

## Tauopathies

### Progressive Supranuclear Palsy

PSP, also known as Steele Richardson Olszewski syndrome, was originally described in 1964 in a seminal report of 9 cases.<sup>2</sup> Characterized by early falls and supranuclear ophthalmoplegia, PSP patients also develop dysarthria, dysphagia, rigidity and frontal/executive cognitive difficulties. This classical presentation is now labeled as Richardson's syndrome.<sup>3</sup> It is now recognized that there are at least four additional distinct clinical subtypes associated with PSP neuropathology: PSP-parkinsonism (PSP-P), PSP-pure akinesia with gait freezing (PSP-PAGF), PSP-corticobasal syndrome (PSP-CBS) and PSP with apraxia of speech (PSP-PNFA). Over time, many PSP patients with atypical presentations will progress to more closely resemble Richardson's syndrome. PSP-parkinsonism initially resembles idiopathic Parkinson's disease and presents with asymmetric limb symptoms, tremors and a moderate response to levodopa that is lost over time. PSP-PAGF is characterized initially by difficulty with gait initiation progressing to more typical symptoms of PSP including axial rigidity, bdykinesia, micrographia, hypophonia with lack of response to levodopa. PSP-CBS presents with cortical sensory loss, apraxia, dystonia while PSP-PNFA is characterized by language deficits.<sup>4</sup> These atypical subtype presentations are important to recognize as current PSP diagnostic criteria requires early falls and vertical gaze palsy, which may preclude additional PSP patients from participating in clinical trials.

Early clinical trials in PSP focused on modulation of neurotransmitter activity. Given the prominent parkinsonism found in PSP, dopaminergic therapy was understandably the first to

be tested in clinical trials. However, likely because PSP pathology involves additional basal ganglia, brainstem and cerebellar structures compared to the more isolated pathology of Parkinson's disease, involving dopaminergic output via substantia nigra pars reticulata, dopamine replacement therapy has been found to be of limited benefit in PSP.<sup>5</sup> Early clinical studies in PSP were also limited, open label case series that suggested patients were minimally responsive to levodopa, although since there were no placebo treated patients included, it is difficult to know whether there were any true benefits of levodopa therapy.<sup>6-8</sup>

Other early clinical trials in PSP employed available pharmacological therapy to correct possible alterations in the cholinergic and Gamma-Amino Butyric Acid (GABA)ergic pathways in PSP, and also produced limited evidence of benefit. PSP was thought to have cholinergic deficit based on observed loss of cholinergic neurons in post mortem studies.<sup>9,10</sup> Postmortem studies of PSP patients also suggested reduced GABAergic neurotransmission in the basal ganglia.<sup>11</sup> An early randomized, double blind cross over trial using the acetylcholinesterase inhibitor physostigmine in 8 PSP patients revealed inconsistent and marginal improvements in memory.<sup>12</sup> Subsequently, a more centrally active cholinesterase inhibitor, donepezil, was tried in a small case series of six PSP patients with no clear effects, while a randomized, placebo controlled, double blind cross over trial in 21 patients found treatment related improvements in memory but worsened motor function and activities of daily living (ADL).<sup>13,14</sup> This was further confirmed in another cholinesterase inhibitor open label case series using rivastigmine in 5 PSP patients, with observed positive effects on memory but decreased motor function as measured by the Unified Parkinson's Disease Rating Scale (UPDRS).<sup>15</sup> Based on these convergent studies, cholinesterase inhibitors are not recommended for treatment of PSP.

Correction of GABAergic deficits in PSP was briefly explored with a small double blind, placebo controlled trial using zolpidem in 10 patients which found transient improvements in eye movements and Unified Parkinson's Disease Rating Scale (UPDRS) scores over a period of hours.<sup>16</sup> Subsequently a small randomized, placebo controlled, investigator blinded trial using gabapentin over 5 weeks also showed improvements in error rates on a the voluntary saccade inhibition, antisaccade task, a surrogate for inhibitory frontal function.<sup>17</sup> Such early clinical trials were limited by small size and selection of therapeutic agents aimed at symptomatic support rather than targeting potential disease modifying substrates. Little evidence exists to support long term treatment of PSP patients with GABAergic agents.

### **Corticobasal degeneration**

CBD was first described as a asymmetric motor disorder with features of apraxia, rigidity, myoclonus, dystonia and other cortical features such as alien limb behavior and sensory loss.<sup>18</sup> However, it is now known that CBD has an extremely varied presentation. Pathologically proven CBD have been described to present with aphasia, behavioral variant frontotemporal dementia(bvFTD), executive-motor dysfunction and even posterior cortical atrophy.<sup>19</sup> In another series of pathologically confirmed CBD cases, only 5 of 19 cases have been correctly diagnosed.<sup>20</sup> Thus the rarity of CBD and the difficulty of its diagnosis

resulted in a dearth of treatment trials, and any treatment reports without pathological correlation will call into question whether CBD was truly targeted.

Neuropathological examination of PSP and CBD has revealed tau protein to be the main protein aggregation and likely plays a prominent role in pathogenesis. Despite the heterogeneous presentation of PSP as described above, the accuracy of clinical diagnosis remains quite good. A post mortem study of 143 cases of parkinsonism over a 10 year period found that the clinical diagnosis for PSP had a sensitivity of 84.2% and specificity of 96.8%.<sup>21</sup> In contrast, the pathological diagnostic accuracy for CBD is extremely poor. The variability of pathology has led to the proposal of Corticobasal syndrome (CBS) for the clinical syndrome and CBD for the pathological diagnosis involving tau protein.<sup>22</sup> A clinicopathological case series performed at UCSF in which 40 patients with initial presentations of CBS had histopathology examination, 35% were CBD, 23% were Alzheimer's disease(AD), 13% PSP and 13% had frontotemporal lobar degeneration with TDP inclusions.<sup>19</sup> Another series of 21 CBS presentations resulted in only 5 with CBD pathology.<sup>20</sup> Thus one can conclude that the majority of clinical PSP diagnosis will have a tau pathology, while CBD patients will be much more difficult to identify. As there is increasing interest in targeting tau as a strategy for disease modifying treatment, the ability to accurately identify tauopathies underlying a clinical syndrome will be crucial.

New clinical research criteria are available for CBD that will help to accurately identify cases during life.<sup>23</sup> Moreover, the ability to rule out cases of CBS due to AD using amyloid PET imaging and CSF biomarkers ( $A\beta$  and tau), and rule in tau pathology using new tau specific PET ligands is likely to have a major impact on the ability to identify populations of CBS patients with likely CBD pathology during life. Recently the tau specific PET ligand PBB3 was shown to have increased uptake in an amyloid negative CBS patient<sup>24</sup> suggesting this and other agents such as 18F T807 may help identify CBS patients suitable for targeted therapeutics.<sup>25</sup>

### Targets for PSP and CBD

**Tau**—Tau is a microtubule-associated protein localized to neuronal axons that generates a stable state in microtubules by increasing the polymerization rate and decreasing the depolymerization rate in tubulin.<sup>26</sup> Tau-related neuronal dysfunction in neurological disease may occur by two non-mutually exclusive mechanisms, either gain or loss of function. Gain of function occurs when tau aggregates, which may be toxic to neurons and glia.<sup>27,28</sup> Tau hyperphosphorylation is also seen in disease states. This may promote aggregation of insoluble tau species and decrease microtubule binding leading to loss of function.<sup>29</sup> Loss of tau function may lead to altered regulation of cytoskeletal rearrangements or unstable microtubules with impaired ability to transport cellular constituents.<sup>30</sup> Viable strategies for treatment focusing on tau may include: inhibition of aggregation, inhibition of phosphorylation, reduction of tau levels and microtubule stabilization. The strongest evidence for efficacy from pre-clinical models of tau-mediated neurodegeneration exists for agents that reduce tau protein levels. Mice with reduced tau levels are resistant to multiple neuronal insults including amyloid toxicity, kainate-induced seizures, and even diabetes related neuronal injury.<sup>31,32</sup> Interestingly, the presence of tau does not seem to be critical for

normal function in adult mice since a number of transgenic mouse lines that lack tau have been found to survive to adulthood with none to few measurable deficits.<sup>34</sup>

**Tau Gain of Function therapies**—Methylene blue derivatives, in particular leucomethylthioninium with a suitable counter-ion (LMTX), a reduced version of methylthioninium, is an inhibitor of tau aggregation and is now being investigated in two phase 3 clinical trials for AD and bvFTD.<sup>34</sup> Depending on the results, this agent may be a rational treatment choice for PSP or CBD, but would require further clinical trials to demonstrate efficacy in these disorders. Pathological tau species are frequently hyperphosphorylated. Protein kinase inhibition may prevent phosphorylation, and glycogen synthase kinase 3 (GSK-3) has been an early target of therapies meant to block tau phosphorylation. Lithium chloride and tideglusib are both thought to be GSK-3 inhibitors and have been used in clinical trials for PSP (and CBD for lithium). Neither agent was successful as lithium was tolerated by only 1 of 14 patients.<sup>35</sup> Tideglusib did not demonstrate efficacy on the clinical endpoints in a Phase 2 clinical trial in PSP, however there were treatment-related differences in progressive brain atrophy in a small subgroup of patients who underwent longitudinal volumetric MRI scans as part of the study.<sup>36,37</sup> This suggests that modulating tau phosphorylation via kinase inhibition may remain a potentially viable approach to treatment of tau-related neurodegeneration. Modulating phosphatase activity to remove phosphate groups or more specific kinase inhibitors remain a possible intervention to ameliorate tau pathology and remain an active area of study. In addition, modulating other post-translational modifications of tau such as acetylation and glycation may be other promising therapeutic strategies.<sup>38</sup> Decreasing total tau protein levels via antisense oligonucleotide mediated reduction of mRNA levels is actively being investigated in a number of academic laboratories and pharmaceutical companies.<sup>39</sup>

The most advanced strategies for reducing endogenous tau levels involve immunologic approaches targeting a variety of different tau epitopes. Recent studies demonstrating that pathogenic tau species are transmitted transynaptically provide support for reducing tau levels in the extracellular space. Immunotherapeutic approaches to tau reduction can be characterized as active or passive immunization. Active immunization involves introduction of foreign antigen into the subject, inducing a B-cell response and antibody generation. Previous AD clinical trials using active immunization raised safety concerns as one with AN1792 was associated with meningoencephalitis.<sup>40</sup> The use of smaller tau peptides may decrease the risk of inflammation while retaining the ability to generate antibodies that clear tau pathology in the cortex.<sup>41</sup> Human tau transgenic mouse models immunized with tau antigens have been shown to perform better on sensorimotor tests suggesting decreased cognitive impairment.<sup>42,43</sup> At least one anti-phosphorylated tau vaccine is currently in clinically development.<sup>44</sup>

Passive immunization has the advantage of a lower risk of autoimmune side effects, and several approaches have been described in tau transgenic mice. Antibodies directed against various tau epitopes have been administered to mouse models prior to the onset of pathology, demonstrating reduction in tau tangles, pathological tau and improved motor tasks.<sup>45,46</sup> Recently, an anti-tau monoclonal antibody that targets a pathological form of tau that is able to seed other pathologic conformations that spread transcellularly, was shown to

block seeding activity and improve cognitive deficits in tau transgenic mice after pathology onset.<sup>47</sup> This antibody is not thought to enter neurons and its mechanism may involve blocking of transsynaptic spread and promotion of microglia tau uptake.

Taken together, proof of concept has been demonstrated in animal models using both active and passive tau immunization, with measurable improvements in clearance of pathogenic forms of tau as well as memory, motor tasks. It remains to be seen whether certain tau conformations are better targets for immune clearance and whether different tau conformations are associated with different tauopathies. There is no reported experience with tau therapeutics in humans yet and human proof of concept will require pharmacodynamic biomarkers that can demonstrate that the candidate therapy is engaging its target (i.e., reducing pathogenic tau in the CNS). For therapies aimed at dramatically reducing tau levels, cerebrospinal measurements of tau protein concentrations may be good biomarkers of target engagement. However, for other therapies that target post-translational modification of tau or reduction of specific tau species, demonstration of target engagement may be more challenging.

**Tau Loss of Function therapies**—The failure of tau to bind to microtubules is thought to lead to impaired intracellular transport via microtubule destabilization.<sup>48</sup> Stabilization of microtubules has been proposed as a strategy to compensate for loss of tau function and has generated interest in Alzheimer's disease research as well. Taxanes, a class of cancer drugs derived from taxol, a drug that stabilizes microtubules, and a related class of compounds called epothilones, with better blood brain barrier penetration were initially developed for treating cancer, but are now being investigated as therapies for tau related neurodegeneration. The leading compound in this class, Epothilone D, was found in transgenic mouse models to improve axonal microtubule density and decreased axonal dystrophy. In addition, spatial learning deficits improved in treated mouse, at a fraction of the dose utilized in human cancer trials.<sup>49,50</sup> A clinical trial of Epothilone D for Alzheimer's Disease was recently abandoned and further development plans for this compound are unknown. Recently, Davunetide, a peptide derived from the growth factor activity dependent neurotrophic protein (ADNP) which may also promote microtubule stability, failed to show efficacy in a pivotal clinical trial in PSP patients (unpublished data). Microtubule stabilizing agents continue to be explored as potential therapies despite these setbacks. TPI-287, a taxane based microtubule stabilizing agent has entered phase I clinical trial for Alzheimer's disease and may be a suitable candidate for PSP, CBD patients treatment as well.<sup>51</sup>

### **Mitochondrial dysfunction**

A variety of evidence suggests that mitochondrial dysfunction may contribute to pathogenesis of PSP.<sup>52</sup> The main function of the mitochondrial respiratory chain, five protein complexes (I-V) located in the inner membrane, is to maintain adequate cellular concentrations of adenosine triphosphate (ATP). There is now increasing evidence that failure of mitochondrial energy production may contribute to neuronal cell death. *In vivo* imaging studies using proton and phosphorous magnetic resonance spectroscopy (MRS) have shown decreased levels of high energy phosphates without alterations in N-acetylaspartate, a marker of neuronal integrity in PSP patients.<sup>53</sup> This suggests



mitochondrial dysfunction may be a contributor to PSP neuronal dysfunction independent of neuronal death. Cytoplasmic hybrid cells (cybrids) were created from combining human neuroblastoma or osteosarcoma cell line lacking mitochondrial DNA with mitochondria from PSP patients' platelets. These cybrids showed reduced complex I activity, ATP-production and indications of oxidative damage.<sup>54-56</sup> Finally a PSP-like disease in Guadeloupe has been linked to consumption of fruits rich in complex I inhibitors such as Chamoya.<sup>57</sup>

The evidence above has led to an interest in restoring the function of complex I. Coenzyme Q10 is a physiological electron recipient of complex I and serves as an electron shuttle between complexes I and II to III. In vivo oral administration of CoQ10 has been shown to restore striatal complex I activity, ATP levels and reduce neuronal apoptosis in rats treated with a complex I inhibitor.<sup>58</sup> A small, double-blind, placebo-controlled, randomized trial involving 21 PSP patients were given coenzyme Q10 over 6 weeks, with resulting improved Progressive Supranuclear Palsy Rating Scale (PSPRS), frontal assessment battery and occipital energy levels as measured by MRS compared to placebo.<sup>59</sup> With these encouraging results, a larger phase III trial of coenzyme Q10 in PSP patients for 12 months is currently underway.<sup>60</sup> Another strategy utilizing the free radical scavenger pyruvate, cellular energy buffer creatine and cofactor booster niacinamide, was attempted but has not progressed beyond phase I.<sup>61</sup>

## **$\alpha$ -Synucleinopathies**

### **Dementia with Lewy Bodies**

DLB is characterized by the combination of dementia, parkinsonism, and frequently accompanied by other symptoms such as visual hallucination, fluctuating cognition, autonomic dysfunction and random eye movement (REM) sleep behavioral disturbance.<sup>62</sup> Pathologically, DLB is characterized by its namesake, an intraneuronal inclusion containing alpha synuclein in the brain stem, neocortex, limbic and forebrain regions. In addition to destruction of the substantia nigra causing characteristic parkinsonism, cholinergic nucleus basalis deficits are seen as well, leading to an interest in cholinesterase inhibitor therapy.<sup>63-65</sup> Most DLB trials to date have focused on symptomatic treatments that modulate neurotransmitters or their receptors, and includes patients with a diagnosis of Parkinsons disease dementia (PDD), suggested to be onset of cognitive symptoms one year after motor symptoms.<sup>66</sup> It has recently been demonstrated that alpha synuclein can oligomerize and spread trans-cellularly similar to tau.<sup>67</sup> Monoclonal antibodies to alpha-synuclein have been demonstrated to be beneficial in animal models of DLB and thus represent a promising new avenue for disease modifying therapies.<sup>68</sup> In addition, concurrent Alzheimer's pathology is common in DLB<sup>69</sup> and therefore disease-modifying therapies targeting beta amyloid or tau may also eventually find use in DLB. Below we discuss recent trials focused on symptomatic agents for DLB and PDD.

In a large, randomized, double blind controlled trial with 120 DLB patients over 20 weeks, rivastigmine was shown to reduce apathy, delusions, anxiety, hallucinations as well as improve scores on cognitive assessment.<sup>70</sup> This was followed by a 3 week post treatment follow up, where patients treated with rivastigmine performed significantly better on



cognitive testing and the Neuropsychiatric inventory (NPI), with the benefits lost after drug discontinuation.<sup>71</sup> A small double cross over study with donepezil was conducted in 8 patients was subsequently performed in 2004, demonstrating a significant improvement on cognitive screening tests.<sup>72</sup> The most recent trial utilizing a cholinesterase inhibitor was conducted in a 48 multi-center trial in Japan, with 140 patients receiving donepezil or placebo over 12 weeks. Mini-mental state examination (MMSE), behavioral measures, and Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus) were found to be superior on 5mg/day and 10mg/day doses when compared to placebo, while care giver experienced fewer burdens at 10mg/day dose via the Zarit Caregiver Burden Interview (ZBI), suggesting cholinesterase inhibitors are of benefit to patients with DLB.<sup>73</sup>

The effect of the NMDA-receptor antagonist memantine in DLB has recently been of interest due to its efficacy in AD.<sup>74,75</sup> The first clinical trial involved 32 DLB patients along with 40 Parkinson's disease dementia (PDD) patients provided preliminary suggestions that memantine may be beneficial, as patients in the memantine group had significantly better clinical global impression of change (CGIC) scores.<sup>76</sup> However it should be noted the effects were mainly driven by the PDD group. In a subsequent larger multi-center study with 75 DLB and 120 PDD patients, DLB patients on memantine showed improvement on the Alzheimer's disease cooperative study (ADCS)-clinical global impression of change scores as well as on NPI scores. This was not seen in PDD or total population scores.<sup>77</sup> These clinical trials were unfortunately confounded by the inclusion of both DLB and PDD, and therefore the effect of memantine in DLB remains inconclusive, although possibly beneficial.

There has also been interest in controlling psychiatric symptoms such as visual hallucinations in DLB with atypical anti-psychotics. A post-hoc analysis of a large Alzheimer's disease trial revealed 29 possible DLB patients with reductions in delusion, hallucination when treated with olanzapine.<sup>78</sup> However, a subsequent prospective trial in DLB patients using quetiapine with 23 DLB patients did not demonstrate any treatment benefit.<sup>79</sup> Of note, pimavanserin, a novel serotonin receptor inverse agonist recently tested in a six week, randomized, double-blind, placebo controlled study involving 199 PDD patients with psychosis resulted in a significant decrease in symptoms without worsening motor function and may be of interest in DLB patients as well.<sup>80</sup>

### **Multiple System Atrophy**

MSA clinical features include Parkinsonism, cerebellar ataxia, pyramidal signs associated with alpha synuclein pathology in glial cytoplasmic inclusions. In addition, MSA patients often present with early and severe autonomic involvement, presenting as urinary incontinence and orthostatic hypotension.<sup>81</sup>

Due to the dangers of postural instability from orthostatic hypotension, considerable attention has been directed towards blood pressure control in MSA. A synthetic norepinephrine precursor (3,4-DL-threo-dihydroxyphenylserine) was tested in 10 patients with autonomic failure (six with MSA) in a randomized, double blind, controlled trial, resulting in increased supine and upright blood pressure.<sup>82</sup> L-threo-dihydroxyphenylserine or droxidopa, was subsequently developed and evaluated in a phase III clinical trial to assess

efficacy in neurogenic orthostatic hypotension, including MSA patients.<sup>83</sup> The FDA previously failed to approve droxidopa and requested more phase III data. Several concerns such as changing the primary endpoint mid-trial, minimal follow up of 1 week and compromise of blinding may be offset by the therapy's orphan drug status and illustrate the complexities of clinical trials for rare neurodegenerative disease. As of this writing, the Cardiovascular and Renal Drugs Advisory Committee of the FDA has recommended approval of droxidopa, although final approval is pending.<sup>84</sup>

Other placebo-controlled treatment trials using potential disease modifying therapeutics such as riluzole, a trial which included PSP and MSA patients, or minocycline have not shown any effects.<sup>85,86</sup>

## Future Considerations

Rapid development of successful therapies will require close collaboration between academic laboratories, clinical research centers, the pharmaceutical industry and the FDA. The cooperation of the pharmaceutical industry is especially critical with its large therapeutic compound libraries, clinical trials expertise, funding and established infrastructure. The lack of effective therapies has translated into highly motivated patients and caregivers in clinical trial participation, which may reduce recruitment time. As few drugs are beneficial symptomatically, there is little exclusion criteria when it comes to concomitant medications.

PSP may be an especially attractive target as it has a consistent, measurable phenotype with very strong clinical-pathological links to pure tau pathology, which provides a synergistic motivation as many pharmaceutical companies are also involved in Alzheimer's treatment research. The rarity of APD also allows developers to apply for orphan drug status with the FDA, potentially allowing for accelerated approval. Finally, a first to market therapy will be strongly positioned and may lead to rapid development of indications for other neurodegenerative disorders.

## Clinical Trial Designs

Neurodegenerative disease researchers are facing an environment of many possible treatment candidates, but each with low a priori probability of efficacy. Since many APD syndromes are relatively rare disorders, difficulty of recruitment due to low disease prevalence is also a serious consideration. Futility trial designs have been proposed as a more efficient method to screen drugs for human efficacy, but are also potentially problematic. A futility design's null and alternative hypotheses are reversed to prove that a drug does not work. This method increases the sensitivity but lowers the specificity and uses a smaller sample size, reflecting the need to search for an effective candidate in a vast library.<sup>87</sup> Other adaptive study designs, defined by the FDA “ as a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study”, such as multiple drug selection, group sequential analysis, have been proposed to increase efficiency and conserve resources in other neurodegenerative disease trials, and may be useful in atypical parkinsonisms.<sup>88</sup>

Due to the marked variation in clinical progression, randomized, placebo-controlled clinical trials are necessary to demonstrate the efficacy of therapeutic agents in APD. There are two standard approaches: cross-over designs and parallel designs. The primary advantage of cross-over design is enhanced power, a significant attribute when testing rare disease. However, such designs have many limitations in neurodegenerative disease populations where disease progresses over time, necessitating relatively short treatment periods so as not to be confounded by disease progression. Cross-over designs also need to be powered to test for confounding effects and demonstrate insignificant carry over effects while assuring patients return to baseline prior to the start of each arm. Parallel designs avoid the confounding effect of disease progression, are relatively less complex compared to cross-over trials and are likely to remain the gold standard despite requiring more patients for power. ‘Lead In’ designs where patients are followed for a period before treatment begins allow patients to be their own control, thus reducing sample size, but many not be suitable for neurodegenerative disease and its variable course.

As there are limited numbers of biomarkers available that can convincingly demonstrate effects on underlying disease biology in APD, and none that are validated, innovative trial designs have been proposed to delineate between symptomatic and disease modifying therapy. The delayed withdrawal design is a two-arm, two-period design in which patients on active therapy are switched to placebo during the second period. Theoretically, if the therapy is purely symptomatic, the active therapy group should deteriorate to the level of the placebo group. Using similar logic, a delayed start design is a two-arm, 2-period design in which a placebo group is switched to active treatment during the second period. If the active treatment is purely symptomatic, then the initial placebo group may “catch up” to the initial active group. Details, variations and concerns of these designs have been reviewed elsewhere, and it should be mentioned that such designs have not been successful in other related indications such as idiopathic PD.<sup>89</sup>

## Conclusion

The atypical parkinsonian disorders are a spectrum of uniformly fatal neurodegenerative disease, which, despite sharing common symptoms of its namesake, have a heterogeneous pathophysiology that has yet to be elucidated completely. Current empirical treatments provide only minimal symptomatic relief. Recent advancements in the understanding of molecular basis of some of these disorders, especially those with tau proteinopathy, have reached sufficient maturity to provide scientific rationale for potential disease modifying treatments. The relative rarity of these diseases and their variable progressions will require innovations in clinical trials methodology to conserve resources, identify efficacious therapy and accelerate development.

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**Table 1**

## PSP clinical trials

drug	study design	n	dx	citation	results
physostigmine	randomized, placebo controlled, double blind, cross over	8	PSP	12	marginal and inconsistent changes in long term memory
donepezil	randomized, placebo controlled, double blind, cross over	21	PSP	14	improved memory, worsened ADL/mobility
Zolpidem	double-blind, placebo controlled, cross over	10	PSP	16	Transient improvement in eye movements, UPDRS
gabapentin	randomized, investigator blinded	14	PSP	17	decreased errors in antisaccades
Lithium	phase 1	14	PSP, CBD	35	terminated due to adverse events
tideglusib	double-blind, placebo-control, randomized	n/a	PSP	37	did not meet primary endpoint of change in PSPRS
davunetide	double-blind, placebo-control, randomized	313	PSP	‡	no effect
CoQ10	double-blind, placebo-control, randomized	21	PSP	59	improved PSPRS, occipital energy level
CoQ10	double-blind, placebo-control, randomized	n/a	PSP, APD	60	not yet available
pyruvate, niacin, Cr	double-blind, placebo-control, randomized	n/a	PSP	61	unknown

ADL = activities of daily living

UPDRS = Unified Parkinson Disease Rating Scale

PSPRS = Progressive Supranuclear Palsy Rating Scale

‡unpublished data

**Table 2**

## DLB Clinical Trials

drug	study design	n	dx	citation	results
rivastigmine	randomized, double blind, placebo controlled	120	DLB	70	improved NPI and cognitive scores
donepezil	double cross over with placebo	8	DLB	72	improved cognitive screening results
donepezil	randomized, double blind, placebo controlled	140	DLB	73	improved cognition and caregiver burden
memantine	randomize, double blinded, placebo controlled	32 DLB	PD, DLB	76	improved CGIC, driven by PD group
memantine	randomized, double blind, placebo controlled	75 DLB	PD, DLB	77	improved CGIC and NPI in DLB group
quetiapine	randomized, double blind, placebo controlled	40 DLB	DLB, PDD, AD	79	no change

NPI = neuropsychiatry index

CGIC = cognitive global impression of change