



Four-Repeat Tauopathies: Current Management and Future Treatments

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Abstract

Four-repeat tauopathies are a neurodegenerative disease characterized by brain parenchymal accumulation of a specific isoform of the protein tau, which gives rise to a wide breadth of clinical syndromes encompassing diverse symptomatology, with the most common syndromes being progressive supranuclear palsy-Richardson's and corticobasal syndrome. Despite the lack of effective disease-modifying therapies, targeted treatment of symptoms can improve quality of life for patients with 4-repeat tauopathies. However, managing these symptoms can be a daunting task, even for those familiar with the diseases, as they span motor, sensory, cognitive, affective, autonomic, and behavioral domains. This review describes current approaches to symptomatic management of common clinical symptoms in 4-repeat tauopathies with a focus on practical patient management, including pharmacologic and nonpharmacologic strategies, and concludes with a discussion of the history and future of disease-modifying therapeutics and clinical trials in this population.

Keywords 4R-tauopathy (4R-tau) · progressive supranuclear palsy (PSP) · Richardson's syndrome (PSP-RS) · corticobasal syndrome (CBS) · corticobasal degeneration (CBD) · atypical parkinsonism

Introduction

Aggregation of tau is the key pathologic feature in a range of neurodegenerative diseases, collectively termed tauopathies [1]. The term “tau” refers to the protein product of the microtubule-associated protein tau gene (*MAPT*), and the number of spliced copies of the microtubule binding repeat (MTBR) domain determines whether the tau is a 3-repeat (3R) or a 4-repeat (4R) isoform [2]. In the healthy adult brain, 3R-tau and 4R-tau are found in equal numbers, but pathological conditions may give rise to abnormal expression and aggregation of 4R-tau [3, 4]. As defined by neuropathology, 4R tauopathies are considered a subtype of frontotemporal lobar degeneration due to tau (FTLD-tau), and they are classified according to the morphologic appearance, histologic localization, and anatomical distribution of primarily 4R-tau aggregates into progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD),

globular glial tauopathy (GGT), and FTLD-tau due to *MAPT* mutation [5–7].

The accumulations of insoluble, predominantly 4R-tau protein tend to affect characteristic brain regions and follow a typical anatomical pattern of deposition and spread, leading to diverse but well-defined clinical syndromes (Table 1), with the most widely known being progressive supranuclear palsy-Richardson's syndrome (PSP-RS), marked by early falls because of postural instability and progressive ocular motor dysfunction, and corticobasal syndrome (CBS), defined by asymmetric motor features (e.g., akinesia, rigidity, dystonia, myoclonus) and higher cortical signs (e.g., apraxia, cortical sensory deficits, alien limb) [8, 9]. 4R-tauopathies, however, can also present clinically with parkinsonism similar to Parkinson's disease, pure akinesia with gait freezing (PAGF), primary lateral sclerosis (PLS), the nonfluent variant of primary progressive aphasia (nfvPPA), the behavioral variant of frontotemporal dementia (bvFTD), and an amnesic syndrome similar to Alzheimer's dementia [8–11]. In later stages of the disease, mixed features of many syndromes may be present.

The correlation of phenotypic clinical presentation and underlying neuropathological entity is challenging in 4R-

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Table 1 Histopathologic subtypes of 4R-tauopathy and presenting clinical phenotypes

4R-Tau pathology	Associated clinical syndromes
Progressive supranuclear palsy (PSP)	Progressive supranuclear palsy-Richardson's syndrome (PSP-RS), Corticobasal syndrome (CBS), Parkinsonism similar to Parkinson's disease, nonfluent variant of primary progressive aphasia (nfvPPA), behavioral variant of frontotemporal dementia (bvFTD), Primary akinesia with gait freezing (PAGF), Primary lateral sclerosis (PLS)
Corticobasal degeneration (CBD)	Corticobasal syndrome (CBS), Progressive supranuclear palsy-Richardson's syndrome (PSP-RS), Nonfluent variant of primary progressive aphasia (nfvPPA), Behavioral variant frontotemporal dementia (bvFTD), Amnesic syndrome similar to Alzheimer's dementia
Argyrophilic grain disease (AGD)	Amnesic syndrome similar to Alzheimer's dementia, Behavioral variant of frontotemporal dementia (bvFTD)
Globular glial tauopathy (GGT)	Wide variety of clinical phenotypes, commonly with behavioral symptoms, atypical parkinsonism, and/or motor neuron disease (full description still developing)

tauopathies. A given neuropathological entity can have heterogeneous clinical presentations, and it is often difficult to predict the underlying pathology based on the clinical syndrome. Differentiation between 4R-tau neuropathological subtypes prior to autopsy has proven elusive, not only because of the overlap of symptomatology within the 4R-tauopathies but also because of overlap with clinical syndromes caused by neuropathologic protein aggregates seen in other neurodegenerative diseases, such as Alzheimer's or TAR DNA binding protein 43 (TDP-43) proteinopathies. As an example, one clinicopathologic study found that less than half of cases with a clinical diagnosis of corticobasal syndrome were found to be due to 4R-tauopathy (35% CBD, 13% PSP), and underlying CBD *versus* PSP could not be reliably differentiated based on clinical features alone [12].

Nevertheless, the 2017 Movement Disorder Society PSP diagnostic criteria identified 4 functional domains commonly seen in PSP syndromes (oculomotor dysfunction, postural instability, akinesia, and cognitive dysfunction) that have been proposed as clinical predictors of underlying PSP pathology [9]. These criteria have a high specificity for predicting PSP pathology, especially in the presence of ocular motor dysfunction, but sensitivity is low in early stages of the illness [13]. Similarly, 5 clinical phenotypes account for over 85% of patients with CBD pathology, and 4 of them comprise proposed clinical diagnostic criteria for CBD [14]. Because clinical CBD syndromes extensively overlap with PSP syndromes, for the purpose of this review, we will consider 4R-tauopathies as one disease spectrum and discuss treatment without regard to specific diagnosis [15].

Despite ongoing efforts in clinical trials, there are no FDA-approved treatments that reverse, stop, or delay progression of 4R-tauopathies, and current management is focused on ameliorating symptoms, maintaining function, and maximizing quality of life. As the disease progresses, symptoms can arise in multiple domains, with motor features often prominent, and the many options that are available to manage these symptoms can easily be overlooked in the routine care of 4R-tauopathy patients (Table 2). Therefore, whereas several excellent comprehensive reviews of 4R-tauopathy are available [16–19], herein, we will focus on the practical clinical management of 4R-tauopathies for providers, including pharmacologic and nonpharmacologic approaches. Finally, we will conclude with a discussion of past and current clinical trial efforts to find novel disease-modifying therapeutics in this population with great unmet medical need.

Current Symptomatic Management

Motor Symptoms

Bradykinesia/Rigidity

In line with pathological evidence of neuronal loss in the substantia nigra [20], patients with 4R-tauopathy often show features of an akinetic and rigid parkinsonism, but the response to dopamine replacement is typically modest and short-lived, and a prominent and sustained response is exclusionary for a diagnosis of CBD [14, 21, 22]. However, phenotypes of PSP with predominant parkinsonism (PSP-P)

Table 2 Symptomatic management of 4R-tauopathy

Symptom	Pharmacologic management	Nonpharmacologic management
Motor symptoms		
Bradykinesia/rigidity	Levodopa (trial is recommended) Amantadine (second-line) Dopamine agonist (avoid)	Physical/occupational therapy referral
Dysphagia		Speech language pathologist referral Compensatory modifications Comfort feeding/PEG tube Occupational therapy referral
Dystonia	Botulinum toxin (first-line) GABA agonists (use with caution) Dopaminergic/anticholinergic agents (avoid)	Passive stretching Guided muscle relaxation Strengthen antagonist muscles Surgical consultation (severe cases)
Gait freezing	Levodopa (trial is recommended) Amantadine	Walker-mounted laser pointers Visual and rhythmic cues Arc turning
Hypophonia	Levodopa	Lee Silverman Voice Treatment (BIG) Personal voice amplifier
Imbalance/falls	Levodopa (trial is recommended) Vitamin D, calcium Bisphosphonates	Physical/occupational therapy referral Frequent exercise (treadmill) Multicomponent physical activity programs Assistive devices
Motor speech difficulty		Bone density screening Speech language pathologist referral MBS or FEES Augmentative and alternative communication devices
Myoclonus	Levetiracetam (use with caution) Clonazepam (use with caution) Piracetam, gabapentin, and valproic acid (no evidence for use)	
Pseudobulbar affect	Dextromethorphan–quinidine	Pocket education cards
Sialorrhea	Botulinum toxin (use with caution) Glycopyrrolate/scopolamine (avoid)	Speech language pathologist referral Occupational therapy referral
Tremor	Levodopa, amantadine (rest tremor) Botulinum toxin (severe dystonic tremor)	Adaptive devices (weighted silverware)
Visual impairment	Artificial tears (dry eyes) Botulinum toxin (blepharospasm, eyelid apraxia)	Neuro-ophthomology referral (prisms) Occupational therapy referral Eyelid crutches (poorly tolerated) Tinted glasses
Weight loss		High-calorie supplementation Favorite foods
Cognitive symptoms		
Executive dysfunction		Safety screen Occupational therapy referral Compensatory technology Cardiovascular exercise Heart-healthy diet Cognitive and social engagement
Aphasia		Address sleep or mood difficulty Speech language pathologist referral Audiology screen Augmentative and alternative communication devices

Table 2 (continued)

Symptom	Pharmacologic management	Nonpharmacologic management
Memory dysfunction	Acetylcholinesterase inhibitors (avoid if motor or behavioral problems) Memantine (avoid)	Compensatory communication techniques Compensatory technology Establishment of a routine Cardiovascular exercise Heart-healthy diet Cognitive and social engagement Address sleep or mood problems
Behavioral symptoms Problematic behaviors	SSRIs (avoid paroxetine)	DICE model of behavioral intervention Assess for untreated medical or psychiatric problems Address untreated pain Address sleep or mood problems Environmental modification Establishment of a routine/schedule Increase activity (physical activity and hobbies) Cognitive and social engagement Caregiver education and modeling Tailored activity plan Cognitive behavioral therapy (CBT) Mindfulness yoga Guided meditation
Anxiety/depression	SSRIs (avoid paroxetine) SNRI/bupropion (second-line) TCAs (typically not used) ECT (refractory cases) “Activating” antidepressants (e.g., SNRI)	Regular exercise Scheduled activities
Apathy/inertia	Methylphenidate (use with caution) Avoid SSRIs (may worsen apathy) SSRIs (e.g., citalopram) Antipsychotics (avoid if possible) Low-dose lithium (avoid if gait problems)	Music therapy Pet therapy Aromatherapy Massage/touch therapy See “ Problematic Behaviors ”
Other symptoms Insomnia/fatigue	Melatonin Suvorexant Trazodone (use with caution) Benzodiazepines (avoid if possible)	Regular physical exercise Sleep hygiene Screen for sleep disordered breathing Establish a routine Strategic napping Referral to urology
Urinary control	Mirabegron Antispasmodics (e.g., tolterodine, trospium, solifenacin, darifenacin) Anticholinergics (e.g., oxybutynin; avoid if possible) Botulinum toxin	Bladder training Pelvic floor exercises Electrical stimulation techniques
Constipation	Polyethylene glycol, senna, lactulose Bisacodyl suppository	Adult pads Increase fluid intake High-fiber diet Regular physical activity

may show a more measurable and sustained benefit from levodopa, and a cautious dose-escalation trial up to 800 to 1200 mg/day is recommended, both for diagnostic and therapeutic considerations, unless limited by other

symptomatology [18]. Sudden discontinuation of dopaminergic therapy should be avoided, but if side effects such as visual hallucinations, dystonia, or dyskinesias arise, cessation is recommended [23].

Amantadine is another therapeutic often employed to reduce bradykinesia, and although a clinical response is typically seen only in a fraction of cases [24], some authors report effects beyond reducing akinesia and rigidity and suggest improvement in alertness, motivation, and overall function [25, 26]. Dopamine receptor agonists are used less frequently given limited evidence for efficacy and the possibility of developing compulsive behaviors if frontostriatal involvement is present [27–29].

Early involvement of ancillary health fields such as physical therapy and occupational therapy is also recommended to preserve functional independence, and a randomized clinical trial provided strong evidence for this approach by demonstrating functional clinically meaningful improvements on the PSP rating scale using an intensive, aerobic, multidisciplinary, motor–cognitive, and goal-based rehabilitation program in 24 patients with PSP-RS [30].

Dysphagia

Aspiration pneumonia is the leading cause of death in PSP-RS [31], and progressive dysphagia is a key symptom leading to morbidity and mortality in 4R-tauopathies, which may be worsened if behavioral symptoms such as impulsive and rapid eating are present. Vigilance for swallowing symptoms is recommended even in early stages, and some authors recommend routine swallow evaluation every 6 months [18]. A measured approach to dysphagia treatment should carefully weigh reduction in aspiration risk alongside considerations of hydration, quality of life, preferences for end-of-life care, and respect for familial and cultural values.

A referral to a speech–language pathologist (SLP) for an instrumental swallow evaluation such as a modified barium swallow (MBS) exam or fiberoptic endoscopic evaluation of swallowing (FEES) can detect overt or silent aspiration, which can lead to compensatory modifications including change in bolus size, texture, and presentation rate; changes in head posture; education on safe swallowing strategies; tactile and/or verbal cuing; adaptations to mealtime equipment; and assisted hand feeding as indicated [32–35]. Rehabilitative approaches include swallowing exercises, expiratory muscle strength training (EMST), Lee Silverman Voice Training (LSVT), transcutaneous neuromuscular electrical stimulation (NMES) with or without EMG biofeedback, and various neuromodulation techniques [36–40]. However, due to insufficient or low-quality evidence to determine the safety and efficacy of many of these interventions in neurodegenerative dysphagia, there is a particular need for more research in this population.

If dysphagia is accompanied by weight loss, referral to a dietitian can help ensure appropriate caloric and nutritional intake, and offering high-calorie nutritional supplements and favorite foods is often a successful strategy to maintain

weight. Placement of a percutaneous endoscopic gastrostomy (PEG) tube is a challenging and an ethically fraught decision in neurodegenerative disease, and early discussion of this issue should guide later management. However, it should be stressed that the risk of aspiration remains after PEG placement, as it does not prevent the aspiration of gastric contents and saliva, nor does it preclude ongoing oral intake, and in the cases in which dysphagia is accompanied by severe akinesia and rigidity, PEG placement can lead to the prolongation of a very poor quality of life and a difficult decision as to when to withdraw feeding for patients' families. Comfort-based late-stage dysphagia management centers around the identification of feeding strategies for pleasure, accepting that aspiration may occur [41].

Dystonia

Increased tone can be the most prominent feature in 4R-tauopathies, especially when presenting as corticobasal syndrome, in which dystonia is typically asymmetric and may affect an upper/lower extremity or present as cervical dystonia or blepharospasm [42]. Pain as a result of dystonia is sometimes considerable and disabling, and general pharmacologic and nonpharmacologic strategies to manage pain should be employed, in collaboration with a chronic pain or palliative care specialist when necessary.

Local paralysis of focal dystonic muscles by botulinum toxin is the mainstay of treatment for dystonia, with resultant improvement in dystonic posturing and pain reported in a subset of patients [29, 43–45]. Oral pharmacologic strategies for dystonia include muscle relaxants working through GABA agonism (e.g., clonazepam, tizanidine, baclofen), though treatment effect is often disappointing, and systemic side effects such as sedation and increased fall risk limit their utility [18, 29]. Dopaminergic (e.g., levodopa) and anticholinergic agents (e.g., benztropine, trihexyphenidyl) have not been found to be effective in treating dystonia, and anticholinergics should be avoided because of worsening cognition and mood [29, 46].

Controlled studies are lacking to support the use of dystonia-targeted physical therapy intervention in 4R-tauopathies, but interventions such as passive stretching to mitigate contractures, guided muscle relaxation techniques, and strengthening of antagonist muscles may be beneficial and pose limited risk to the patient [47, 48]. Use of modified assistive devices may also support function, whereas severe limb deformities from dystonia may require consultation with plastic surgery.

Imbalance/Falls

Postural instability and falls are central to the diagnostic criteria for Richardson's syndrome, and decreased regional

glucose metabolism during locomotion has been observed in subcortical and cortical locomotor centers in PSP, supporting dysfunction of these brain regions as central to the disease [49, 50]. In addition, 4R-tauopathy patients may also have axial rigidity, dystonia, visual impairment, and impulsivity, which can exacerbate imbalance and lead to a high fall risk early in the disease [50, 51].

Frequent exercise with careful monitoring to avoid injury from falls, including treadmill exercise, is beneficial for preserving balance and reducing falls in PSP-RS [30, 52, 53], and in our experience, many of the structured multicomponent physical activity programs studied in Parkinson's disease, which include tai chi, dance therapy, boxing training, and Feldenkrais-based exercise, can improve quality of life in 4R-tauopathy patients [54–58]. For patients with gait freezing, use of ancillary devices such as walker-mounted laser pointers, visual and rhythmic cues, and arc turning can be employed [18]. In a single case report, transcranial magnetic stimulation (TMS) reduced freezing and falling; however, this is still considered experimental and currently the approach cannot be recommended [59].

Weighted walkers (such as the U-Step walker) in combination with physical therapy have been shown in case reports to prevent falls and preserve independence [53], and assistive devices such as wheelchairs and mobility scooters should be introduced before injurious falls become frequent. Also, given the high risk of injurious falls including bone fracture [51], age-appropriate bone density screening should be considered, with initiation of calcium, vitamin D, and bisphosphonates if indicated.

Involuntary Movements (Tremor/Myoclonus)

Tremor in 4R-tauopathies can be resting, postural, kinetic, dystonic, or mixed, but tremor typically occurs much less frequently than in diseases such as idiopathic Parkinson's disease, and data on pharmacologic efficacy specifically for tremor in this population are limited [60, 61]. As with standard treatment of tremor, a careful review of medications for offending agents should be conducted prior to initiation of pharmacologic therapy. A trial of dopaminergic agents (e.g., levodopa, amantadine) for patients with disabling rest tremor is appropriate, and treatment of action tremor with typical agents may be considered. Botulinum toxin can be considered in advanced cases of dystonic tremor, and adaptive devices are available for a range of action tremors, including weighted and motion-canceling silverware.

Myoclonus, often triggered by motor or sensory stimulation, is commonly associated with CBS [62]. Pharmacologic treatment strategies include levetiracetam and clonazepam, though levetiracetam is associated with worsening behavioral changes, and the use of benzodiazepines is limited by sedation and increased fall risk [18,

63, 64]. Piracetam, gabapentin, and valproic acid have been proposed as second-line agents [63], though the evidence base for use in this cohort is poor.

Motor Speech Difficulty and Voice Disorders

Motor speech difficulty is common in 4R-tauopathies and can present either as focal or mixed dysarthrias, apraxia of speech, or hypophonia. Patients with PSP-RS most frequently present with a mixed dysarthrophonia characterized by hypokinetic and spastic features, with ataxic speech being less common [65–68]. Motor speech characteristics in CBS are less well described but include a spastic or hypokinetic dysarthria with or without apraxia of speech [69, 70]. In the nonfluent variant of primary progressive aphasia (nfvPPA), apraxia of speech and a heterogenous range of dysarthrias are common.

Regardless, speech therapy is recommended with an SLP, giving early consideration to augmentative and alternative communication (AAC) aids (e.g., low- or high-technology pictographic boards, voice banking, and speech-generating devices) [71]. AAC is ideally implemented prior to the development of anarthria or significant cognitive impairments, involves the patient's communication partners, and adapts to the patient's motor, cognitive, visuospatial, and ecological needs over time [72]. Treatments that directly target speech articulation and intelligibility include overarticulation and rate modification [73–75].

For hypophonia, the Lee Silverman Voice Treatment (LSVT) program has been shown to reduce motor speech and voice symptoms in patients with PD, and can be considered in this population with or without use of a personal voice amplifier [76].

Pseudobulbar Affect

Pseudobulbar affect (PBA) is characterized by inappropriate, disproportionate, or uncontrollable laughing and/or crying, and the social impact and resultant embarrassment can lead to restriction of social activities and a lower quality of life [77]. Dextromethorphan–quinidine is FDA approved to treat PBA in a number of neurologic conditions, and efficacy has been demonstrated in clinical trials in dementia, stroke, traumatic brain injury, and ALS [78–80]. In our experience, dextromethorphan–quinidine is also effective at treating bulbar symptoms in PSP-RS. Careful questioning is often necessary to identify the presence of pseudobulbar symptoms, but subsequent patient and family education alone can reduce embarrassment and anxiety. Pocket or wallet-sized education cards can be carried and passed out in public to increase awareness of PBA, which may facilitate social engagement and acceptance.

Sialorrhea

The mechanism of chronic excess saliva in 4R-tauopathies is unclear, but may be a result of impaired oral salivary clearance due to orobuccal apraxia or dysphagia. Anticholinergic agents like glycopyrrolate produce less CNS toxicity than scopolamine, the use of which should be avoided because of significant systemic adverse effects on cognition, gait, and balance [81]. Botulinum toxin injection to the salivary glands can reduce saliva production, but may worsen dysphagia [63]. SLPs or occupational therapists can be helpful in implementing techniques such as biofeedback or automatic cuing, whereas a dentist can help ensure good oral hygiene.

Visual Impairment

Ocular motor impairments frequently accompanied by diplopia are a core feature of PSP-RS, but may be seen in other 4R-tauopathies as the disease progresses. Other symptoms such as square wave jerks, blepharospasm, eyelid apraxia, dry eye syndrome, reduced blink rate, and photosensitivity may be present, and the resultant visual impairment may contribute to falls and impact daily life by causing difficulty with reading, eating, and maintaining appropriate social eye contact. Visuospatial processing impairment is less common, though may be present, particularly in CBS.

Botulinum toxin has been FDA approved for the treatment of blepharospasm since 1989, and many studies have reported that approximately 90% of patients will see a clinical benefit with this approach [82]. Botulinum toxin has also been employed to treat eyelid apraxia [83], and as with other applications of this agent, technical considerations regarding muscle selection should be done in consultation with an experienced provider. Eyelid “crutches” for the treatment of eyelid apraxia are typically poorly tolerated by patients.

Pharmacologic options for gaze palsy are limited, but intriguingly, short-lived motor improvement was seen after treatment with zolpidem in small trials and a case report, though sedation limits the utility of this benefit [84, 85]. Referral to a neuro-ophthalmologist or neuro-optometrist to be fitted for prisms is often the best option available to improve visual function. Finally, artificial tears are a safe and effective treatment for dry eyes, and tinted glasses may help with photosensitivity.

Occupational therapists are often an excellent resource for patients with visual impairment of any cause, and many creative strategies are available to improve visual function. Examples include ensuring appropriate home lighting, removing clutter, improving visual contrasts, and the use of tilted mirrors and assistive reading technology (e.g., bookstands, magnifying glasses, and audio books), or the simple use of an eye patch to eliminate diplopia.

Cognitive Symptoms

Executive Dysfunction

Cognitive impairment can occur even in motor-predominant syndromes, and subtle changes in executive function can often be uncovered with careful questioning and formal neuropsychological testing. If significant executive dysfunction is present, a thorough safety screen should be conducted that includes an assessment for medication mismanagement, financial risk and scams, home safety in the kitchen (e.g., use of stove), driving risk, and unsecured firearms.

Management of executive dysfunction includes implementing strategies such as environmental modifications (e.g., structured routine, minimizing distractors, simplifying tasks) and compensatory technology (e.g., daily planners, mobile devices), which may be facilitated through a referral to an occupational therapist [86]. General recommendations on lifestyle modifications for other dementias may apply in this population and are reasonable to consider. Typical interventions include increasing cardiovascular exercise, adopting a heart-healthy diet, ensuring adequate sleep and nutrition, and staying cognitively and socially engaged [87]. The use of medications for cognitive impairment typically employed for Alzheimer’s disease (AD) is discussed under “[Memory Dysfunction](#)” below.

Aphasia

In patients with cortical language dysfunction, such as the agrammatism and loss of fluency seen in nfvPPA [11], ongoing management by an SLP is recommended. Standard SLP rehabilitative interventions initially target syntax and, as the disease progresses, include reading, spelling, and word finding, and a “Life Participation” approach aims to maximize functional communication and participation in desired life activities [88–90]. Given the high prevalence of hearing loss in elderly patients, and the association of hearing loss with dementia [91, 92], an audiology screening should also be considered.

Intriguingly, studies in nfvPPA suggest that video-implemented script training (VISTA) may improve intelligibility, speech production and grammar in trained and/or untrained topics, and research is ongoing to better understand the efficacy of this intervention [93, 94]. Given access challenges to academic centers where specialized care is available, aphasia therapy over telehealth has also been demonstrated to be as effective as in person therapy in patients with primary progressive aphasia [95]. Finally, in limited studies, transcranial direct current stimulation (tDCS) has been shown to be safe and potentially effective [96, 97], and several current clinical trials are planned or underway to determine the utility of tDCS in patients with primary progressive aphasia.

In addition to the provision of AAC devices (discussed in “[Motor Speech Difficulty and Voice Disorders](#)”), compensatory interventions for aphasia can train communication partners in adapting their communication style to facilitate their loved one’s communication and comprehension [98, 99]. Basic principles include the following: [1]) eliminate distractions such as multiple speakers or background noise; [2]) establish attention and then speak face to face; [3]) keep sentences short and direct; [4]) stay on one topic at a time with frequent clarification and repetition; [5]) for patients with yes/no confusion, frame questions to provide lexical options (e.g., “chicken or fish?”); [6]) use and encourage patients to use nonspeech modalities such as gestures, facial expressions, writing, drawing, and pointing at pictures; and [7]) be patient and allow enough time for a response.

Memory Dysfunction

The role of medications such as the acetylcholinesterase inhibitors (AChEI) typically employed in Alzheimer’s disease is controversial in 4R-tauopathies. Cholinergic neuron loss has been observed in postmortem studies in PSP [100], so use of AChEIs in this population is biologically plausible, but in a randomized clinical trial of donepezil in 21 patients with PSP-RS, a small positive effect on memory was more than offset by a dose-limiting worsening of motor symptoms, leading the authors to recommend against its use in this cohort [101]. Additionally, in patients presenting with frontal lobe impairments, AChEIs can worsen behavioral symptoms [102, 103]. A trial of AChEI may be justifiable if cognitive symptoms dominate the clinical picture without motor or behavioral features, as in amnesic presentations similar to AD.

Multiple studies of memantine in patients with frontotemporal dementias have shown no benefit or even worsening of cognition in some individuals [104–106], so routine use of this agent is not recommended. However, if AD biomarker studies (such as amyloid PET or CSF abeta/tau) support AD as an underlying cause of CBS, which may occur in up to ~40% of cases, AChEI or memantine might be more reasonably considered. Nonpharmacological strategies employed in Alzheimer’s disease are also useful in patients with memory impairment due to a 4R-tauopathy, including the use of a daily planner and mobile devices and establishing a daily routine.

Behavioral Symptoms

Problematic Behaviors

Typical behavioral changes in 4R-tauopathies are impulsivity and apathy, but disruptive behavioral changes can be a presenting or late feature [9, 12, 107], and behavioral impairment is the defining feature of bvFTD presentations, with

diagnostic criteria that include disinhibition, apathy, loss of sympathy/empathy, unusual compulsions, and hyperorality (impulsive overeating) [108]. If present, these behaviors can cause substantial distress to the patient’s family and loved ones, contributing to caregiver burden and burnout, and management of these behaviors is a frequent reason for referral to a cognitive and behavioral specialist. Whereas evidence of serotonergic deficit has prompted the use of selective serotonin reuptake inhibitors (SSRIs) to blunt impulsive and sexual behaviors in this cohort [109, 110], the centerpiece of treatment for diverse behavioral symptoms is working with available caregivers to develop nonpharmacologic strategies to modify behavior.

A model for behavioral intervention called DICE (describe, investigate, create, evaluate) is recommended, whereby a careful and structured investigation into root causes of problematic behavior is followed by the development of an action plan, with subsequent re-evaluation after implementation [111]. The developers of the DICE model also recommend searching for preventable/treatable causes of distress including untreated medical or psychiatric comorbidities, untreated pain, poor sleep hygiene, boredom and lack of sensory stimulation, a confrontational or overly nuanced caregiver communication style, an unpredictable daily routine, or an uncomfortable environment (e.g., chaotic, poorly lit, lack of recreational choices). Additionally, the development of a tailored action plan has been shown to reduce problematic behaviors in frontotemporal dementia [112].

Agitation/Aggression

Though agitation is infrequent and typically mild in 4R-tauopathies compared to other neurodegenerative diseases [113], when present, aggression poses a substantial challenge to caregivers and providers. The core of management is in providing behavioral strategies to the caregiver for redirection and environmental modification as discussed above. Specific strategies for management of agitation include implementation of any of a number of safe and low-cost activities: [1]) music therapy; [2]) pet therapy; [3]) aromatherapy, such as lemon balm or lavender oil; [4]) massage or touch therapy; [5]) initiation of regular physical activity such as walks or exercise training; [6]) scheduling of favorite hobbies; [7]) and person-centered communication skills training for caregivers [114].

Due to lack of clinical trials and low incidence of aggression in 4R-tauopathy, much of the rationale for pharmacologic management is necessarily extrapolated from other dementia cohorts. Similar to randomized clinical trial data on agitation in Alzheimer’s disease [115], we see a modest positive effect with selective serotonin reuptake inhibitors such as citalopram. Antipsychotics should be avoided or only used for short durations in crisis situations, especially given the

FDA black box warning of increased mortality in elderly patients with dementia and data from large multicenter clinical trials such as CATIE-AD, which showed that atypical antipsychotics were no more effective than SSRIs for behavioral control, and associated with a high rate of side effects such as extrapyramidal symptoms, sedation, and weight gain [116]. Other approaches commonly employed in other neurodegenerative disease including carbamazepine, valproic acid, and benzodiazepines have no role in aggression management in 4R-tauopathies because of cognitive and motor side effects. An ongoing trial is assessing the effect of low dose lithium on agitation and aggression in 60 patients with bvFTD (NCT02862210), though a trial in PSP-RS and CBS was stopped because the drug was poorly tolerated (NCT00703677).

Anxiety/Depression

Frequent screening for mood symptoms is recommended in all 4R-tauopathy syndromes, as patients are at high risk of suicide, and serotonergic deficit may be amenable to treatment with an SSRI [117]. Generally, SSRIs such as paroxetine should be avoided due to a larger anticholinergic effect [118], whereas citalopram, escitalopram, sertraline, and fluoxetine are commonly prescribed. If apathy is prominent, a serotonin–norepinephrine reuptake inhibitor (SNRI) or bupropion is a reasonable second-line agent. Tricyclic antidepressants were historically used for depressive symptoms, but cognitive, motor, and urologic side effects limit current utility [119, 120]. Electroconvulsive therapy (ECT) was effective in a case report of refractory suicidal ideation in a patient with PSP-RS [121].

Cognitive behavioral therapy (CBT), either self-guided or provided by a licensed psychologist, may be an effective nonpharmacologic intervention for mood symptoms [122]. Mindfulness yoga reduced symptoms of depression and anxiety in a PD cohort, and may be similarly useful in 4R-tauopathy [123]. Numerous popular applications for guided meditation on mobile devices also can be safely recommended to patients, even if data on efficacy are lacking.

Apathy

Loss of motivation is often an early and unrecognized feature of many neurodegenerative diseases, including 4R-tauopathies, and may be mistaken for depressed mood. Apathy can be difficult to treat, but general strategies include selecting an activating antidepressant such as an SNRI, while avoiding SSRIs that may worsen apathy, e.g., citalopram and escitalopram [18]. A clinical trial is ongoing to assess the efficacy of intranasal oxytocin on treating apathy in patients with bvFTD (NCT03260920). Stimulants, such as methylphenidate, have clinical trial evidence for treatment of apathy in

Alzheimer's disease [124–126], but evidence for generalizability of these results to the 4R-tauopathy cohort is lacking. Regular exercise and scheduled activities are reasonable practical approaches without supportive research evidence.

Other Symptoms

Insomnia/Fatigue

Unlike in Alzheimer's disease, wake-promoting neurons are generally preserved in 4R-tauopathies [127], and therefore, sleep problems typically involve insomnia rather than hypersomnia [128]. In PSP-RS, severe insomnia is a characteristic feature, but unfortunately, evidence for effective therapeutics is limited, though an ongoing clinical trial is assessing the efficacy of zolpidem and suvorexant *versus* placebo (NCT04014387). Melatonin and trazodone are commonly prescribed, whereas benzodiazepines should be avoided. REM behavior disorder (RBD) can be present but is considerably less common than in synucleinopathies, and if early and prominent, RBD is an exclusion for PSP by MDS criteria. Sleep disordered breathing is a common comorbidity and screening for obstructive sleep apnea is recommended [129].

Advising on good sleep hygiene and cognitive behavioral therapy for sleep are 2 nonpharmacologic alternatives. Establishing a healthy sleep routine can also help with symptoms of fatigue, and the use of scheduled outings can help conserve limited energy, whereas breaks/naps can be used to recharge. Regular physical activity and exercise can be helpful for both sleep and energy levels.

Urinary Control/Constipation

Problems with urination in PSP-RS can include frequency, urgency, retention, and incontinence [130]. Typical pharmacologic agents such as anticholinergics (e.g., oxybutynin) should be avoided due to side effects of cognitive impairment and increased risk of dementia [131], and α 1-adrenoceptor antagonists (e.g., tamsulosin) are associated with orthostatic hypotension that could increase falls [132]. Antispasmodics (e.g., tolterodine, trospium, solifenacin, darifenacin) are a reasonable alternative. Newer agents, such as mirabegron, have been proposed to lead to less cognitive impairment [133], though specific studies in 4R-tauopathies have not been conducted. Alternatives include the use of bladder training, pelvic floor exercises, and adult pads. Electrical stimulation therapies such as percutaneous tibial nerve stimulation (PTNS) and sacral neuromodulation therapy are occasionally employed. Intradetrusor injection of botulinum toxin can also be effective, and referral to a urologist is recommended for assistance in management.

Constipation is a common problem, often exacerbated by decreased fluid intake if urinary symptoms or dysphagia are

present. Increased fluids, a high fiber diet, and regular physical activity and exercise are the foundation of treatment. If needed, polyethylene glycol, senna, lactulose, and bisacodyl suppositories are available over the counter.

General Considerations

Education/Caregiver Support

Many patients, caregivers, and providers are unfamiliar with 4R-tauopathies and their associated clinical syndromes, and education about the disease process can be a key therapeutic intervention, especially early in the disease course. Several resources are available for high-quality information about many syndromes caused by 4R-tau including CurePSP (www.psp.org), the Association for Frontotemporal Degeneration (www.theaftd.org), the PSP Association (pspassociation.org.uk), Rare Dementia Support (www.raredementiasupport.org), and the Alzheimer's Association (www.alz.org). Patients interested in observational research in the USA can be referred to the ALLFTD research consortium (www.allftd.org), whereas European and Canadian patients can be referred to the Genetic Frontotemporal Dementia Initiative (genfi.org.uk).

Given the multifactorial symptoms in 4R-tauopathies, caregiver burden is often high, so frequent screening for caregiver burnout and increasing caregiver support are key factors to successful management [134]. Several resources are available through organizations such as the Family Caregiver Alliance (www.caregiver.org), and options are available through social media platforms for those living remotely or who prefer not to attend in person. We recommend a multidisciplinary approach with a careful review of available resources and coping strategies at each visit.

End-of-Life Planning

Due to the progressive nature of neurodegenerative disease, discussion of goals of care should happen as early as possible, especially as judgment and reasoning may be impaired in later stages. Advance care planning should involve clarifying any limitations on treatments, including artificial feeding, resuscitation, and intensive care interventions, which can be recorded in documents such as the Physicians Orders for Life-Sustaining Treatment (POLST) form (www.polst.org). Financial and medical power of attorney forms should be completed, along with creation of a will or trusteeship, and an elder law attorney can be helpful if issues arise. Finally, early decisions on end of life, including preferred place of care, place of death (e.g., home, hospice, hospital), and funeral plans, can ensure a patient's wishes are respected through the end of their disease [135]. Autopsy and brain

donation are options that can provide definitive diagnosis and assist in research efforts to find disease-modifying treatments.

Future Disease-Modifying Treatment

Currently, most proposed mechanisms for disease-modifying treatment of 4R-tauopathies directly or indirectly target tau, though historically several early interventions were antioxidants purported to reduce mitochondrial stress and oxidative damage. The 2 overarching hypotheses being tested in tau-targeted clinical trials are that clinical improvement can be achieved by [1]) reducing a toxic gain of function caused by pathologic tau aggregates or [2]) restoring a loss of normal tau function [136]. Strategies that follow from the first hypothesis aim to reduce tau gene expression, prevent post-translational modifications that promote aggregation, or clear aggregates, usually via an immunologic mechanism, whereas strategies that target loss of function have focused on microtubule stabilization. Discussed below are all disease-modifying therapeutics that have reached the clinical trial phase in a 4R-tau-related clinical syndrome, grouped by mechanism (Table 3).

Antioxidants

As in many neurodegenerative diseases, oxidative stress and mitochondrial impairment have been observed in PSP, and antioxidants have been proposed as a therapeutic strategy [148, 149]. Results have been published from 2 randomized placebo-controlled trials for coenzyme Q10 (CoQ10), and in an early phase 2 study, a modest positive effect was seen after 6 weeks of treatment with 5 mg/kg of CoQ10 in 21 patients on the PSP Rating Scale, but these results were not replicated in a larger trial conducted over 12 months in 61 patients, which did not achieve its target enrollment and was therefore underpowered to test the hypothesis that CoQ10 could slow disease progression [137, 150]. Two other trials in PSP-RS have been registered on nutrient combinations with purported antioxidant activity: α -lipoic acid with L-acetyl carnitine (Juvenon, NCT01537549) and pyruvate with creatinine and niacinamide (NCT00605930), but no efficacy was seen in the Juvenon trial with a high rate of side effects, and the second trial was stopped after the manufacturer of the supplement went bankrupt [151].

Neuroprotective

Riluzole is a benzothiazole currently used in the treatment of amyotrophic lateral sclerosis, with putative anti-excitotoxic activity through a range of pharmacologic effects, including

Table 3 Disease-modifying clinical trials in 4R-tauopathy clinical syndromes

Therapeutic	Mechanism	Cohort	Trial	Phase	Status	Result
CoQ10	Antioxidant	PSP-RS	NCT00328874	2	Completed	Safe, possibly effective [42]
		PSP-RS or CBS	NCT00532571	2/3	Completed	Not available
		PSP-RS	NCT00382824	2/3	Completed	Safe, no effect seen [137]
α -Lipoic acid and L-acetyl carnitine (Juvenon)	Antioxidant	PSP-RS	NCT01537549	1/2	Completed	Possibly harmful
Pyruvate, creatine, and niacinamide	Antioxidant	PSP-RS	NCT00605930	N/A	Early terminated	Not available
Riluzole	Neuroprotective	PSP-RS	NCT00211224 (NNIPPS)	3	Completed	Safe, no effect seen [138]
Rasagaline (Azilect)	MAO-B inhibitor	PSP-RS	NCT01187888	3	Completed	Safe, no effect seen [139]
Lithium	GSK-3 β inhibitor (nonselective)	PSP-RS or CBS	NCT00703677	1/2	Completed	Not tolerated
Valproate (valproic acid)	GSK-3 β inhibitor (nonselective)	PSP-RS	NCT00385710	2	Completed	Harmful [140]
Tideglusib (NP031112, Nypta, Zentyler, NP12)	GSK-3 β inhibitor (selective)	PSP-RS or PSP-P	NCT01049399 (TAUROS)	2	Completed	Safe, no effect seen [141]
ASN120290 (ASN-561)	OGA inhibitor	PSP-RS	Not yet listed	2	Not yet recruiting	
Young plasma	Cellular signaling	PSP-RS	NCT02460731	1	Completed	Safe, no effect seen [142]
Salsalate	Tau anti-acetylation	PSP-RS	NCT02422485	1	Completed	Safe, no effect seen [142]
TRx0237 (methylene blue)	Tau aggregation inhibitor (TAI)	bvFTD	NCT01626378	3	Completed	Safe, no effect seen [143]
AZP2006	Tau aggregation inhibitor (TAI)	PSP-RS	NCT04008355	2	Not yet recruiting	
Davunetide (NAP, AL-108)	Microtubule stabilization	PSP-RS	NCT01110720	2/3	Completed	Safe, no effect seen [144]
TPI 287	Microtubule stabilization	PSP-RS or CBS	NCT02133846	1	Completed	Harmful [145]
AADvac-1	Active immunization (vaccine)	nvPPA	NCT03174886 (AIDA)	1	Ongoing	
BIIB092 (gosuranemab, BMS-986168, IPN007)	Tau N-term monoclonal antibody N-terminal (aa 15-24)	PSP-RS	NCT02460094	1	Completed	Safe, engaged target [146]
		PSP-RS	NCT03068468 (PASSPORT)	2	Completed	No benefit
		CBS, nvPPA, MAPT	NCT03658135 (TauBasket)	1	Early terminated	Not yet available
ABBV-8E12 (C2N 8E12, tilavonemab)	Tau N-term monoclonal antibody N-terminal (aa 15-24)	PSP-RS	NCT02494024	1	Completed	Safe [147]
		PSP-RS	NCT02985879	2	Early terminated	No benefit
UCB 0107	Tau mid-domain monoclonal antibody	PSP-RS	NCT04185415	2	Ongoing (international)	–
Tolfenamic acid	Degrades tau transcription factor	PSP-RS	NCT04253132	2	Ongoing	–

inhibition of glutamate-mediated apoptosis [152]. As part of a larger study in “Parkinson’s-Plus” diseases, riluzole was tested in 362 patients with PSP-RS, but no effect was seen on survival after 36 months [138].

MAO-B Inhibition

The type B monoamine oxidase (MAO) inhibitor rasagaline advanced into clinical trials for PSP-RS based on history of

safe use in Parkinson's combined with evidence of neuroprotection in cellular and animal models, possibly through an increase of endogenous neurotrophic factors [153]. Unfortunately, in a 12-month randomized placebo-controlled trial of rasagiline (1 mg daily) in 44 patients with PSP-RS, no effect was seen on progression as measured by the primary outcome, the PSP Rating Scale, and, although underpowered, no trend towards efficacy was observed [139].

GSK-3 β Inhibition

Glycogen synthase kinase 3 beta (GSK-3 β) is a serine/threonine kinase that phosphorylates tau and has been shown to promote the formation of the neurofibrillary tangles seen in Alzheimer's disease [154]. In addition to this role in AD pathology, GSK-3 β is also involved in a wide range of cellular processes, including differentiation, growth, motility, and apoptosis [155]. Lithium is more commonly known as a mood stabilizer, but a GSK-3 β -dependent reduction in tau hyperphosphorylation was found in mouse models [156], and a clinical trial was started to evaluate lithium in PSP-RS, but lithium was very poorly tolerated and the trial was stopped early due to a high discontinuation rate (NCT00703677). Valproate is another mood stabilizer with putative action on through GSK-3 β inhibition [157], but a randomized controlled trial in 28 patients with PSP-RS showed no difference on disease progression, with possible worsening on measures of gait, again suggesting poor tolerability [140]. It should be noted that both lithium and valproate are nonselective for GSK3 β , and thus, observed toxicity may be due to off-target effects.

Tideglusib is a small molecule designed as a selective GSK-3 β inhibitor [158], but in TAUROS, a phase 2 randomized controlled trial in 146 patients with PSP-RS, 52 weeks of treatment with tideglusib was well tolerated but lacked efficacy [141]. Some authors have suggested that because no measures of target engagement were incorporated into the above trials, it was not possible to determine whether sufficient GSK-3 β inhibition occurred to have an effect [159]. However, development for tideglusib has been discontinued, and no other GSK-3 β inhibitors are in clinical development at present, though approaches using other kinase inhibitors are being tested in Alzheimer's disease and could be considered in 4R-tauopathies.

OGA Inhibition

A glycosylation process called O-GlcNAcylation involves attachment of an N-acetylglucosamine group (GlcNAc) to serine/threonine sites, and these O-GlcNAc residues are removed by the enzyme O-GlcNAcase (OGA). Decreased O-GlcNAcylation levels are associated with pathologic tau hyperphosphorylation, and, in the human AD brain, O-

GlcNAcylation levels are decreased 50%, which provides rationale for the development of an OGA inhibitor in tauopathies [160, 161]. The first novel OGA inhibitor was MK-8719, developed by Merck, which was well tolerated in healthy controls and showed good target engagement as measured by the use of a novel OGA radiotracer [18F]MK-8553 [162]. Despite Merck announcing a trial for PSP patients, MK-8719 never advanced into clinical trials in this cohort, and development has been discontinued [163].

ASN120290 is another novel OGA inhibitor, and preclinical data in 4R-tauopathy transgenic mice show an increase in O-GlcNAcylated tau and a decrease in phosphorylated tau [164]. In phase 1 studies, ASN120290 was safe and well tolerated [165], and the developer, Asceneuron, has announced the intention to move it into phase 2 clinical trials for the PSP-RS.

Cellular Signaling

Young plasma (i.e., fresh frozen plasma derived from healthy donors under the age of 30) advanced into clinical trials for Alzheimer's disease and PSP-RS without a definitive mechanism, but with evidence of functional improvement in cognition in mouse models of AD and aging [166–168]. In a pilot open-label trial in 5 patients with PSP-RS, young plasma was found to be safe, but no evidence for efficacy was seen on a range of outcomes [142].

Inhibition of Tau Acetylation

Clearance of tau is dependent on proteasomes, and acetylation of tau prevents ubiquitination and routing to the proteasome system, promoting tau aggregation [169]. In 4R-tau transgenic mice, treatment with salsalate, a nonsteroidal anti-inflammatory agent with inhibitory action on the acetyltransferase p300, decreased tau aggregation and rescued memory deficits, providing support for clinical trials [170]. However, in a small open-label trial in 9 patients with PSP-RS, salsalate (2250 mg daily) was safe and well tolerated, but no effect was seen on a range of outcomes including the PSP Rating Scale after treatment for 6 months [142].

Tau Aggregation Inhibitors

Methylene blue is a phenothiazine that was found to disrupt high-affinity tau-tau bonds, and in transgenic mice, it decreased tau aggregates and rescued memory if given prior to symptom onset [171–173]. A reduced formulation of methylene blue called TRx0237 was tested in a phase 3 randomized control trial for 220 patients with bvFTD, and at 200 mg daily was found to be safe, but no effect was seen on any primary or secondary endpoint compared to placebo [143], and a parallel randomized controlled trial in 891 patients with mild to

moderate Alzheimer's disease also failed to show a benefit [174]. However, methylene blue is a biologic dye that turns urine and feces blue, and 8 mg was included in placebo to preserve blinding, and under the hypothesis that this low dose may be effective, which would confound prior analyses, a new randomized controlled trial is enrolling to test low-dose TRx0237 in 450 patients with mild AD (NCT03446001).

AZP2006 is another agent with a putative mechanism of decreasing tau aggregation via blocking of phosphorylation, and although details on mechanism have not been published, in a phase 1 trial in France, AZP2006 was reportedly well tolerated [175]. A phase 2 clinical trial in PSP-RS has been announced, with a plan to treat with 2 doses of AZP2006 in 36 PSP-RS patients for 29 weeks (NCT04008355).

Microtubule Stabilizers

An alternative hypothesis for dysfunction in tauopathies is that tau loss of function, specifically loss of microtubule stabilization, may be driving pathology, and thus far, 2 agents have been tested in clinical trials in 4R-tauopathy that are proposed to act through microtubule stabilization. The first is davunetide, a neuropeptide growth factor with diverse neuroprotective activity in cell and animal models [176–178]. Unfortunately, in one of the first large multicenter randomized control trials in PSP-RS, davunetide did not meet its primary endpoint in 360 patients treated for 52 weeks [144]. The second agent, TPI 287, a taxane derivative, was evaluated in a basket design for AD, PSP, and CBS patients, but a dose-related worsening of falls and cognitive outcomes was seen in the 4R-tauopathy arms, and this agent is no longer in clinical development [145].

Immunotherapies

Approaches that harness the immune system to clear tau aggregation have generated significant interest in the 4R-tauopathy clinical trial world at present, and both active and passive immune strategies are being investigated. Active immunization, i.e. vaccination, was the first area of investigation, but early studies looking at full-length tau inoculation in mouse models provoked severe inflammation and further tau aggregation [179], which incidentally provided the first evidence of tau “seeding” hypothesis as a mechanism of pathogenic spread, later supported in other experimental models [180]. More recent therapeutic active vaccination strategies, such as AADvac1, use fragments of tau that do not trigger tau aggregation but do provoke a B-cell-mediated immune response, and in transgenic rat models, AADvac1 reduced tau aggregation and improved motor function [181]. In addition to several ongoing trials in AD which have demonstrated clear immunogenicity [182, 183], AADvac1 is being tested in a phase 1 study in 30 patients with nfvPPA, and the trial is

designed to assess safety and immunogenicity in this population (NCT03174886), with results expected in late 2020.

Passive immune clearance occurs via infusion of monoclonal antibodies designed to target particular epitopes on the tau protein, though the appropriate epitope to target is controversial and remains a matter of ongoing investigation. BIIB092 (gosuranemab) is a monoclonal IgG4 antibody against the N-terminal region of tau (amino acids 15–23), and in cell culture and animal models, it reduced both full-length tau and extracellular tau fragments [184]. A 3-month phase 1 study in 58 PSP-RS patients showed BIIB092 to be safe and demonstrated target engagement by reduction in N-terminal tau [146]. However, an interim analysis in a subsequent phase 2 study in PSP-RS patients (PASSPORT, NCT03068468) found no trend towards efficacy on primary endpoints, and PASSPORT was terminated early for futility. A parallel study with a basket design (TauBasket) was providing expanded access in other 4R-tauopathies including CBS, nfvPPA, and MAPT, but this study was terminated due to the futility analysis results from PASSPORT.

ABBV 8E12 (tilavonemab) is a second monoclonal antibody that targets the N-terminal (amino acids 25–30) [185–187], and a phase 1 study in 32 PSP patients showed ABBV 8E12 was safe [147], but an interim analysis in a subsequent phase 2 study in 378 PSP-RS patients (NCT02985879) also showed futility, and this trial was terminated early.

An alternative epitope is the midregion of tau, which is closer to the microtubule binding repeat regions, and in a seeding model of tau in transgenic mice, only antibodies that targeted the mid-domain suppressed tau aggregation, whereas N-terminal antibodies did not [188]. A monoclonal antibody to the mid-domain (amino acids 235–246), UCB0107, recently completed Phase 1 studies in healthy controls, and an international Phase 2 trial in 16 patients with PSP-RS has been announced and is currently recruiting (NCT04185415), while a US trial is in development but no information is publicly available.

Gene Expression

Given the diverse roles of tau in the human brain, regulation of tau at the gene level has been approached cautiously, but reassuringly, tau knockout mice have a very mild phenotype [189]. Currently, the only clinical trial putatively affecting tau expression in 4R-tauopathy is a recently announced phase 2 randomized controlled trial of tolfenamic acid in PSP-RS (NCT04253132), which promotes the degradation of specificity protein 1 (Sp1), a transcription factor that upregulates tau [190]. However, given the recent successes in employing an antisense oligonucleotide approach in spinal muscular atrophy and Huntington's disease [191, 192], and data showing that ASO-mediated reduction of tau translation by 50% reduced

tau aggregation and prevented neuronal loss in transgenic mouse models [193], there is substantial enthusiasm for testing tau-targeted ASOs in 4R-tauopathies. MAPTRx is a non-selective tau-targeted ASO developed by Ionis that is being tested in a randomized controlled trial in 46 patients with mild AD (NCT03186989), with results expected in late 2020.

Conclusion

Twenty disease-modifying therapeutics have been entered into clinical trials for the treatment of a 4R-tauopathy-related syndrome at the time of this review, and increasingly, therapeutics targeting the neurofibrillary tau tangles in Alzheimer's disease are being cross-purposed into this cohort. However, although patients with 4R-tauopathies are increasingly being included in clinical trials, no approach to date has specifically targeted 4R-tau, which represents both an unmet medical need and an unexplored avenue for research. Over the last several decades, trial design in 4R-tauopathies has advanced considerably, especially for PSP-RS, in which the underlying neuropathology is highly predictable, and the rate of decline is typically faster than in other neurodegenerative disease, allowing a reliably identifiable and homogenous clinical cohort, with a shorter trial design needed than in Alzheimer's disease. Additionally, novel "basket" designs borrowed from the oncological trial literature are allowing trials in 4R-tauopathy clinical syndromes that are typically without available experimental treatments (NCT03658135, NCT02133846).

Selection of clinically relevant outcomes has been facilitated by several multicenter clinical and observational trials showing striking consistency in several clinical endpoints [194], including the PSP Rating Scale [195], the Schwab and England Activity of Daily Living scale (SEADL) [196], the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [197], and neurofilament light chain (NfL) concentrations in the blood and cerebrospinal fluid [198]. And although the current tau positron emission tomography (PET) radiotracers do not appear sensitive for 4R-tau deposits [199], several more recent and promising efforts may yet yield a 4R-tau imaging biomarker that could replace the current use of volumetric MRI measures of midbrain atrophy to detect PSP-RS.

Taken together, the rapid pace of drug development and recent innovations in trial design will hopefully herald a new age in the treatment of 4R-tauopathies, and a clinically meaningful disease-modifying therapeutic will become available in the coming years. In the interim, numerous pharmacologic and nonpharmacologic approaches can ameliorate symptoms and maintain function for patients suffering from 4R-tauopathies, and a multidisciplinary approach to their care

can lead to a significant improvement in quality of life, as these patients urgently await a needed treatment.

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