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Preclinical, phase I, and phase II investigational clinical trials for treatment of progressive supranuclear palsy.

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Journal

Expert opinion on investigational drugs, 27(4)

ISSN

1354-3784

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Publication Date

2018-04-01

DOI

10.1080/13543784.2018.1460356

Peer reviewed

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To cite this article: Ali Shoeibi, Nahid Olfati & Irene Litvan (2018) Preclinical, phase I, and phase II investigational clinical trials for treatment of progressive supranuclear palsy, Expert Opinion on Investigational Drugs, 27:4, 349-361, DOI: [10.1080/13543784.2018.1460356](https://doi.org/10.1080/13543784.2018.1460356)

To link to this article: <https://doi.org/10.1080/13543784.2018.1460356>

Accepted author version posted online: 30 Mar 2018.
Published online: 09 Apr 2018.

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REVIEW

Preclinical, phase I, and phase II investigational clinical trials for treatment of progressive supranuclear palsy

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ABSTRACT

Introduction: Our understanding of the pathological basis of progressive supranuclear palsy (PSP), as the most common atypical parkinsonian syndrome, has greatly increased in recent years and a number of disease-modifying therapies are under evaluation as a result of these advances.

Areas covered: In this review, we discuss disease-modifying therapeutic options which are currently under evaluation or have been evaluated in preclinical or clinical trials based on their targeted pathophysiologic process. The pathophysiologic mechanisms are broadly divided into three main categories: genetic mechanisms, abnormal post-translational modifications of tau protein, and transcellular tau spread.

Expert opinion: Once the best therapeutic approaches are identified, it is likely that some combination of interventions will need to be evaluated, but this will take time. It is critical to treat patients at early stages, and development of the Movement Disorder Society PSP diagnostic criteria is an important step in this direction. In addition, development of biological biomarkers such as tau PET and further refinement of tau ligands may help both diagnose early and measure disease progression. In the meantime, a comprehensive, personalized interdisciplinary approach to this disease is absolutely necessary.

ARTICLE HISTORY

Received 21 December 2017
Accepted 29 March 2018

KEYWORDS

Progressive supranuclear palsy; neurodegenerative disorder; tauopathy; clinical trial

1. Introduction

Recent advances have greatly changed our understanding of the clinical phenotypes, underlying genetic and pathophysiologic mechanisms of progressive supranuclear palsy (PSP). PSP is the most common primary tauopathy and atypical parkinsonian disorder.

Since its first description by Steele, Richardson, and Olszewski in 1964 [1], contemporary clinicopathological studies have revealed that the typical presentation of PSP is only one of the phenotypes of the disease. Diagnosing the classical phenotype of supranuclear vertical gaze palsy, early and prominent postural instability and symmetrical parkinsonism (Richardson syndrome, PSP-RS), has improved by the inclusion of slowing of vertical saccades, an earlier oculomotor disturbance and by a higher index of suspicion of the disease. The inclusion of postural instability during the first year of disease and slowing of vertical saccades or supranuclear vertical palsy has allowed increasing the specificity of the diagnostic criteria (National Institutes of Neurological Diseases-Society for PSP NINDS-SPSP) [2]. However, this diagnostic criteria is not very sensitive because it only identifies the PSP-RS but not the various clinical variants including: PSP-parkinsonism, PSP-corticobasal syndrome, PSP-behavioral variant of frontotemporal dementia, PSP-pure akinesia and gait freezing, PSP-primary lateral sclerosis, PSP-cerebellar, and PSP-speech apraxia [3,4] (Table 1). In spite of various phenotypes at disease onset, at more advanced stages of the disease, most clinical variants share common findings that are

more typical for PSP-Richardson [3]. This clinical heterogeneity in association with dependence on pathology for definite diagnosis adds to the difficulties for development of a disease modifying therapy. New diagnostic criteria of the various PSP phenotypes will hopefully allow an earlier diagnosis of PSP-RS and of all the phenotypes [5].

PSP-RS affects 5–6% of patients presenting with parkinsonism [6] with a prevalence of 5–7 cases per 100,000. It is a relatively rapid progressive neurodegenerative disorder with a mean time to death from diagnosis of 5–8 years [7,8].

Treatment of PSP is traditionally focused on symptomatic approaches [9]. However, the effects of these treatments, which are commonly not comprehensive and personalized, have usually been at best marginal, transient, and without modification in the course of the disease progression. A number of double blind randomized clinical trials have been performed [10–13] or are currently ongoing to evaluate the effects of therapies targeting hypothesized pathogenic mechanisms (Table 2).

Designing and performing clinical trials targeting PSP patients face significant challenges, including difficulties in early diagnosis and choosing appropriate inclusion/exclusion criteria, especially considering PSP variants, lack of sensitive and rigorous methods/biomarkers to non-invasively measure target-binding and treatment effects, in addition to relative rarity of the disease. However, the completion of recent clinical therapeutic trials have shown their feasibility in large PSP samples, providing hope of finding

Article highlights

- Progressive supranuclear palsy is the most common primary tauopathy and atypical parkinsonian disorder. The effect of current treatments for PSP have usually been at best marginal, transient, and without modification in the course of the disease progression.
- Current investigational treatments are directed to three pathogenetic mechanisms of the disease including genetic mechanisms, abnormal post-translational modifications of tau protein, and transcellular spread of tau pathology.
- Antisense oligonucleotides as well as anti-tau antibodies/vaccine are the most promising therapeutic options under investigation considering their success in other proteinopathies.
- To allow better design of future clinical trials it is essential to identify diagnostic biomarkers to diagnose PSP early and to measure disease progression accurately.

Table 1. Approximate relative frequency of clinical features in early stage prototypic and variant PSP phenotypes.

Clinical syndrome	PSP-R	PSP-P	PSP-PGF	PSP-bvFTD	PSP-CBS
Postural instability	+++	After 2 years	+++	After 2 years	+/-
Freezing of gait	++	++	+++	After 2 years	++
Vertical supranuclear gaze palsy	+++	After 2 years	-/?+	After 2 years	+/-
Oculomotor apraxia	-	-	-	-	++
Ideomotor apraxia	-/+	-	-	-	+++
Dystonia	Axial	-	-	-	Limb
Non-fluent aphasia	+	-	-	-/+	+/?
Executive dysfunction	+++	+/+	-?	+++	++
Behavioral frontal lobe syndrome	++	+	-	+++	-

R: Richardson, P: parkinsonism, PGF: progressive gait freezing, bvFTD: behavioral variant of frontotemporal dementia, CBS: corticobasal syndrome.

disease modifying treatments that could slow down the progression of this relentlessly progressive disorder. This is quite relevant in view of the continuous failure of therapeutic trials dealing with more than one aggregated protein such is the case in Alzheimer's disease (AD).

2. Hypothesized pathogenicity

Current ongoing randomized-placebo-controlled studies focus on processes leading to tau conformational changes and its transcellular spread in addition to genetic dysregulation producing altered tau isoform ratios as main underlying pathogenic processes [14–16] (Figure 1).

2.1. Genetic mechanisms

Tau is a microtubule-associated protein coded by the microtubule-associated protein tau (MAPT) gene on chromosome 17q21.31. Mutations in the MAPT gene have been found in a number of patients with tauopathies that resemble PSP [17,18] and further confirm the central role of tau in PSP. Genetic studies in PSP showed an inversion polymorphism producing variants called H1 and H2, containing the MAPT gene on chromosome 17q21.31, to be associated with PSP, with the H1/H1 haplotype conferring the greatest risk for PSP. However, the exact pathogenic mechanism

for increasing risk of PSP in patients with H1/H1 haplotype polymorphism is still unknown [14]. Genome-wide association studies also showed single nucleotide polymorphisms in the MAPT gene, as well as other genes, including STX6, EIF2AK3, and MOBP, as risk factors for PSP [14]. EIF2AK3 codes for RNA-like endoplasmic reticulum kinase (PERK) that is a regulator of unfolded protein response. Polymorphism near the MOBP gene is associated with over-expression of the SLC25A38 gene, which codes for the protein appoptosin, and subsequently leads to cleavage and accumulation of tau protein [19]. Currently a number of investigational therapeutics for PSP is directed to lower MAPT gene transcription or its mRNA translation [20–22].

Physiologically, tau assembles and stabilizes microtubules (MT) and probably maintains integrity of nuclear DNA, mainly in the central nervous system [23,24]. Based on alternate splicing of exons, expression of the MAPT gene produces two sets of tau isoforms in equal proportions, a 3-repeat (3R) and a 4-repeat (4R) MT-binding site protein. Either of 3R or 4R tau could have 0, 1, or 2 near N-terminal inserts, hence, the shortest and longest tau isoforms are 0N3R and 2N4R, respectively. An increased 4R to 3R tau ratio has been shown to be associated with tau hyperphosphorylation and neuronal toxicity and is the major underlying pathologic basis of PSP [25,26].

2.2. Abnormal post-translational modifications

To perform its regulatory functions, tau undergoes a number of physiologic post-translational modifications (PTMs), mainly phosphorylation. Extensive and aberrant PTMs are believed to impair tau clearance, lead to its aggregation and interfere with cell metabolism [24]. Different sets and sequences of abnormal PTMs could produce various patterns of tau deposition and neuronal system involvement that produces clinically and pathologically distinct categories of tauopathic disorders [15,25,27].

Pathological PTMs of the tau protein include, but are not limited to, hyperphosphorylation, acetylation, decreased O-GlcNAcylation (by increasing hyperphosphorylation) and cleavage at specific sites. These modifications decrease tau solubility and lower its affinity to bind to MTs, leading to tau accumulation in the form of neurofibrillary tangles or other conformations, as well as destabilization of MTs [19,28,29].

Tau phosphorylation is mediated by a number of kinases including proline-directed signal transducer kinases consisting of cyclin-dependent kinase 5 (CDK5), mitogen-activated protein kinases and notably glycogen synthase kinase-3 (GSK3), also cyclic AMP-dependent protein kinase, tyrosine kinases (including Fyn, Syk, c-Abl, and other kinases), calcium/calmodulin-dependent kinase II, MT affinity regulating kinases, and c-Jun N-terminal kinases among many others [30].

Although PSP is considered a relatively rare disorder, pathologically it shares some common features with other neurodegenerative tauopathies, including corticobasal degeneration (CBD), frontotemporal lobar degenerations (FTLD) and AD [31]. Hence, we can expect that a clinical therapy focusing on a specific type of tauopathy might potentially benefit patients with the other 3R or 4R types.

Studies on brain extracts showed that in PSP brains, tau is less phosphorylated than in AD brains (45 vs. 16 epitopes) and its phosphorylation is more labile than in AD [32]. Moreover, it has

Table 2. Main investigational therapeutic options for PSP and other tauopathies based on their pathogenic mechanisms.

Treatment strategy	Pathologic process	Mechanism of pathogenesis	Specific targets	Therapeutic option
Controlling PTMs	Abnormal phosphorylation	<ul style="list-style-type: none"> Loss of MT binding Redistribution to cell body Resistant to degradation Prone to aggregation 	<ul style="list-style-type: none"> GSK3β CDK5 Brain specific calpain Tyrosine kinases ROCK Other kinases 	<ul style="list-style-type: none"> Tideglusib^a Sodium valproate^a Lithium^a RNA interference silencing of the GSK3β Saracatinib CDK5 inhibitors ROCK inhibitors Calpain inhibitors
	Abnormal acetylation	<ul style="list-style-type: none"> Reduced ubiquitination Reduced degradation 	Acetylated tau	Salsalate ^a
	Loss of O-GlcNAcylation	Hyper-phosphorylation	O-linked N-acetylglucosaminidase (OGA)	<ul style="list-style-type: none"> ASN120290 MK-8719^a
Tau immunotherapy	Extracellular tau	Tau pathology spread to adjacent normal cells	<ul style="list-style-type: none"> Non-phosphorylated N-terminus residues 25–30 of eTau N-terminally truncated eTau 	<ul style="list-style-type: none"> ABBV-8E12^a BIIB092^a
	Abnormally modified tau	Propagation of tau pathology	<ul style="list-style-type: none"> Phosphorylation activation domain of tau Phosphorylated tau at other residues 	<ul style="list-style-type: none"> Armanezumab AADvac1 ACI-35 AV-1980D
MAPT gene expression reduction	Increased 4R:3R tau ratio Increased total tau	<ul style="list-style-type: none"> Prone to aggregation Overcrowding and interference to normal cell metabolism 	MAPT gene	Antisense oligonucleotides (IONIS-MAPT Rx)
Preventing tau aggregation	Tau aggregation	Overcrowding and interference to normal cell metabolism	Tau monomers	TRx0237
Enhancing tau function	MT destabilization	<ul style="list-style-type: none"> Impaired axonal transport Loss of synapses 	Microtubules	<ul style="list-style-type: none"> Davunetide^a TPI-287^a
Enhancing mitochondrial function	Impaired oxidative metabolism	Mitochondrial complex I dysfunction	<ul style="list-style-type: none"> Mitochondrial complex I Oxidative metabolism pathway 	<ul style="list-style-type: none"> CoQ10^a α-lipoic acid + L-acetyl carnitine^a Pyruvate+creatine + niacin amide^a
Enhancing Tau degradation	Impaired tau degradation	Tau accumulation	<ul style="list-style-type: none"> Proteasome Autophagy pathway 	<ul style="list-style-type: none"> Rolipram Nilotinib/Bosutinib AZP2006^a

^aDrugs that entered/being evaluated in clinical phase of trials in PSP patients.

Figure 1. Three main (a, b, and c) hypothesized pathways of tau pathogenicity in PSP and potential therapeutic targets. (a) Over-expression of 4R tau; Antisense oligonucleotides (ASOs) could potentially reduce expression of 4R tau or all six isoforms. (b) Abnormal post-translational modifications; many kinases that are involved in tau hyperphosphorylation, OGA enzyme and acetylated tau are potential targets. (c) Transcellular tau spread; pathogenic tau strains are probably capable of entering into adjacent cells, both neurons and glia, and propagate tau pathology. Blocking of this spread is a promising new therapeutic strategy. Other proposed mechanisms include neuroinflammation, mitochondrial abnormality and oxidative injury. All mechanisms finally lead to tau aggregation, causing impairment of cell metabolic machine (Toxic gain of function), and MT instability (loss of function), culminating in synapse loss and cell death (d).

been shown that 35kDa-tau, a cleaved form of tau protein truncated at the N-terminal, is present in PSP and CBD but is absent in AD and pure 3R tauopathy brains [32]. Another signature of tau pathology in PSP is probably lack of C-terminally cleaved tau at Asp421 in its glial lesions or truncation at Glu391 in either neuronal or glial lesions. This pattern has also been found in CBD but not in AD, which shows more Asp421 cleaved tau in early to mid-stage and more Glu391 truncated tau in late stage neurofibrillary tangles [33]. However, phosphorylation at Ser422, as a regulator of tau cleavage at Asp421, has been found in both non-AD and AD tauopathies and is perceived to be an early event in the course of most tauopathic disorders [33,34].

2.3. Transcellular spread of tau pathology

Different mechanisms have been proposed for spread of abnormal proteins to adjacent normal cells, including tunneling nanotubes, exosomes and release and uptake at normal or damaged synapses [35,36]. During release and reuptake of extracellular tau (eTau), the protein would be accessible to therapeutic antibodies. In fact, studies have shown, *in vitro* and *in vivo*, that tau stably disseminates specific amyloid 'strains' that are capable of producing cell clones with identical pattern of tau pathology

[37]; nevertheless, this theory of prion-like spread has yet some drawbacks and criticisms [36].

The different hypothesized mechanisms are further discussed below in related sections (Figure 1).

3. Investigational approaches

3.1. Tau gene expression and RNA translation reducers

Antisense oligonucleotide (ASO) has been used *in vitro* and *in vivo* to reduce the expression of the tau gene [21,22]. They might prevent the over-expression of the pathologic 4R tau [20]. In a recent study, DeVos et al. administered IONIS-MAPT Rx (an ASO) to transgenic PS19 tauopathy mice for three months [22]. They showed that treated mice had less tau mRNA, less tau inclusions and tau pathology, better survival and function, and more preserved hippocampal volume with no significant loss of normal tau function. Results were reproducible in a primate, cynomolgus monkey. ASOs might be a promising future therapeutic approach for PSP patients. At present, IONIS-MAPT Rx is being evaluated in a phase I/II clinical trial targeting patients with mild AD (clinicaltrials.gov, NCT03186989). It is estimated that 44 patients will receive multiple ascending-dose (four levels) intrathecal infusions of

IONIS-MAPT Rx every 4 weeks over 13 weeks, data are expected for 2020. Primary outcome measures are safety and tolerability with secondary endpoints being cerebral spinal fluid (CSF) pharmacokinetics and exploratory endpoints are pharmacodynamic biomarkers and clinical outcomes [38].

3.2. Tau post-translational modification controllers

Tau protein undergoes a number of modifications for different purposes, including regulation of its function (binding to and stabilizing MTs), degradation, and aggregation. Most widely studied tau modifications as potential treatment targets are phosphorylation, acetylation, and O-GlcNAcylation.

3.2.1. Tau phosphorylation inhibitors

It is believed that the hyperphosphorylation of tau is responsible for changing the trans isoform into cis tau [39], redistribution of tau from its main location in axons into the pericarian and dendrites [40], resistance against degradation by the proteasome [41], and aggregation of tau [24]. Tau phosphorylation and dephosphorylation is mediated by a number of kinases and phosphatases.

3.2.1.1. GSK3 inhibitors. GSK3 is the main enzyme that phosphorylates tau and has been related to hyperphosphorylated tau deposits in PSP [42]. GSK3 is not capable of phosphorylating the normal tau protein. It is only activated after a change in tau structure that exposes the tau's phosphatase activating domain on the N-terminous side. It mainly acts on a preconditioned (primed) tau protein [43]. GSK3 phosphorylates tau at specific serine residues, decreases its affinity for MTs and enhances its folding into paired helical filaments and forming intracellular aggregates. GSK3 is also involved in neuronal apoptosis [44,45] and has a wide range of substrates in different parts of the body including effects on fetal development. The therapeutic effect of inhibiting this kinase in transgenic tau mice models has been shown [46,47] and led to studies in PSP. GSK3 inhibitors have broadly been categorized into three groups: (1) ATP-competitive inhibitors (competing for its ATP binding site), (2) non-ATP-competitive inhibitors, and (3) substrate competitive inhibitors [48].

Two ATP-competitive GSK3 inhibitors, including sodium valproate [13] and lithium (clinicaltrials.gov, NCT00703677), and a non-ATP-competitive GSK3 inhibitor, tideglusib [11], were recently studied in PSP. In the phase II double-blind placebo-controlled clinical trial of sodium valproate, 28 PSP patients were randomized to 1:1 ratio to receive either 1500 mg daily oral sodium valproate or placebo for 24 months. No significant changes in clinical outcomes were reported. Lithium was evaluated in a phase I/II open-label trial. Among 17 PSP patients entered the trial only one completed the 28-week study period and study had to be discontinued early because of lack of tolerance.

Tideglusib is an irreversible blocker of GSK3 β that showed promising results in preclinical studies in tau mouse models by decreasing tau phosphorylation and improving cognitive performance [49–51]. In a large phase II, double-blind, placebo-controlled trial on 146 PSP patients, tideglusib was administered at two dose levels of 600 mg ($n = 60$), 800 mg ($n = 55$), and placebo ($n = 31$) once daily for 52 weeks. Although no significant clinical benefits were observed in the tideglusib

arms [11], in a subgroup ($n = 37$, 28 on tideglusib and 9 on placebo) the rate of brain atrophy progression measured by MRI decreased significantly in the treatment arm [52]. Changes were significant for measurements performed on the whole brain and on parietal and occipital lobes on the *post hoc* analysis. While these areas are believed to be less affected with tau pathology in PSP [53], the investigators argue that this reflects the higher sensitivity of methods used for brain volume calculations to find changes in these larger brain areas and also higher expression of GSK3 β in these regions, hence probably indirectly confirming target-binding of the investigational drug. On the other hand, studies in subgroup of patients are prone to statistical issues and have to be replicated.

Evaluation of methods of the GSK3 trials reveals a number of factors that could be accountable, at least in part, for their negative results. Patients included in these trials were in mild to moderate stages of disease severity (PSP Rating Scale (PSPRS) score lower than 40), inclusion of patients in earlier stages might have allowed better identification of therapeutic effects [11]. On the other hand, despite recent advances, our understanding of regulation of tau phosphorylation is still limited and the role of other kinases (described below), enzymes and regulating molecules in this complex process are yet to be established. A complete discussion of this point is beyond the scope of this review, but in view of the positive results of *in vitro* and animal studies other GSK3 inhibitors which may be more potent are still under investigation. RNA interference silencing of the GSK3 β isoform has been effective in lowering phosphotau and improving function in mice tauopathy models [54,55]. New inhibitors including AZD1080, BTA-EG₄ and compounds based on 2-(4-aryl-2-methylpiperazin-1-yl)-pyrimidin-4-ones are under evaluation [56–58] and if successful, they could enter clinical trials of tauopathies, including PSP.

3.2.1.2. CDK5 inhibitors/calpain inhibitors. CDK5 overactivation leads to tau hyperphosphorylation and further phosphorylation by GSK3 ('priming' for GSK3) resulting in aggregation and neurodegeneration [44,59,60]. Increased levels of CDK5 have been observed in PSP patients [61] and knocking down the CDK5 gene or use of CDK5 inhibitors have showed therapeutic effect on tau pathology [62–64]. CDK5 activity is regulated by a polypeptide, p35; cleavage of p35 peptide, probably mediated by calpain (calcium-dependent) proteases [65,66], leads to formation of p25 which causes CDK5 hyper-activation [67]. It has been shown that p25 is associated with tau pathology and neurodegeneration [67,68]. Preclinical CDK5-directed therapeutic approaches currently are focusing on p25 inhibition [62,64] and also on silencing the CDK5 RNA translation using microRNA interference [60,63]. The proposed role of calpain proteases as regulators of the function of CDK5 and the hypothesis that stress induced calcium toxicity might induce function of calpain proteases [69] have created another line of research focusing on inhibition of brain specific calpain subtypes [70,71].

3.2.1.3. Other kinase inhibitors. A number of other relevant tau kinases have also been investigated. Rho-associated protein kinase (ROCK) inhibitors are under evaluation for the treatment of PSP, CBD, and other tauopathies based on

studies indicative of increased ROCK in PSP and CBD brains [72]. AZD0503 (saracatinib) is a Fyn tyrosine kinase inhibitor evaluated in AD in a phase Ib trial indicative of general safety [73] that is currently being investigated in a phase II AD trial (clinicaltrials.gov, NCT02167256).

3.2.2. *Tau acetylation inhibitors*

Degradation of tau protein by means of the ubiquitin-proteasome system requires ubiquitination of tau lysine residues. Acetylation of tau and phosphotau effectively prevents their ubiquitination and degradation and allows further phosphorylation by other kinases leading to MT dysfunction and tau aggregation [28,74]. Salsalate, a non-acetylated dimer of salicylic acid, is an acetylation inhibitor currently under investigation in a PSP pilot futility phase I clinical trial to assess its safety and tolerability (clinicaltrials.gov, NCT02422485). Salsalate has also anti-inflammatory properties through suppression of NF- κ B activation [75], but unlike salicylic acid has no antiplatelet or cyclooxygenase inhibition effect [76]. In a recent study on mice traumatic brain injury model (a model of tauopathy), salsalate improved recovery of motor function and decreased microglial and other inflammatory cells recruitment and activation *in vitro* [77]. Considering the significant pathological microglial activation in PSP [78], salsalate is believed to act with both mechanisms of anti-microglial and anti-acetylation. A preclinical study on PS19 mice tauopathy model showed that treatment with salsalate can be associated with lower tau pathology, less hippocampal atrophy, and better memory function [79].

3.2.3. *Tau O-GlcNAcylation enhancers*

O-linked- β -N-acetylglucosamine transferase (OGT) is an enzyme involved in transferring O-linked- β -N-acetylglucosamine (O-GlcNAc) from UDP-N-acetylglucosamine (product of glucose metabolism in hexosamine biosynthesis pathway) to the serine or threonine residues of proteins, including tau. Recent studies have shown that decreased tau O-GlcNAcylation leads to its hyperphosphorylation [80]. These results have been confirmed by evaluating brain autopsies of AD patients [81] and preclinical studies showing reduction of tau pathology in multiple tauopathy mice models by inhibition of O-linked N-acetylglucosaminidase (OGA), the enzyme that removes O-GlcNAc moieties from the tau protein [29,82,83].

3.2.3.1. ASN120290 (ASN-561). ASN120290 (ASN-561) is a small molecule that inhibits OGA. It has a better CNS penetration than previously studied compound, thiamet-G [84]. Previous studies on JNPL3 mice showed that thiamet-G leads to decrease in tau phosphorylation with simultaneous increment in tau O-GlcNAcylation [29]. Preclinical studies on P301S mice treated with daily oral doses of ASN-561 for 3.5 months showed a decrease in tau pathology and sustained pharmacodynamic response [85]. ASN120290 is expected to enter its phase I trial on healthy volunteers to assess safety, tolerability, pharmacokinetic and pharmacodynamic in the near future.

3.2.3.2. MK-8719. MK-8719 is a small molecule that selectively inhibits OGA. Its pharmacodynamic and clinical efficacy has been assessed in a Tg4510 transgenic tauopathy mice model [86]. In this study, administration of a single dose of MK-8719 significantly reduced pathological tau formation and increased O-GlcNAcylated proteins (O-protein) in mouse brain and was

accompanied with less brain atrophy, measured by MRI, and with a lower level of inflammatory markers. A phase I study with a specific PET tracer ($[^{18}\text{F}]$ MK-8553) also showed target engagement. In this study, administration of 5–1200 mg single dose of MK-8719 well tolerated in 16 healthy volunteers with no safety concerns [86]. Pharmacokinetic evaluations showed high oral bioavailability, moderate to large volume of distribution, and increasing plasma concentration and O-protein response in proportion to dose increments in studied animals and healthy volunteers [87]. MK-8719 seems to be a good candidate for evaluation in patients with PSP [88].

3.3. *Tau immunotherapy*

Vaccination against tau, as well as antibodies directed to the different pathogenic tau epitopes are promising new therapeutic approaches for tauopathies [3]. Although tau is an intracellular protein, and there is evidence that it is possible to slow down disease progression by intracellular antibodies [89,90], targeting eTau during its transneuronal spread is also investigated [35,91,92]. Although 'passive immunization' was the term originally used to explain mechanism of action of anti-tau antibodies, recent studies by removing effector function of antibodies have shown that monoclonal anti-tau antibodies need not necessarily to activate the immune system to slow down the spread of tau pathology, at least in animal mouse models [93]. Currently two humanized anti-tau antibodies, both binding to eTau, are under investigation for PSP.

3.3.1. *ABBV-8E12 (C2N-8E12)*

Kfoury et al. [94] in their study to assess the mechanism of spread of tau protein between cells produced a murine antibody, HJ9.3, capable of blocking extracellular propagation of fibrillar tau *in vitro*. The antibody was directed to the repeat domain of eTau aggregate. In a subsequent study by Yanamandra et al. [91], effect of similar set of antibodies, including HJ8.5, an IgG2b antibody against non-phosphorylated N-terminus residues 25–30 of human tau, was assessed in a P301S mouse model of tauopathy. After three months of intraventricular infusion of antibodies they demonstrated a marked decrease in tau pathology and its seeding activity that was accompanied with clinical improvement in behavioral tasks. Clinical improvement in motor and sensorimotor tasks and decrease in brain atrophy in P301S mouse was also shown with peripheral administration of the same antibodies in other studies [95]. The humanized form of this anti-extracellular fibrillar tau antibody has recently been evaluated in a phase I double-blind, placebo-controlled trial (see ABBV-8E12, clinicaltrials.org, NCT02494024). In this trial, 30 PSP patients received a single intravenous infusion at different doses (five dose levels, 2.5–50 mg/kg) or placebo. Researchers reported acceptable safety and tolerability with a predictable pharmacokinetic of the drug, producing a one month half-life and a CSF: plasma concentration ratio of 0.4% for the lower and 0.16–0.27% for upper dose levels [96]. The main reported adverse events were dermatitis, falls, urinary tract infection, headache, fatigue, and sore throat. One patient had subdural hematoma after falling and another one suffered from increased agitation after infusion. Some of these side effects are related to disease (i.e. falls), and others to cardiac

electrodes (i.e. dermatitis). Phase II studies of ABBV-8E12 for treatment of mild to moderate PSP (clinicaltrials.gov, NCT02985879) and AD (clinicaltrials.gov, NCT02880956) have started 2017 and 2016 respectively. The primary outcome measure for the PSP trial is change in PSPRS score. In this trial, two different doses of ABBV-8E12 are being assessed against placebo in 180 PSP patients with less than 5 years of symptom duration. Trial duration is 52 weeks for each patient.

3.3.2. BIIB092 (BMS-986,168)

Griswold-Prenner et al. [97] studied IPN002, a murine anti-tau antibody directed to an N-terminally truncated eTau (15–24 epitopes), in the P301L mice tauopathy model and found that it effectively attaches to the secreted eTau and decreases tau pathology. They developed an IgG4 humanized form of this antibody, IPN007 (BMS-986,168). Bright et al. [98] showed that IPN002 binds to and neutralizes eTau (but not intracellular tau) *in vitro* in pluripotent stem cells derived from familial AD patients, and *in vivo* in P301L mice tauopathy model. BMS-986,168 entered its phase I trial in 2014 (clinicaltrials.gov, NCT02294851), to assess safety, tolerability, pharmacokinetic, pharmacodynamics, and immunogenicity of a single ascending intravenous infusion of BMS-986,168 on healthy volunteers. In 2015, entered phase I trial that evaluated safety and tolerability of multiple ascending doses in 48 mild-moderate PSP patients (including 12 receiving placebo) in their first 5 years of the disease (clinicaltrials.gov, NCT02460094). The primary results confirmed its general safety and the CSF pharmacodynamics (eTau concentration) were indicative of efficacy by a mean CSF free eTau suppression of 90–96% at day 29 and 91–97% at day 85 after treatment with the intravenous infusions of 150–2100 mg antibody every 4 weeks [99] (clinicaltrials.gov, NCT02460094). These patients continued participating in a long-term BIIB092 intravenous monthly administration. A phase II double-blind, placebo-controlled trial of BIIB092 on an estimated 396 PSP patients has started in 2017 and data are expected in 2020 (clinicaltrials.gov, NCT03068468).

3.3.3. Armanezumab

Armanezumab is a humanized anti-tau antibody that binds to the 'phosphatase activation domain' of the tau protein. This epitope in the tau N-terminal (amino acids 2–18) is hidden in the normal paperclip-shaped tau molecule, but is exposed in pathologically modified tau in early stages of aggregation [100]. Agadjanyan et al. added this antibody to brain homogenates of post-mortem AD, frontotemporal dementia and Pick's disease patients and found that it effectively binds to fibrillar and oligomeric tau while keeping the normal paperclip-shaped tau intact [101]. Armanezumab also reduced seeding of tau pathology in the brain lysate of P301S tau mouse model and reduced the total amount of tau pathology in this tau mice model.

3.3.4. Tau vaccines

Although primary animal studies of immunizing mice with full-length tau resulted in induction of neurofibrillary tangle-like pathology with neuronal damage and gliosis [102], recent trials showed that active tau immunotherapy could be feasible

and safe [103]. There are two types of vaccines against non-phosphorylated tau (AADvac1) and AD-specific phosphorylated tau (ACI-35) that were tested in animal models and both are now being evaluated in AD; the AADvac1 is being also evaluated in non-fluent primary progressive aphasia.

3.3.4.1. AADvac1. AADvac1 is an active tau vaccine consisting of a 12-peptide sequence of tau protein deemed to be responsible for tau oligomerization (amino acids 294–305 (KDNKHVPGGGS) inside the repeat domain of 4R tau) [104,105]. Preclinical studies on rat AD models showed that immunization with this peptide produces antibodies that preferentially block pathologic, but not normal, tau, have a favorable safety profile and reduce truncated tau, tau oligomers and full-length tau [104]. Results of the first phase I trial (clinicaltrials.gov, NCT01850238) extending to a follow-up open-label trial (clinicaltrials.gov, NCT02031198), in 30 patients with mild to moderate AD, were indicative of effective immunogenicity and acceptable safety accompanied with stable cognitive assessment measures and no attributable brain atrophy [103]. Another phase I study is ongoing in an estimated 30 patients with non-fluent primary progressive aphasia (clinicaltrials.gov, NCT03174886). Considering the shared neurofibrillary pathology among different tauopathies, positive results might pave the way for using this tau vaccine for PSP phenotypes.

3.3.4.2. AV-1980D. A DNA-tau vaccine, AV-1980D, has been developed based on the same epitope as above-mentioned Armanezumab antibody and was evaluated in THY-Tau22 transgenic mice [106] showing reduction in tau pathology after five monthly immunizations. Further studies are needed to assess safety and pharmacokinetic of these agents in animal models before it can be translated into therapeutic clinical trials.

3.4. Tau aggregation inhibitors

These are small molecules that bind mainly to tau monomers, either covalently or non-covalently, thereby, preventing them from aggregation. Considering their effect on tau monomers, these agents are believed to act at early stage in the tauopathies. A number of tau aggregation inhibitors have been tested *in vitro*, however *in vivo* studies are limited due to their toxicity [107].

3.4.1. TRx0237

TRx0237 is a stable crystalline leucomethylthioninium salt (LMTX), a reduced form of methylthioninium (methylene blue). Preclinical studies showed that this compound prevents tau aggregation in early stages and dissolves paired helical filaments of AD and enhances tau clearance by means of proteasome or autophagy [108,109]. *In vivo* studies in tauopathy mice models showed reduction of tau pathology and improved learning [110] but a double-blind placebo-controlled trial completed in 2016 that evaluated the primary clinical efficacy of TRx0237 in 891 mild to moderate AD patients showed no benefit [111]. Results of other trials in AD and behavioral variant of FTD have not yet been reported.

3.5. Microtubule stabilizers

Based on the loss of function theory, at least part of neurodegenerative symptoms are due to impaired tau function, mainly MT assembly and stabilization [112,113].

3.5.1. Davunetide

AL-108/NAP (Davunetide), a neuroprotective and neural growth factor oligopeptide was the first MT stabilizing agent studied in a clinical trial for PSP [10]. Preclinical studies on a double mutant tauopathy mouse model (P301S;K257T) were indicative of significant reduction in tau phosphorylation (at Ser202 location), increase in soluble tau and better cognitive performance in the mice treated with davunetide [114]. Davunetide also showed a significant clinical improvement in two cognitive subtests in a double-blind randomized clinical trial in patients with amnesic type of mild cognitive impairment [115]. However, in a recent large, double-blind, placebo-controlled phase II/III clinical trial on 313 PSP patients, intranasal davunetide (30 mg, twice daily) for 52 weeks failed to show any significant effect on clinical, MRI or CSF outcome measures [10]. In this study researchers used CSF concentrations of neurofilament light chain (NfL) as a biomarker of disease progression in a subset of patients and interestingly reported a positive correlation of this measure to oculomotor subscale of PSPRS and also volume of superior cerebellar peduncle measured on MRI indicating that CSF NfL could be used as a marker of disease progression in future trials as confirmed in more recent studies [116]. The same issue stated above on GSK3 β inhibitor trials in regard to inclusion of patients on early stages may also be applicable for the davunetide trial.

3.5.2. Taxanes

Taxanes bind to MTs and stabilize them. Epothilone D, the first taxane evaluated for a tauopathy was unsuccessful in a clinical trial of AD patients (clinicaltrials.gov, NCT01492374), despite its promising effects in transgenic tau mice studies [117].

TPI-287 is a taxoid with good CNS penetration and is currently being evaluated for its safety and tolerability in patients with PSP and those with corticobasal syndrome, both primary 4R tauopathies, in a phase I trial (clinicaltrials.gov, NCT02133846). In this trial, 22 PSP patients receive 2 mg/m², 6.3 mg/m², or 20 mg/m² of TPI-287 or placebo (11 subjects on each arm) every 3 weeks for total of 4 infusions and are assessed primarily for safety, tolerability, and clinical, MRI and CSF biomarker measures, in addition to plasma pharmacokinetic and CSF concentrations. In its preclinical proof of concept study, TPI-287 reduced hyperphosphorylated tau and improved contextual learning and memory in PS19 transgenic tauopathy mice model [118].

3.6. Mitochondrial function enhancers

Mitochondrial dysfunction and accumulation of products of oxidation in involved brain regions and muscle in PSP patients [119,120] indicate its role in the pathogenesis. *In vivo* lower rate of glucose metabolism in affected brain areas in positron emission

tomography (PET) [121] and in phosphorous magnetic resonance spectroscopy (P-MRS) [122] studies further support therapeutic approaches to improve oxidation.

3.6.1. Coenzyme Q10

To enhance the complex I function, Coenzyme Q10 (CoQ10) was tried in two studies in PSP. The first phase II double-blind, placebo-controlled trial assessed the effect of 5 mg/kg/day of CoQ10 for 6 weeks in 21 PSP patients (10 patients received CoQ10 and 11 placebo) [123]. This small trial showed a significant effect of CoQ10 in decreasing PSPRS score and cerebral low-energy metabolism (measured by P-MRS and H-MRS). Analysis of the results shows that the PSPRS subscales limb scores is responsible for this significant result, since there were none of the other subscales improved significantly. Moreover, there were no differences in the UPDRS part III, which also includes the limb evaluation. In addition, of the 10 patients analyzed in the CoQ10 arm, 8 had a lower disease severity manifested by a stage 2 based on the PSPRS score, and the remaining two were in stage 3, however, in the placebo arm, five patients were in stage 2 and six in stage 3. The lack of consistency in the results of similar endpoints and milder disease severity in the treatment arm may in part explain the observed improvements.

A subsequent larger trial performed between 2006 and 2012 that included 61 PSP patients [12] did not confirm the findings of the first study. The patients received 2,400 mg of CoQ10 ($n = 31$) or placebo ($n = 30$) for 12 months. This study showed that there were no significant between-group differences in the total and all subscale PSPRS scores and UPDRS scores, although a trend toward statistical significance was observed comparing PSPRS scores at the end of trial ($p = 0.068$). Unfortunately, this study had a relatively high drop-out rate of 41%. At baseline, the patients who dropped-out (from both arms) were not significantly different to those who remained in the trial. Patients who dropped out from the treatment arm performed worse on the PSPRS at the 3rd and 6th months and at the 3rd month on the UPDRS than those completing the trial, while those who dropped out from the control arm only had worse UPDRS scores than those remained in that arm at 9th month.

3.6.2. Nutrient combinations

Two nutrient combinations, including α -lipoic acid with L-acetyl carnitine (Juvenon) (clinicaltrials.gov, NCT01537549, started in 2012) and pyruvate with creatine and niacinamide (clinicaltrials.gov, NCT00605930, started in 2008) were evaluated in PSP patients but these trials have not been published because the factory providing the high dose of nutrients went bankrupt interrupting the study. However, primary data of the Juvenon trial indicated that mean cerebral oxidative stress markers (changes of cerebral lactate and glutathione levels measured by MRS), analyzed in 7 out of 11 patients (3 out of 11 patients did not complete the study and 1 was not included in the analysis for unknown reason) was 4 (SD:1.67) at baseline compared to 4.6 (SD: 1.41) after one month treatment with 600 mg/1.5 g daily α -lipoic acid and L-acetyl carnitine capsules (clinicaltrials.gov, NCT01537549). Considering lack of a placebo arm, the lack of randomization and the exclusion of subjects in this open study, we believe that Juvenon has no role in changing

mitochondrial energy metabolism in PSP patients. Twenty-three adverse events were reported in this trial among 11 patients including gastrointestinal disturbances ($n = 5$), change in odor of urine, breath, or sweat ($n = 4$); bronchoconstriction/cough ($n = 1$); skin disorder ($n = 2$), and leg cellulitis ($n = 1$). Moreover, in view of the number of side effects these patients experienced there does not seem to exist a justification to conduct further trials with this nutrient.

3.7. Other mechanisms

3.7.1. Young plasma transfusion

Preclinical studies transfusing young plasma to aging mice [124] led to study the possibility that transfusion of young plasma might decrease the progression of neurodegeneration in PSP patients. A phase I clinical trial is currently ongoing to assess the safety, tolerability, pharmacodynamic of transfusions, as well as clinical, MRI, and CSF tau and phosphotau measures in 10 PSP patients treated by young plasma transfusion (clinicaltrials.gov, NCT02460731). Transfused plasma is derived from under 30 year-old healthy males and is injected to PSP patients with a dose of four units monthly for 6 months.

3.7.2. Tau degradation enhancers

Tau is normally degraded by lysosomal system (i.e. autophagy) or by the proteasome complex. Both of these pathways are being evaluated as potential targets for enhancing tau degradation.

3.7.2.1. Rolipram. A recent study showed that 26S proteasome dysfunction, secondary to loss of its ability to use ATP due to attachment of tau oligomers to its 19S subunit, could partly be accountable for tau accumulation and neurodegeneration [125]. In this preclinical study, administration of rolipram, an agent that increases cyclic AMP, activates protein kinase A (PKA) in a tauopathy mouse model (rTg4510), and thereby increasing proteasome activity and tau degradation.

3.7.2.2. Nilotinib/bosutinib/AZP2006. Nilotinib (Tasigna) is a tyrosine kinase inhibitor that was approved by the FDA for the treatment of chronic myeloid leukemia and mainly acts as an autophagy inducer. In a recent preclinical study on a PSP mouse model, TauP301L, daily treatment with nilotinib or other tyrosine kinase inhibitor, bosutinib, resulted in phosphotau clearance and improved motor symptoms [126]. Nilotinib is currently under investigation in a randomized, double-blind, placebo-controlled phase II trial in patients with mild to moderate AD to assess its safety and also its effect on CSF biomarkers (including total tau, phosphotau 231/181) and amyloid beta 42/40 levels) (clinicaltrials.gov, NCT02947893). Patients will receive 150 mg daily oral nilotinib (one capsule) for 6 months followed by 300 mg daily for another 6 months. Estimated enrollment for this trial is 42 patients and data are expected in 2019.

AZP2006 is a small molecule that has been claimed to enhance autophagic clearance of tau and other abnormal proteins, and based on AlzProtect company report [127] is in clinical development for PSP. No data have been published of

its preclinical development or phase I trial in healthy volunteers. AZP2006 was granted orphan designation from FDA in 2017 and European Medicines Agency in 2015 [128,129].

4. Expert opinion

There has been a long trajectory since the initial description of PSP in 1963 in Toronto, to the understanding the role of tau aggregation in the etiopathogenesis, and the subsequent identification of an array of possible therapeutic approaches to slow down the progression of this primary tauopathy. The various interventions above described under development could be divided in three main mechanisms to alter tau pathology [3]:

- (1) Modulation of MAPT gene expression with ASOs,
- (2) Modulation of tau PTMs, such as hyperphosphorylation, acetylation, oxidation and O-GlcNAc modification, as well as modulation of pathways for degradation, including ubiquitination (by the ubiquitin protein system) and autophagy (by the lysosome) pathways, and
- (3) Inhibition of transcellular tau propagation through immunization (vaccines or antibodies against tau) or modulating the inflammation.

In my view, the modulation of the MAPT gene expression with ASOs is one of the most promising therapeutic approaches. The success of ASOs in two unrelated proteinopathies: spinal muscular atrophy and Duchenne muscular dystrophy make this approach one of the most relevant at present. The development of morpholinos that induce skipping exon 1 and 5, masking their 5'-splice sites and the benefit of ASOs in a transgenic mice model of the entire human MAPT gene showed the feasibility of this approach in PSP [21]. Moreover, the development of selective ASOs in transgenic mice expressing human mutant P301S tau that reversed the tau pathology and later shown in the Cynomolus monkeys not only demonstrate the feasibility and likely success of using these oligonucleotides in AD, but also its promising benefit in PSP due to the fact that the P301S tau transgenic mice is a 4-repeat tauopathy [22]. It is hoped that therapeutic trials with ASO will be soon started in PSP.

The use of vaccines or antibodies against tau is also likely to be of benefit in slowing the spread of PSP. In fact, once successful therapeutic approaches are identified, it is likely that like in oncology, we will need to determine which is the best combination of therapies that target different mechanisms.

In addition, to further increase the likelihood of therapeutic success in PSP and related tauopathies, it is essential to identify diagnostic biomarkers to early diagnose them. The development of the Movement Disorder Society PSP diagnostic criteria is an important step in this direction, but these criteria need validation [130].

In addition, while the PSPRS [131] is a good outcome measure, it is necessary to find biological biomarkers to measure disease progression. The recent development of tau PET and further refinement of tau ligands may help both, diagnose early and measure disease progression.

It is hoped that this research will lead to the identification of therapies that in the near future will be able to cure PSP at early stages. In the meantime, a comprehensive, personalized interdisciplinary approach to this disease is absolutely necessary [16].

It is expected that a better understanding of the genetic and environmental factors at play in PSP would one day allow us identify subjects who could be at risk of developing this disease. Subjects at risk will be then tested with early disease biomarkers in order to confirm if they have PSP, so they could receive these interventions preclinically, prior to symptom development.

Funding

This paper is not funded.

Declaration of interest

I Litvan is a member of the Biotie/Parkinson Study Group Medical Advisory Board. She is an investigator in NIH Grants: 5P50AG005131-31, 5T35HL007491, 1U01NS086659, and 1U54NS092089-01; Parkinson Study Group, Michael J Fox Foundation, AVID Pharmaceuticals, Abbvie/C2N Diagnostics and Biogen/Bristol-Myers Squibb studies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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•• **Standard clinical rating scale for measuring PSP severity.**