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MOVEMENT DISORDERS (S FOX, SECTION EDITOR)

Progressive Supranuclear Palsy: an Update

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Abstract

Purpose of review Progressive supranuclear palsy (PSP) is a 4R tau neuropathologic entity. While historically defined by the presence of a vertical supranuclear gaze palsy and falls in the first symptomatic year, clinicopathologic studies identify alternate presenting phenotypes. This article reviews the new PSP diagnostic criteria, diagnostic approaches, and treatment strategies.

Recent findings The 2017 International Parkinson and Movement Disorder Society PSP criteria outline 14 core clinical features and 4 clinical clues that combine to diagnose one of eight PSP phenotypes with probable, possible, or suggestive certainty. Evidence supports the use of select imaging approaches in the classic PSP-Richardson syndrome phenotype. Recent trials of putative disease-modifying agents showed no benefit.

Summary The new PSP diagnostic criteria incorporating the range of presenting phenotypes have important implications for diagnosis and research. More work is needed to understand how diagnostic evaluations inform phenotype assessment and identify expected progression. Current treatment is symptomatic, but tau-based therapeutics are in active clinical trials.

Keywords Progressive supranuclear palsy · Clinical diagnostic criteria · Diagnostic imaging
Progressive supranuclear palsy/therapy

Introduction

Progressive supranuclear palsy (PSP) was first described as a clinical entity in 1964 by Steele et al. [1]. PSP neuropathologic criteria were formalized in the 1990s [2, 3]. It is now clear that the initially described phenotype—currently labeled Richardson's syndrome (PSP-RS)—is only one of many clinical phenotypes associated with PSP pathology, particularly at disease onset. The heterogeneity in clinical presentation is acknowledged in the updated PSP diagnostic criteria published in 2017 [4••]. This update will highlight recent advances in PSP, focusing on diagnosis and therapeutic approaches.

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Definitions/Vocabulary

PSP is a neuropathologic entity. It is the most common primary tauopathy and falls in the family of 4R tauopathies, reflecting the accumulation of the tau isoform with four repeats in the microtubule-binding domain [5]. Pathologic diagnostic criteria require neurofibrillary tangles (NFTs) and neuropil threads in the pons, substantia nigra, subthalamic nucleus, and pallidum (at least three locations) and a low-to-high density of NFTs or neuropil threads in additional areas [2]. In addition to the NFTs and neuropil threads, microscopic features include tufted astrocytes, oligodendroglial coiled bodies, neuronal loss, and gliosis [2].

With the increase in pathologically confirmed cases of PSP over the past 20 years, it is clear that localization of tau pathology is a major driver of clinical phenotype. Brainstem-predominant PSP pathology results in pure akinesia at one extreme. Cortical-predominant PSP results in focal cortical syndromes at the other extreme [5]. The causes of this heterogeneity in location of pathologic burden remain largely unknown. The appreciation of phenotypic variability within pathologically confirmed PSP requires that "PSP" be ideally reserved for pathologic diagnosis with in-life descriptions using the range of PSP

Table 1 Clinical phenotypes associated with PSP pathology

Phenotype	Abbreviation	Description/key features
PSP-Richardson's syndrome	PSP-RS	Vertical ocular motor dysfunction, early onset postural instability and falls
PSP-ocular motor	PSP-OM	Predominant ocular motor dysfunction
PSP-postural instability	PSP-PI	Predominant postural instability
PSP-parkinsonism	PSP-P	Clinical phenotype resembling Parkinson's disease (later development of symptoms of PSP-RS)
PSP-frontal	PSP-F	Behavioral or frontal cognitive presentation (can be similar to behavioral variant frontotemporal dementia)
PSP-progressive gait freezing	PSP-PGF	Presentation with an isolated gait disorder with start hesitation and progressive freezing of gait
PSP-corticobasal syndrome	PSP-CBS	Corticobasal syndrome (1 movement disorder sign and 1 cortical sign)
PSP-speech/language disorder	PSP-SL	Progressive apraxia of speech and/or nonfluent/agrammatic primary progressive aphasia
PSP-primary lateral sclerosis[a]	PSP-PLS	Primary lateral sclerosis
PSP-cerebellar ataxia[a]	PSP-C	Cerebellar ataxia as initial and predominant symptom

PSP: progressive supranuclear palsy

[a] These phenotypes not included in new diagnostic criteria as specificity for PSP is low

clinical phenotypes (Table 1) and assessment of the likelihood of underlying PSP pathology [4••, 6•].

Diagnostic Criteria

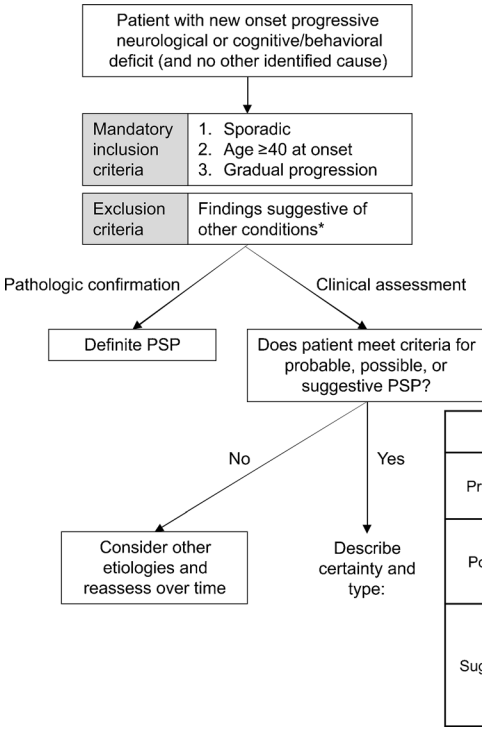
The International Parkinson and Movement Disorder Society (MDS) PSP study group published the MDS-PSP criteria in 2017 [4••] in appreciation of the spectrum of clinical phenotypes associated with PSP pathology. Until publication of these new criteria, the clinical criteria from the National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) were the most widely used criteria for in-life PSP diagnosis [7]. The NINDS-SPSP criteria require a vertical supranuclear gaze palsy and prominent postural instability with falls in the first year of disease onset for diagnosis of probable PSP. For possible PSP, either a vertical supranuclear gaze palsy or slowed vertical saccades plus postural instability with first-year falls are required. Supportive criteria include proximal more than distal symmetric akinesia or rigidity, abnormal neck posturing (particularly retrocollis), poor levodopa responsiveness, early dysphagia and/or dysarthria, and early onset of specific cognitive behavioral features [7].

Both the "probable" and "possible" categories in the NINDS-SPSP criteria have high specificity for PSP pathology [4••]. However, the NINDS-SPSP criteria describe the clinical PSP phenotype subsequently coined PSP-RS [8], which accounts for only a fraction of PSP neuropathologic diagnoses, ranging from 24% in one series [9] to 54% in another [8]. This corresponds to low sensitivity [4••] and, commonly, 3–4 years between disease onset and diagnosis [10].

The MDS-PSP criteria aim to reflect the PSP cliniconeuropathological advances achieved in the 20 years since publication of the NINDS-SPSP criteria and by doing so to optimize early diagnosis with both improved sensitivity and specify [4••]. The MDS-PSP study group developed the new criteria through a systematic review of the literature [6•, 11•], compilation of a large autopsy-confirmed PSP case series [6•], and expert consensus using modified Delphi techniques [4••].

Under the new criteria, a clinical diagnosis of PSP should be entertained in individuals 40 years old or older with gradual onset and progression of a neurologic phenotype that can be associated with PSP (Table 1) and which is occurring in a sporadic manner. Exclusion criteria are divided into (1) mandatory exclusion criteria and (2) context-specific exclusion criteria which need to be verified only if there are findings suggestive of an alternate diagnosis. Mandatory exclusion criteria reflect features that are more suggestive of other diagnoses, i.e., predominant episodic memory impairments, autonomic features, unexplained visual hallucinations, fluctuations in alertness, appendicular ataxia, multi-segmental upper and lower motor neuron signs, sudden onset, stepwise or rapid progression, identifiable causes of postural instability, a history of encephalitis, and/or imaging showing either severe leukoencephalopathy or relevant structural abnormalities. Context-specific exclusion criteria include imaging, laboratory, and genetic findings more consistent with diagnoses that may mimic PSP (e.g., prion disease, inherited disorders) [4••]. Even with a supranuclear gaze palsy, consideration of alternate diagnoses is important as a supranuclear gaze palsy is a neuroanatomic localizing feature not specific to PSP [12, 13].

Application of the MDS-PSP criteria (Fig. 1) requires assessment of core clinical features associated with varying levels of certainty or predictive value for PSP pathology (Table 2). Core features are categorized within four functional domains: ocular motor dysfunction, postural instability within 3 years, akinesia, and cognitive dysfunction (Table 2). Additional supportive clinical features are levodopa resistance, a hypokinetic, spastic dysarthria, dysphagia, and photophobia [4••]. Supportive imaging



Predominance Type

	PSP-RS	PSP-PGF	PSP-P	PSP-F	PSP-OM	PSP-SL	PSP-CBS	PSP-PI
Probable	(O1 or O2) + (P1 or P2)	(O1 or O2) + A1	(O1 or O2) + (A2 or A3)	(O1 or O2) + C2				
Possible	O2 + P3	A1			O1	(O1 or O2) + C1	(O1 or O2) + C3	
						Probable 4R-tauopathy		
Suggestive	O3 + (P2 or P3)		(A2 or A3) + (O3, P1, P2, C1, C2, CC1**, CC2, CC3, or CC4)	C2 + (O3 or P3)	O2 or O3	C1	C3	P1 or P2

Fig. 1 Application of MDS-PSP criteria. *MDS* International Parkinson and Movement Disorder Society, *PSP* progressive supranuclear palsy, *PSP-RS PSP*-Richardson's syndrome, *PSP-PGF PSP*-progressive gait freezing, *PSP-P PSP*-parkinsonism, *PSP-F PSP*-frontal, *PSP-OM PSP*-ocular motor, *PSP-SL PSP*-speech/language disorder, *PSP-CBS PSP*-corticobasal syndrome, *PSP-PI PSP*-postural instability. *Exclusion criteria are divided into mandatory exclusion criteria and context-specific exclusion criteria which need to be verified only if there are findings suggestive of an alternate diagnosis (see text). **CC1, CC2, CC3, and CC4 describe supportive clinical clues: CC1 levodopa resistance, CC2 hypokinetic, spastic dysarthria, CC3 dysphagia, CC4 photophobia

findings (see section below)—either (1) predominant midbrain atrophy or hypometabolism or (2) postsynaptic striatal dopaminergic degeneration—allow the added label of "imaging supported diagnosis" [4••]. Each core feature, clinical clue, and imaging finding has a specific definition described in the criteria [4••]. Clinical application of the MDS-PSP criteria results in both a "predominance type" (phenotype) and an assessment of certainty (probable, possible, suggestive), with differing phenotypes associated with different levels of certainty (Fig. 1). Individuals with possible PSP-corticobasal syndrome (PSP-CBS) or PSP-speech/language disorder (PSP-SL) also qualify for a diagnosis of "probable 4R tauopathy" (Fig. 1).

Table 2 MDS-PSP criteria core clinical features

Functional domain	Lower certainty (Level 3)	(Level 2)	Higher certainty (Level 1)
Ocular motor dysfunction	O3: Frequent macro square wave jerks or eyelid opening apraxia	O2: Slow velocity of vertical saccades	O1: Vertical supranuclear gaze palsy
Postural instability (within 3 years)	P3: Pull-test with >2 steps backward	P2: Tendency to fall on the pull-test	P1: Repeated unprovoked falls
Akinesia	A3: Parkinsonism (with tremor +/- asymmetry +/- levodopa responsiveness)	A2: Levodopa-resistant, predominantly axial akinetic-rigid parkinsonism	A1: Progressive freezing of gait within 3 years
Cognitive dysfunction	C3: Corticobasal syndrome	C2: Frontal cognitive/ behavioral presentation	C1: Speech/ language disorder (naPPA or progressive AoS)

naPPA nonfluent/agrammatic variant of primary progressive aphasia, *AoS* apraxia of speech

Diagnostic Testing

Neuroimaging markers are the most widely studied diagnostic modalities in individuals with, or suspected to have, PSP. To date, however, most neuroimaging in PSP focuses on individuals with the PSP-RS phenotype.

As part of the effort developing the MDS-PSP criteria, working group members performed a systematic review of the diagnostic utility of neuroimaging for improving the diagnosis of PSP [11•]. Neuroimaging studies were classified using a five-tier framework: (1) research tool, (2) supportive of clinical diagnosis, (3) supportive of early clinical diagnosis, (4) supportive of pathologic diagnosis, and (5) definitive biomarker of actual pathology. No neuroimaging biomarkers were classifiable as level 4 or 5 for either PSP-RS or other phenotypes [11•].

Magnetic resonance imaging (MRI) markers, [18F] fluorodeoxyglucose positron emission tomography (FDG-PET), and dopamine-based imaging have the most supportive evidence for use in individuals with PSP-RS. Certain findings using these modalities and tau-based imaging have lesser degrees of supportive evidence [11•].

Corresponding to the midbrain pathology in PSP-RS, structural MRI in this PSP phenotype commonly shows midbrain atrophy. This can result in characteristic MRI findings including the "hummingbird" [14] or "penguin silhouette" [15] signs on midsagittal MRI and the "morning glory" [16] or "Mickey Mouse" [17] signs on axial MRI. However, the presence of these signs can be influenced by factors during imaging acquisition [18–20], and clinical experience suggests that these signs may be over-described, particularly by untrained physicians. Quantitative midbrain measurements are more helpful in distinguishing PSP-RS from Parkinson's disease (PD) and multiple system atrophy (MSA). These include measures of midbrain area and midbrain-pons area ratio and the recently described magnetic resonance parkinsonism index (MRPI) [11•]. The MRPI, an index which incorporates the ratio of middle cerebellar peduncle (MCP) and superior cerebellar peduncle (SCP) width in addition to the midbrain-pons area ratio [21], is also the only biomarker identified by the recent systematic review as clinically useful in non-PSP-RS phenotypes, specifically PSP-P [11•]. Whether midbrain findings add substantially to diagnosis in individuals with a PSP-RS phenotype remains uncertain, but evidence of predominant midbrain atrophy may increase diagnostic confidence, supporting the label of "imaging supported diagnosis" in the MDS-PSP criteria [4••].

Other structural MRI features can also be seen in individuals with PSP, including atrophy of the frontal lobes and various subcortical structures including the thalamus, subthalamus, caudate, putamen, and globus pallidus [11•]. Quantitative measurements are generally superior to visual assessments of atrophy [11•]. While there is some evidence to suggest that frontal atrophy may distinguish PSP-RS from PD and MSA-Parkinson type (MSA-P), the diagnostic utility of atrophy patterns, apart from midbrain regions, remains uncertain.

Additional promising MRI-based approaches include use of diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) measurements to assess microstructural damage of gray and white matter structures in PSP and diffusion tensor imaging (DTI) to assess white matter tract degeneration [11•]. Quantitative annualized MRI volume changes may be useful as a clinical trial endpoint [22] but are not currently used for diagnosis or clinical management.

MRI is also used as a tool to help exclude PSP from structural neurological conditions. In clinical presentations with rapid progression, MRI should be used to investigate for the possibility of prion disease. For individuals with acute onset or stepwise progression, MRI is important for evaluating for strokes or hemorrhage that could suggest cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), strokes of other etiologies, or severe cerebral amyloid angiopathy [4••] that may mimic PSP phenoytpes.

Other currently available imaging modalities that can be of diagnostic utility in PSP include FDG-PET and dopamine-based imaging. On FDG-PET, frontal and midbrain hypometabolism are commonly seen in patients with PSP-RS and may be helpful in supporting consideration of PSP in other presenting phenotypes [11•]. In the MDS-PSP criteria, demonstration of predominant midbrain hypometabolism is sufficient to qualify for an "imaging supported diagnosis" label [4••].

Dopamine imaging includes measures of striatal presynaptic dopamine binding (dopamine transporter [DaT] imaging using [^{123}I]-FP-CIT SPECT or [^{18}F]-FP-CIT-PET) and postsynaptic dopaminergic function (e.g., [^{123}I]-IZBM SPECT or [^{18}F]-DMFP-PET, not available in some countries including the USA). Reduced striatal DaT binding is highly sensitive for PSP-RS but is also present in other parkinsonian disorders (PD, MSA-P, and CBS), and there is no difference in binding between diagnoses [11•]. Thus, reduced striatal DaT binding is consistent with PSP but cannot distinguish between parkinsonisms, and its utility is described as supportive of a PSP clinical diagnosis but "sensitive only" [11•]. Postsynaptic dopamine dysfunction is also common in PSP-RS but of unclear value in distinguishing between alternate parkinsonisms [11•]. In the MDS-PSP criteria, demonstration of postsynaptic striatal dopaminergic degeneration on imaging is felt to increase confidence enough to quality for the "imaging supported diagnosis" label [4••].

While not currently clinically available, in vivo tau PET imaging is an area of active research pursuing in-life evidence of PSP pathologic changes. Numerous publications in the last year alone report on use of tau imaging in

individuals with or suspected to have PSP [23–30], some of which have neuropathologic correlation [23–25]. Studies enrolling patients with clinical diagnoses of PSP are mixed on the diagnostic potential of ^{18}F-AV-1451/^{18}F-flortaucipir binding in PSP [27–30], reflecting both its potential and its limitations. Neuropathologic studies suggest that the ^{18}F-AV-1451 tracer has less affinity for tau aggregation in PSP compared to its stronger binding to the tau filaments comprising NFTs and the dystrophic neurites seen in Alzheimer-related tau pathology, relating to different tau isoforms, phosphorylation, and aggregation patterns in different pathologies [23, 24]. The ^{18}F-THK-5351 tracer is less studied in PSP, with only one study including three patients with clinically probable PSP. This study showed significantly higher ^{8}F-THK-5351 retention in the midbrain and globus pallidus of the individuals with probable PSP compared to healthy controls and patients with Alzheimer's disease (AD) [26]. However, there are similarities in these two tau tracers, and both have limitations including off-target binding, inconsistency between types of validation studies (ex vivo versus in vivo), and limited ligand specificity for 4R tau [11•, 31]. More work is needed before there is a clinical role for tau imaging in diagnosing PSP.

There is currently no role for non-imaging biomarkers in diagnosing PSP in the clinical setting. Existing studies of potential cerebrospinal fluid (CSF) [32–38] and serum [37, 39, 40] biomarkers lack pathologic correlation, but neurofilament light chain concentrations in the CSF and blood show promise as a potential biomarker [32, 35, 36, 39, 40]. In certain clinical situations, blood or CSF studies may be used to exclude diagnoses that can mimic PSP presentations (e.g., AD [in patients with PSP-CBS], Wilson's disease, Neimann-Pick disease type C, hypoparathyroidism, neuroacanthocytosis, neurosyphilis, Whipple's disease, prion disease, paraneoplastic encephalitis), particularly in individuals with young onset symptoms [4••].

Currently, genetic studies do not play a role in diagnosing PSP. PSP is considered a sporadic disease under the new criteria, though it is recognized that patients with mutations in the microtubule-associated protein tau (*MAPT*) may have presentations similar to those of PSP [4••]. In the MDS-PSP criteria, *MAPT* mutations are described under the context-specific exclusion criteria as defining inherited rather than sporadic PSP [4••]. Even in the absence of identified causative mutations, *MAPT*-specific polymorphisms and haplotypes increase the risk of PSP [41] and the link to the *MAPT* H1 haplotype is so strong that *MAPT* H2 haplotype homozygosity makes the diagnosis of PSP unlikely [4••]. Other loci, such as myelin-associated oligodendrocyte basic protein (*MOBP*), are also associated with PSP and CBD, both 4R tauopathies [41, 42], but currently, there is no role for routine genetic testing in PSP. Certain identified gene variants are exclusion criteria for PSP given neuropathological differences (e.g., *C9orf72*, *GBA*, *NPC1* or *2*, *PRNP*), but such testing is only performed when there are suggestive historical or exam features [4••].

Clinical Course

Many natural history studies focus on the PSP-RS presentation and may or may not include pathologic confirmation. One series of 100 pathologically confirmed PSP cases included patients with PSP-RS, PSP-P, PSP-postural instability (PSP-PI), PSP-ocular motor (PSP-OM), PSP-CBS, PSP-frontotemporal dementia (PSP-FTD), and unclassified phenotypes [9]. Mean disease duration (± SEM) for all phenotypes was 8.7 (0.4) years with a range from 2 to 28 years. Individuals with the PSP-RS phenotype had the shortest mean disease duration (7.3 ± 0.6, range 4–17 years), and individuals with the PSP-P phenotype had the longest disease duration (12.8 ± 1.5, range 4–28 years) [9]. It is likely that individuals with the PSP-progressive gait freezing (PSP-PGF) also have a long disease duration, with a pathologic case series describing a mean disease duration of 13 years (range 5–21 years) [43] and case reports describing disease durations of 6, 13, and 15 years [44, 45]. Predictors of shorter survival in PSP—derived from cohorts of individuals with pathologically proven PSP or in-life PSP-RS diagnoses using prior PSP diagnostic criteria—include the PSP-RS phenotype (versus PSP-P) and early dysphagia, cognitive symptoms, or falls [46]. A natural history study of individuals with PSP-RS identified pneumonia as the most common cause of death [47], and this is likely still accurate, with pneumonia and sepsis described as the most common causes of death listed on death certificates for individuals with advanced parkinsonism [48]. Future studies using the MDS-PSP criteria phenotypes will inform the natural history of the different subtypes and assist in counseling patients and families regarding expected progression.

Treatment Approaches

Treatment for individuals suspected to have PSP remains symptomatic and supportive, with ongoing clinical trials striving to identify disease-modifying therapies often targeting the underlying tau pathology.

For motor (parkinsonian) symptoms, levodopa combined with a dopa decarboxylase inhibitor (e.g., carbidopa) is generally tried, with typically modest to no success in most PSP phenotypes but potential benefit in the PSP-P predominance type. Levodopa responsiveness is no longer an exclusion criterion for PSP but is associated with a lower level of certainty in the MDS-PSP criteria (A3, Table 2). Overall, evidence for mild to moderate benefits with levodopa is low [49], but given limited therapeutic options, levodopa is generally tried at doses of up to 1000 mg daily. Other

dopaminergic agents are rarely of benefit; amantadine is sometimes tried with limited supportive evidence [49]. Botulinum toxin injections can be used for focal dystonias including apraxia of eyelid opening [49].

The potential value of physical therapy is of increasing interest particularly given evidence of benefit for individuals with PD, and a recent trial showed improvement in the Progressive Supranuclear Palsy Rating Scale (PSPRS) [50] in patients with PSP-RS treated with two different therapy approaches, though there was no difference between groups [51]. A non-randomized pre-post study also suggested potential benefit of the Lee Silverman Voice Treatment in individuals with PSP, though benefits in PSP were less frequently significant than those observed in PD patients [52].

While case reports and series suggest promising experiences with unilateral or bilateral pedunculopontine nucleus (PPN) deep brain stimulation (DBS) in patients with suspected PSP, a recently published randomized controlled trial of unilateral PPN DBS in eight individuals with PSP-RS showed no benefit in gait, postural stability, and fall PSPRS subitems when comparing ON and OFF stimulation conditions at 6- and 12-month follow-up. Three of the enrolled subjects experienced surgical complications [53]. DBS is currently not recommended for PSP outside of research settings [49].

There are no accepted treatments for cognitive symptoms in individuals with suspected PSP, with small trials and case series of cholinesterase inhibitors suggesting that these drugs may help cognition but worsen motor function [49]. It is critical to address potentially treatable symptoms in PSP such as depression, but no PSP-specific recommendations for such symptomatic management exist.

To date, studies of potentially disease-modifying therapies have failed to demonstrate efficacy in individuals suspected to have PSP. Randomized, placebo-controlled trials of riluzole [54], davunetide [36], tideglusib [55], high-dose coenzyme Q10 [56], sodium valproate [57], and rasagiline [58] showed no impact on primary endpoints tracking disease progression, though study limitations include sample size (for some studies) and lack of evidence that the agents had the intended effect through theorized mechanisms. Current investigations of tau-focused PSP therapies include TPI-287, a microtubule stabilizer, C2N-8E12/ABBV-8E12 and BMS-986168/BIIB092, both anti-tau monoclonal antibodies, and salsalate, a tau acetylation inhibitor (Table 3). Microtubule stabilizers are hoped to compensate for microtubule dysfunction associated with loss of tau function; anti-tau monoclonal antibodies are hoped to impede the spread of pathogenic tau, and tau acetylation inhibitors are hoped to inhibit acetylation of soluble tau and thus limit hyperphosphorylation.

Regardless of investigational and symptomatic treatment approaches used through the disease course, palliative care is an important component of PSP treatment with hospice as a valuable resource in late stages [59].

Table 3 Active PSP tau-based clinical trials on Clinicaltrials.gov

Agent (mechanism)	NCT number (phase)	Status	Estimated enrollment	Population enrolled[a]	Primary outcome measure
TPI-287 (microtubule stabilizer)	NCT02133846 (Phase 1)	Active, not recruiting	44	- NINDS-SPSP probable or possible criteria as modified for the NNIPPS clinical trial - Possible or probable CBD, CBS subtype	Maximum tolerated dose; safety and tolerability
C2N-8E12/ABBV-8E12 (anti-tau monoclonal antibody)	NCT02494024 (Phase 1)	Completed	32	- NINDS-SPSP possible or probable criteria as modified for the NNIPPS and AL-108-231 clinical trials	Safety and tolerability
	NCT02985879 (Phase 2)	Recruiting	180	- Possible or probable PSPRS - Symptoms < 5 years - Able to walk 5 steps with minimal assistance	Change in PSPRS total score from baseline to week 52; adverse events
BMS-986168/BIIB092 (anti-tau monoclonal antibodies)	NCT02460094 (Phase 1)	Completed	48	- Possible or probable PSP as defined by study (consistent with PSPRS)	Safety and tolerability
	NCT03068468 (Phase 2)	Recruiting	396	- Possible or probable PSP - Able to walk independently or with assistance	Change in PSPRS total score from baseline to week 52; adverse events
Salsalate (tau acetylation inhibitor)	NCT02422485 (Phase 1, open label pilot futility trial)	Recruiting	10	NINDS-SPSP probable or possible PSP criteria as modified from the AL-108-231 trial	Number of patients experiencing drug-limiting toxicity

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NINDS-SPSP National Institute of Neurological Disorders and Stroke-Society for Progressive Supranuclear Palsy, *NNIPPS* Neuroprotection and Natural History in Parkinson Plus Syndromes, *CBD* corticobasal degeneration, *CBS* corticobasal syndrome, *PSP-RS*, Progressive Supranuclear Palsy - Richardson's Syndrome *PSPRS* Progressive Supranuclear Palsy Rating Scale

[a] Each study has additional inclusion/exclusion criteria; see clinicaltrials.gov for full details

Conclusions

The publication of new PSP diagnostic criteria incorporating the range of presenting phenotypes has important implications for how clinicians and researchers diagnose and study this disease. These criteria will allow earlier diagnosis of phenotypes other than PSP-RS, but more work is needed to understand how diagnostic evaluations may help assessment of these phenotypes and to identify their expected progression. Diagnosis remains largely based on clinical history and examination, but structural brain MRI, FDG-PET, and dopamine imaging findings can increase certainty. Current treatment approaches are symptomatic and palliative, but the many tau-based therapeutics in active clinical trials provide patients with PSP with both research opportunities and hope.

Compliance with Ethical Standards

Conflict of Interest Melissa J. Armstrong declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar plasy, nuchal dystonia and dementia. Arch Neurol. 1964;10(4):333–58. https://doi.org/10.1001/archneur.1964.00460160003001.
2. Litvan I, Hauw JJ, Bartko JJ, Lantos PL, Daniel SE, Horoupian DS, et al. Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. Jf Neuropathol Exp Neurol. 1996;55(1):97–105. https://doi.org/10.1097/00005072-199601000-00010.
3. Hauw JJ, Daniel SE, Dickson D, Horoupian DS, Jellinger K, Lantos PL, et al. Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology. 1994;44(11):2015–9. https://doi.org/10.1212/WNL.44.11.2015.
4.•• Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical diagnosis of progressive supranuclear palsy: the Movement Disorder Society criteria. Mov Disord. 2017;32(6):853–64. https://doi.org/10.1002/mds.26987. **This publication describes the new PSP clinical diagnostic criteria incorporating the common presenting phenotypes**.
5. Dickson DW, Ahmed Z, Algom AA, Tsuboi Y, Josephas KA. Neuropathology of variants of progressive supranuclear palsy. Curr Opin Neurol. 2010;23(4):394–400. https://doi.org/10.1097/WCO.0b013e32833be924.
6.• Respondek G, Kurz C, Arzberger T, Compta Y, Englund E, Ferguson LW, et al. Which ante mortem clinical features predict progressive supranuclear palsy pathology? Mov Disord. 2017;32(7):995–1005. https://doi.org/10.1002/mds.27034. **This systematic review identifies the phenotypes associated with the pathologic diagnosis of PSP**.
7. Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology. 1996;47(1):1–9. https://doi.org/10.1212/WNL.47.1.1.
8. Williams DR, de Silva R, Paviour DC, Pittman A, Watt HC, Kilford L, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain. 2005;128(6):1247–58. https://doi.org/10.1093/brain/awh488.
9. Respondek G, Stamelou M, Kurz C, Ferguson LW, Rajput A, Chiu WZ, et al. The phenotypic spectrum of progressive supranuclear palsy: a retrospective multicenter study of 100 definite cases. Mov Disord. 2014;29(14):1758–66. https://doi.org/10.1002/mds.26054.
10. Respondek G, Roeber S, Kretzschmar H, Troakes C, Al-Sarraj S, Gelpi E, et al. Accuracy of the National Institute for Neurological Disorders and Stroke/Society for Progressive Supranuclear Palsy and neuroprotection and natural history in Parkinson plus syndromes criteria for the diagnosis of progressive supranuclear palsy. Mov Disord. 2013;28(4):504–9. https://doi.org/10.1002/mds.25327.
11.• Whitwell JL, Höglinger GU, Antonini A, Bordelon Y, Boxer AL, Colosimo C, et al. Radiological biomarkers for diagnosis in PSP: where are we and where do we need to be? Mov Disord. 2017;32(7):955–71. https://doi.org/10.1002/mds.27038. **This systematic review addresses current knowledge regarding diagnostic imaging in PSP**.
12. Martin WRW, Hartlein J, Racette BA, Cairns N, Perlmutter JS. Pathologic correlates of supranuclear gaze palsy with parkinsonism. Parkinsonism Relat Disord. 2017;38:68–71. https://doi.org/10.1016/j.parkreldis.2017.02.027.
13. Lloyd-Smith Sequeira A, Rizzo JR, Rucker JC. Clinical approach to supranuclear brainstem saccadic gaze palsies. Front Neurol. 2017;8:429. https://doi.org/10.3389/fneur.2017.00429.
14. Kato N, Arai K, Hattori T. Study of the rostral midbrain atrophy in progressive supranuclear palsy. J Neurol Sci. 2003;210(1-2):57–60. https://doi.org/10.1016/S0022-510X(03)00014-5.
15. Oba H, Yagishita A, Terada H, Barkovich AJ, Kutomi K, Yamauchi T, et al. New and reliable MRI diagnosis for progressive supranuclear palsy. Neurology. 2005;64(12):2050–5. https://doi.org/10.1212/01.WNL.0000165960.04422.D0.
16. Adachi M, Kawanami T, Ohshima H, Sugai Y, Hosoya T. Morning glory sign: a particular MR finding in progressive supranuclear palsy. Magn Reson Med Sci. 2004;3(3):125–32. https://doi.org/10.2463/mrms.3.125.
17. Massey LA, Micallef C, Paviour DC, O'Sullivan SS, Ling H, Williams DR, et al. Conventional magnetic resonance imaging in confirmed progressive supranuclear palsy and multiple system atrophy. Mov Disord. 2012;27(14):1754–62. https://doi.org/10.1002/mds.24968.
18. Adachi M, Kawanami T, Ohshima F. The "morning glory sign" should be evaluated using thinly sliced axial images. Magn Reson Med Sci. 2007;6(1):59–60. https://doi.org/10.2463/mrms.6.59.
19. Mori H, Aoki S, Ohtomo K. The "morning glory sign" may lead to false impression according to slice angle. Magn Reson Med Sci. 2007;6(3):183–4; author reply 185. https://doi.org/10.2463/mrms.6.183.
20. Gröschel K, Kastrup A, Litvan I, Schulz JB. Penguins and hummingbirds: midbrain atrophy in progressive supranuclear palsy. Neurology. 2006;66(6):949–50. https://doi.org/10.1212/01.wnl.0000203342.77115.bf.

21. Quattrone A, Nicoletti G, Messina D, Fera F, Condino F, Pugliese P, et al. MR imaging index for differentiation of progressive supranuclear palsy from Parkinson disease and the Parkinson variant of multiple system atrophy. Radiology. 2008;246(1):214–21. https://doi.org/10.1148/radiol.2453061703.
22. Höglinger GU, Schöpe J, Stamelou M, Kassubek J, Del Ser T, Boxer AL, et al. Longitudinal magnetic resonance imaging in progressive supranuclear palsy: a new combined score for clinical trials. Mov Disord. 2017;32(6):842–52. https://doi.org/10.1002/mds.26973.
23. Marquié M, Normandin MD, Meltzer AC, Siao Tick Chong M, Andrea NV, Antón-Fernández A, et al. Pathological correlations of [F-18]-AV-1451 imaging in non-alzheimer tauopathies. Ann Neurol. 2017;81(1):117–28. https://doi.org/10.1002/ana.24844.
24. Passamonti L, Vázquez Rodríguez P, Hong YT, Allinson KS, Williamson D, Borchert RJ, et al. 18F-AV-1451 positron emission tomography in Alzheimer's disease and progressive supranuclear palsy. Brain. 2017;140:781–91. https://doi.org/10.1093/brain/aww340.
25. Smith R, Schöll M, Honer M, Nilsson CF, Englund E, Hansson O. Tau neuropathology correlates with FDG-PET, but not AV-1451-PET, in progressive supranuclear palsy. Acta Neuropathol. 2017;133(1):149–51. https://doi.org/10.1007/s00401-016-1650-1.
26. Ishiki A, Harada R, Okamura N, Tomita N, Rowe CC, Villemagne VL. Tau imaging with [18 F]THK-5351 in progressive supranuclear palsy. Eur J Neurol. 2017;24(1):130–6. https://doi.org/10.1111/ene.13164.
27. Whitwell JL, Lowe VJ, Tosakulwong N, Weigand SD, Senjem ML, Schwarz CG, et al. [18 F]AV-1451 tau positron emission tomography in progressive supranuclear palsy. Mov Disord. 2017;32(1):124–33. https://doi.org/10.1002/mds.26834.
28. Coakeley S, Cho SS, Koshimori Y, Rusjan P, Harris M, Ghadery C, et al. Positron emission tomography imaging of tau pathology in progressive supranuclear palsy. J Cereb Blood Flow Metab. 2017;37(9):3150–60. https://doi.org/10.1177/0271678X16683695.
29. Cho H, Choi JY, Hwang MS, Lee SH, Ryu YH, Lee MS, et al. Subcortical 18 F-AV-1451 binding patterns in progressive supranuclear palsy. Mov Disord. 2017;32(1):134–40. https://doi.org/10.1002/mds.26844.
30. Schonhaut DR, McMillan CT, Spina S, Dickerson BC, Siderowf A, Devous MD Sr, et al. 18 F-flortaucipir tau positron emission tomography distinguishes established progressive supranuclear palsy from controls and Parkinson disease: a multicenter study. Ann Neurol. 2017;82(4):622–34. https://doi.org/10.1002/ana.25060.
31. Perez-Soriano A, Stoessl AJ. Tau imaging in progressive supranuclear palsy. Mov Disord. 2017;32(1):91–3. https://doi.org/10.1002/mds.26851.
32. Magdalinou NK, Paterson RW, Schott JM, Fox NC, Mummery C, Blennow K, et al. A panel of nine cerebrospinal fluid biomarkers may identify patients with atypical parkinsonian syndromes. J Neurol Neurosurg Psychiatry. 2015;86(11):1240–7. https://doi.org/10.1136/jnnp-2014-309562.
33. Wagshal D, Sankaranarayanan S, Guss V, Hall T, Berisha F, Lobach I, et al. Divergent CSF tau alterations in two common tauopathies: Alzheimer's disease and progressive supranuclear palsy. J Neurol Neurosurg Psychiatry. 2015;86(3):244–50. https://doi.org/10.1136/jnnp-2014-308004.
34. Hall S, Öhrfelt A, Constantinescu R, Andreasson U, Surova Y, Bostrom F, et al. Accuracy of a panel of 5 cerebrospinal fluid biomarkers in the differential diagnosis of patients with dementia and/or parkinsonian disorders. Arch Neurol. 2012;69(11):1445–52. https://doi.org/10.1001/archneurol.2012.1654.
35. Scherling CS, Hall T, Berisha F, Klepac K, Karydas A, Coppola G, et al. Cerebrospinal fluid neurofilament concentration reflects disease severity in frontotemporal degeneration. Ann Neurol. 2014;75(1):116–26. https://doi.org/10.1002/ana.24052.
36. Boxer AL, Lang AE, Grossman M, Knopman DS, Miller BL, Schneider LS, et al. Davunetide in patients with progressive supranuclear palsy: a randomised, double-blind, placebo-controlled phase 2/3 trial. Lancet Neurol. 2014;13(7):676–85. https://doi.org/10.1016/S1474-4422(14)70088-2.
37. Bacioglu M, Maia LF, Preische O, Schelle J, Apel A, Kaeser SA, et al. Neurofilament light chain in blood and CSF as marker of disease progression in mouse models and in neurodegenerative diseases. Neuron. 2016;91(2):494–6. https://doi.org/10.1016/j.neuron.2016.07.007.
38. Boman A, Svensson S, Boxer A, Rojas JC, Seeley WW, Karydas A, et al. Distinct lysosomal network protein profiles in parkinsonian syndrome cerebrospinal fluid. J Parkinsons Dis. 2016;6(2):307–15. https://doi.org/10.3233/JPD-150759.
39. Hansson O, Janelidze S, Hall S, Magdalinou N, Lees AJ, Andreasson U, et al. Blood-based NfL: a biomarker for differential diagnosis of parkinsonian disorder. Neurology. 2017;88(10):930–7. https://doi.org/10.1212/WNL.0000000000003680.
40. Rojas JC, Karydas A, Bang J, Tsai RM, Blennow K, Liman V, et al. Plasma neurofilament light chain predicts progression in progressive supranuclear palsy. Ann Clin Transl Neurol. 2016;3(3):216–25. https://doi.org/10.1002/acn3.290.
41. Höglinger GU, Melhem NM, Dickson DW, Sleiman PM, Wang LS, Klei L, et al. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat Genet. 2011;43(7):699–705. https://doi.org/10.1038/ng.859.
42. Kouri N, Ross OA, Dombroski B, Younkin CS, Serie DJ, Soto-Ortolaza A, et al. Genome-wide association study of corticobasal degeneration identifies risk variants shared with progressive supranuclear palsy. Nat Commun. 2015;6(1):7247. https://doi.org/10.1038/ncomms8247.
43. Williams DR, Holton JL, Strand K, Revesz T, Lees AJ. Pure akinesia with gait freezing: a third clinical phenotype of progressive supranuclear palsy. Mov Disord. 2007;22(15):2235–41. https://doi.org/10.1002/mds.21698.
44. Compta Y, Valldeoriola F, Tolosa E, Rey MJ, Martí MJ, Valls-Solé J. Long lasting pure freezing of gait preceding progressive supranuclear palsy: a clinicopathological study. Mov Disord. 2007;22(13):1954–8. https://doi.org/10.1002/mds.21612.
45. Facheris MF, Maniak S, Scaravilli F, Schüle B, Klein C, Pramstaller PP. Pure akinesia as initial presentation of PSP: a clinicopathological study. Parkinsonism Relat Disord. 2008;14(6):517–9. https://doi.org/10.1016/j.parkreldis.2007.11.004.
46. Glasmacher SA, Leigh PN, Saha RA. Predictors of survival in progressive supranuclear palsy and multiple system atrophy: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2017;88(5):402–11. https://doi.org/10.1136/jnnp-2016-314956.
47. Litvan I, Mangone CA, McKee A, Verny M, Parsa A, Jellinger K, et al. Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study. J Neurol Neurosurg Psychiatry. 1996;60(6):615–20. https://doi.org/10.1136/jnnp.60.6.615.
48. Moscovich M, Boschetti G, Moro A, Teive HAG, Hassan A, Munhoz RP. Death certificate data and causes of death in patients with parkinsonism. Parkinsonism Relat Disord. 2017;41:99–103. https://doi.org/10.1016/j.parkreldis.2017.05.022.
49. Stamelou M, Höglinger G. A review of treatment options for progressive supranuclear palsy. CNS Drugs. 2016;30(7):629–36. https://doi.org/10.1007/s40263-016-0347-2.
50. Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. Brain. 2007;30:1552–65.
51. Clerici I, Ferrazzoli D, Maestri R, Bossio F, Zivi I, Canesi M, et al. Rehabilitation in progressive supranuclear palsy: effectiveness of two multidisciplinary treatments. PLoS One. 2017;12(2):e0170927. https://doi.org/10.1371/journal.pone.0170927.
52. Sale P, Castiglioni D, De Pandis MF, Torti M, Dall'armi V, Radicati FG, et al. The Lee Silverman Voice Treatment (LSVT ®) speech

therapy in progressive supranuclear palsy. Eur J Phys Rehabil Med. 2015;51(5):569–74.
53. Scelzo E, Lozano AM, Hamani C, Poon YY, Aldakheel A, Zadikoff C, et al. Peduncolopontine nucleus stimulation in progressive supranuclear palsy: a randomised trial. J Neurol Neurosurg Psychiatry. 2017;88(7):613–6. https://doi.org/10.1136/jnnp-2016-315192.
54. Bensimon G, Ludolph A, Agid Y, Vidailhet M, Payan C, Leigh PN, et al. Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study. Brain. 2009;132(1):156–71. https://doi.org/10.1093/brain/awn291.
55. Tolosa E, Litvan I, Höglinger GU, Burn D, Lees A, Andrés MV, et al. A phase 2 trial of the GSK-3 inhibitor tideglusib in progressive supranuclear palsy. Mov Disord. 2014;29(4):470–8. https://doi.org/10.1002/mds.25824.
56. Apetauerova D, Scala SA, Hamill RW, Simon DK, Pathak S, Ruthazer R, et al. CoQ10 in progressive supranuclear palsy: a randomized, placebo-controlled, double-blind trial. Neurol Neuroimmunol Neuroinflamm. 2016;3(5):e266. https://doi.org/10.1212/NXI.0000000000000266.
57. Leclair-Visonneau L, Rouaud T, Debilly B, Durif F, Houeto JL, Kreisler A, et al. Randomized placebo-controlled trial of sodium valproate in progressive supranuclear palsy. Clin Neurol Neurosurg. 2016;146:35–9. https://doi.org/10.1016/j.clineuro.2016.04.021.
58. Nuebling G, Hensler M, Paul S, Zwergal A, Crispin A, Lorenzl S. PROSPERA: a randomized, controlled trial evaluating rasagiline in progressive supranuclear palsy. J Neurol. 2016;263(8):1565–74. https://doi.org/10.1007/s00415-016-8169-1.
59. Wiblin L, Lee M, Burn D. Palliative care and its emerging role in multiple system atrophy and progressive supranuclear palsy. Parkinsonism Relat Disord. 2017;34:7–14. https://doi.org/10.1016/j.parkreldis.2016.10.013.