CNS Drugs (2018) 32:827–837
https://doi.org/10.1007/s40263-018-0551-3

REVIEW ARTICLE

# Therapeutic Management of the Overlapping Syndromes of Atypical Parkinsonism

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Published online: 27 July 2018


**Abstract**
Progressive supranuclear palsy, corticobasal degeneration and multiple system atrophy account for approximately 10% of neurodegenerative parkinsonism. Considerable clinical overlap exists between these disorders that extends to features considered characteristic of each disease. Clinical diagnostic criteria have attempted to increase the accuracy of clinical diagnosis as accurate diagnosis is necessary to inform prognosis and to facilitate the recognition of disease-modifying treatments. Currently no such treatment exists. Nevertheless, many clinical trials aiming to change the natural history of these diseases are ongoing. The spread and accumulation of abnormal proteins are among the pathophysiological mechanisms targeted. For the time being, however, only symptomatic treatment is available. Levodopa is used to treat parkinsonism, but patients usually show a poor or transient response. Amantadine is also used in practice for the same indication. Botulinum toxin can alleviate focal dystonic manifestations. Addressing non-motor manifestations is limited by the potential of available drugs to impact on other aspects of the disease. Most of the new symptomatic formulations under study are focused on orthostatic hypotension in multiple system atrophy. Exercise, occupational, physical, and speech therapy and psychotherapy should always accompany pharmacological approaches.

**Key Points**

Atypical parkinsonian disorders share clinical and pathological similarities.

Symptomatic treatment is characterized by low efficacy and the potential for adverse drug effects.

Disease-modifying treatments, targeting mechanisms implicated in the development of disease, are under study.

## 1 Introduction

Parkinsonism is a clinical syndrome defined as bradykinesia with rigidity and/or tremor [1]. Parkinson's disease (PD) is by far the commonest cause of parkinsonism. However, approximately 10% of neurodegenerative parkinsonism is caused by three different entities grouped under the term "atypical parkinsonism", namely multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) [2]. These disorders pose a challenge for clinicians as they can be difficult to differentiate from each other, or even from PD. Moreover, they carry a worse prognosis and do not respond well to levodopa, the mainstay of treatment for PD. This work will review the therapeutic options that are available to the clinician and the patient, with a focus on pharmacological treatments, as well as currently studied interventions.

## 2 Presentation and Diagnosis

MSA, PSP and CBD are sporadic adult-onset progressive neurodegenerative diseases, although rare familial cases do exist [3–5]. The mean age at onset is 57, 65 and 64 years,

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respectively, and mean disease duration is approximately 8.5 years for MSA and PSP and 6.5 years for CBD [3, 6, 7]. The unifying clinical feature is the development of parkinsonism characterized by (1) predominance of axial rigidity and bradykinesia and early falls, (2) rare presence of classic, pill-rolling rest tremor, and (3) poor or transient levodopa response. In their classic forms, MSA and PSP present with symmetrical involvement, whereas asymmetry is pronounced in CBD [3–5].

MSA is characterized by autonomic dysfunction, accompanied by parkinsonism and/or cerebellar features [4]. Autonomic dysfunction leads to urogenital (urinary frequency, urgency, incontinence, retention, erectile dysfunction), cardiovascular (orthostatic hypotension), and respiratory (sleep apnoea, stridor) involvement. Ataxia can be evident in gait, oculomotion, limb movements and/or as dysarthria. Rapid eye movement sleep behaviour disorder (RBD) is very common, and patients may also exhibit pyramidal signs [8]. Autonomic dysfunction is invariably present and a requirement for diagnosis according to published criteria [4]. It must be accompanied by either parkinsonian or cerebellar signs, and depending on their relative severity at presentation, two clinical subtypes are described: MSA with predominant parkinsonism (MSA-P) or MSA with predominant cerebellar ataxia (MSA-C). For a diagnosis of probable MSA, urinary incontinence or a drop of more than 30 mmHg/15 mmHg in systolic/diastolic blood pressure within 3 min after standing is required. Less severe orthostatic hypotension or urogenital autonomic dysfunction are enough for a diagnosis of possible MSA. Possible MSA requires one additional feature among a set of clinical or imaging findings.

The classic syndrome of PSP, or Richardson's syndrome, is characterized by the early appearance of postural instability with falls and vertical gaze dysfunction that initially manifests as slow vertical saccades that evolve to a vertical supranuclear gaze palsy [9]. These distinctive findings are accompanied by bradykinesia, rigidity, behavioural changes, impaired executive function, dysarthria and dysphagia [9]. However, it has been demonstrated that PSP has a wide spectrum of potential phenotypes, with Richardson's syndrome being present in only 24% of autopsy confirmed cases [7]. The new clinical diagnostic criteria for PSP have tackled that by defining many of those alternative syndromes in a structured manner suitable for clinical diagnosis [5]. Apart from Richardson's syndrome, the syndromes included in the new criteria are PSP with predominant ocular motor dysfunction (PSP-OM), PSP with predominant postural instability (PSP-PI), PSP with predominant parkinsonism (PSP-P), PSP with predominant frontal presentation (PSP-F), PSP with progressive gait freezing (PSP-PGF), PSP with predominant corticobasal syndrome (PSP-CBS), and PSP with predominant speech and language disorder (PSP-SL). These syndromes are defined based on the clinical particulars of four core clinical features of PSP: ocular motor dysfunction, postural instability, akinesia and cognitive dysfunction. Different combinations of these features provide different degrees of diagnostic certainty (probable, possible and suggestive of PSP). Presentations included in the "suggestive of PSP" category represent early manifestations of the disease.

CBD is the rarest of the three disorders [2]. CBD and its initially described syndrome, i.e. the corticobasal syndrome (CBS), were initially thought to reflect each other, together comprising a single condition [10]. CBS is characterized by asymmetrical motor and higher cortical manifestations such as parkinsonism, dystonia, myoclonus and apraxia, cortical sensory loss, alien limb and cognitive impairment [3]. However, it later became apparent that CBD pathology can lead to a variety of different phenotypes and moreover that CBS can represent a multitude of pathological substrates, including Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD) and PSP [10]. In order to make ante-mortem clinical detection of CBD cases possible, diagnostic criteria were proposed after a review of pathologically confirmed cases [3]. The following syndromes were recognized as the most usual expressions of CBD: CBS, Richardson's syndrome, nonfluent/agrammatic variant of primary progressive aphasia, frontal behavioural-spatial syndrome and AD-resembling dementia. The last syndrome was not included in the diagnostic criteria as it is mainly caused by AD, a far more common condition. Two sets of criteria were created, defining the diagnosis of probable and possible CBD. Their accuracy, however, has been reported to be low [11].

The new sets of diagnostic criteria have drawn into the spotlight the clinical overlap of atypical parkinsonian syndromes. Final clinical diagnoses often differ from initial clinical impression and definite neuropathological diagnoses [3, 6, 12]. The overlap is more obvious for PSP and CBD. Both can manifest with Richardson's syndrome, with CBS, with frontal involvement and with nonfluent/agrammatic variant of primary progressive aphasia (included in PSP-SL). Moreover, the characteristic signs of atypical parkinsonian syndromes that usually guide clinical diagnosis might be relatively specific, but are not diagnostic, and they might not have arisen in the early stages of disease [12, 13]. Supranuclear gaze palsy can develop in MSA and CBD [14], and autonomic involvement can be present in PSP and CBD [13]. Ataxia apart from MSA-C can be a presenting finding in PSP and lead to misdiagnosis [6]. Although the manifestation of a characteristic feature early in the disease course increases its diagnostic value, it is not sufficient to provide diagnostic certainty [12, 13]. For these reasons, neuropathology remains the only way to reach a definite diagnosis.

## 3 Neuropathology

The shared neuropathological substrate of these disorders is the degeneration in the substantia nigra, which is the basis of the clinical parkinsonian syndrome [15]. In addition, they are all characterized by the deposition and accumulation of abnormal, aggregated forms of a certain protein, either tau or alpha-synuclein (α-syn). It is the varying distribution of the aggregates of abnormal tau or α-syn and of the associated degeneration that is thought to determine the different signs and symptoms that accompany parkinsonism in each of these disorders [10]. It is theorized that the abnormal tau and α-syn aggregates have "prion-like" properties, i.e. they can spread between neurons and induce pathological conformations in their normal counterparts [16].

Regarding MSA, its distinctive, highly specific pathological feature is the widespread presence of glial cytoplasmic inclusions (GCIs), accompanied by degeneration of the nigrostriatal (NS) and olivopontocerebellar (OPC) structures [15]. GCIs are oligodendrocyte cytoplasmic inclusions composed of aggregated α-syn [15], thus classifying MSA as a synucleinopathy together with PD. They are distributed across the central nervous system, but accumulate, particularly in areas of grey and white matter associated with motor (both extra-pyramidal and pyramidal) and autonomic functions [17]. The accompanying NS and OPC degenerative changes entail neuronal loss, gliosis and demyelination [18]. The relative degree of involvement of these two systems predicts, to some extent, the clinical subtype of MSA [19].

MSA is classically considered to be a primary oligodendrogliopathy [8]. The burden of GCIs correlates with disease duration and with the degree of degeneration in NS and OPC structures [19], and widespread GCIs are present early in the disease when neuronal degeneration is limited [18]. It has been hypothesized that a-syn aggregation and GCI formation lead to oligodendroglial dysfunction, which in turn impacts neuronal function [8]. Apart from loss of normal oligodendroglial function, neuroinflammation and transmission of misfolded a-syn to neurons, resulting in neuronal a-syn inclusions, could also mediate neuronal involvement [8]. The recent demonstration, however, that neuronal inclusions are more ample and disseminated than earlier thought has upgraded their importance in the pathogenesis of MSA [20].

PSP is characterized by deposition of abnormal, hyperphosphorylated forms of the protein tau [21]. In PSP, tau depositions consist exclusively of 4R-tau, i.e. tau isoforms that contain four repeats of a microtubule binding domain, whereas both 3R and 4R-tau are found in normal brains and in other diseases, e.g. AD [21]. Several tau-immunoreactive inclusions are described in PSP: neurofibrillary tangles (NFTs) are found mainly in the basal ganglia and the brainstem [9]. Tau-immunoreactive lesions in neuronal processes (threads) can also be found in these areas [9]. Oligodendroglial coiled bodies and tufted astrocytes are also present. The latter are a specific feature of PSP [21]. Apart from tau deposition, the pathological findings also encompass neuronal loss and astrogliosis [22]. PSP neurodegenerative changes are particularly severe in the globus pallidus, the substantia nigra and the subthalamic nucleus [22]. These structures are also considered to be affected early in the disease course [21]. There is, however, variability in the distribution of pathology in PSP corresponding to the variation seen in clinical presentations [9]. A higher burden of cortical pathology is expected to underlie cases with significant cortical symptomatology [9].

CBD is 4R-tauopathy, like PSP. Pathologically, neuronal loss and tau-immunoreactive inclusions in neurons and glial cells are observed [23]. Neuronal loss is prominent in the substantia nigra, the superior frontal and parietal cortex and around the central sulcus. Balloon neurons can also be seen in these cortical areas as well as myelin loss in the adjacent white matter. Neuronal tau-immunoreactive inclusions (pretangles and sometimes NFTs) and threads are broadly distributed in cortical areas and in the basal ganglia. Astrocytic plaques, when detected, are almost specific for CBD. Oligodendroglial coiled bodies are common.

The pathophysiology of PSP and CBD is not well understood. Tau is crucial to the degeneration process. In PSP, both gain of tau function and loss of tau function mechanisms could contribute to the development of disease [9]. Loss of tau function could lead to microtubule dysfunction [9]. The spreading of pathology on the other hand could be the expression of the opposite process [9]. Apart from hyperphosphorylation, other abnormal post-translational modifications of tau and also microglial participation could be promoting tau dysfunction [9]. Similar mechanisms could be at play in the case of CBD, as the two disease share many similarities in their clinical presentation [5] and in their pathological and genetic associations [21].

## 4 Treatment

Currently, there is no disease-modifying treatment for atypical parkinsonism. The aim of treatment is thus to relieve symptoms and assist performance in activities of daily living. In general, the pharmacological approach of these disorders is not based on clinical trials, but rather on case series and use of drugs that have shown benefits in other neurodegenerative disorders, such as PD. The symptomatic nature of treatment, the prominent clinical

overlap and the resulting uncertainty of clinical diagnosis allow for a common, symptom-based pharmacological approach for these disorders. This review focuses on medication, but the importance of exercise, occupational, physical, speech therapy and psychotherapy should not be disregarded in clinical practice. Deep brain stimulation is not a therapeutic option for these disorders [24–26]. A frequently overlooked challenge with currently available symptomatic treatment is that of drug safety, which has not been sufficiently studied in atypical parkinsonism or even in PD [27]. Indeed, the interactions or adverse reactions currently encountered in clinical practice, are not well studied.

### 4.1 Parkinsonism

Levodopa is prescribed for bradykinesia and rigidity [8, 24, 26]. Daily doses are slowly increased up to a total of 1–1.5 g/day. A modest, but not long-lasting, clinical benefit can be seen in approximately 30–50% of patients [8, 24, 26]. PSP-P patients might experience a better response to levodopa compared to other PSP phenotypes [26], and MSA-P patients generally respond better to levodopa compared to PSP and CBS [3, 26, 28]. The clinician should always take into account the potential impact of levodopa on other manifestations of atypical parkinsonism that may warrant a dose modification. Levodopa can aggravate orthostatic symptoms and lead to falls and might worsen urinary retention and constipation [29]. It might also induce impulse control disorders and psychotic symptoms [29, 30]. Levodopa-induced dyskinesias might develop in a minority of patients, in particular, in MSA-P, where they usually manifest as painful facial dyskinesias, whereas they are extremely rare in PSP and CBS [3, 26, 28]. If gastrointestinal symptoms arise during initial dosing, domperidone (10 mg three times a day [TDS]), a peripheral dopamine receptor blocker, can be used [29]. Note, however, that domperidone has the potential of QT interval prolongation, and thus co-administration with drugs with similar effects, e.g. selective serotonin reuptake inhibitors (SSRIs), must be cautious [31]. Dopamine agonists and monoamine oxidase B (MAO-B) inhibitors are considered less effective than levodopa [8, 24, 26].

Amantadine (doses slowly increased to 100–200 mg TDS) might be able to ameliorate bradykinesia and rigidity and improve balance in some patients and can be tried as a second-line treatment [8, 24, 26]. High doses (> 400 mg) are rarely tolerable because of adverse effects that include gastrointestinal symptoms, insomnia, confusion, agitation and hallucinations [30]. These effects are more likely to appear if amantadine is co-administered with memantine or anticholinergic medication [32]. Amantadine can also worsen orthostatic hypotension [29].

### 4.2 Dystonia

If the onset of dystonia is associated with a modification in the doses of levodopa, for example, facial painful dystonia after increasing levodopa in MSA patients [28], then a return to the previous regimen might be considered. Otherwise, dystonic manifestations respond well to treatment with botulinum toxin [8, 24, 26]. A potential drawback is that treating cervical dystonia might worsen or elicit dysphagia [26]. Particular caution should be taken when attempting to treat anterocollis in MSA, as the resulting dysphagia might be particularly severe [33]. Benzodiazepines can also be employed to improve dystonia, but can interfere in and aggravate other disease processes [29]. Of particular importance are their negative effects on cognition or sleep apnoea and other respiratory sequelae of MSA [29].

### 4.3 Myoclonus

Clonazepam or levetiracetam can be used to treat myoclonus [24, 29]. Clonazepam is started at a low dose, e.g. 0.5 mg/day, and gradually increased afterwards [29]. As a benzodiazepine it has the potential for important side effects, as described above. Levetiracetam is started at 250 mg/day and then increased to up to 3000 mg/day [24, 29]. It has the potential to induce mood changes (depression, anxiety), drowsiness and agitation [24, 29].

### 4.4 Ataxia

There is no pharmacological treatment available for ataxic manifestations [33]. Non-pharmacological interventions are indicated, mainly physiotherapy, occupational therapy and speech therapy [33].

### 4.5 Cognitive and Behavioural Impairment

There is no specific treatment for cognitive impairment encountered in atypical parkinsonism [34]. Acetylcholinesterase inhibitors are not recommended as they may exacerbate motor symptoms in exchange for a small improvement in memory [34–36]. One possible exception is CBS, where a trial of acetylcholinesterase inhibitors or memantine could be considered because of the possibility of underlying AD pathology [37].

Behavioural manifestations can also be difficult to manage. Treating other neuropsychiatric comorbidities, such as depression, is important as this might ameliorate cognitive impairment or behavioural manifestations [30]. However, it is often a challenge to differentiate between the depression and apathy these patients have. Assessing for potential cognitive or behavioural adverse effects of concomitant medications could also be beneficial, if dosage modification

or discontinuation is possible [30]. Examples include benzodiazepines and anticholinergic medication, including tricyclic antidepressants (TCAs) [29]. Amantadine, in addition to its effect on motor symptoms, might have a positive impact on apathy, but carries the risk of other behavioural adverse effects [26, 30]. Antipsychotics should be avoided when possible as they exacerbate motor manifestations and could affect cognition [24, 30] and also cause agitation and confusion. A trial of acetylcholinesterase inhibitors to improve apathy is justified in CBS for the abovementioned reasons [24].

### 4.6 Depression, Anxiety and Emotional Incontinence

SSRIs are effective in treating depression and anxiety and are preferred over TCAs as this class is associated with a less safe adverse effect profile [34]. More specifically, TCAs can cause confusion and worsen cognition, orthostatic hypotension and urinary retention [29, 34]. Among TCAs, amitriptyline has been reported to have potential desirable effects on ocular motion in PSP patients [26]. The use of trazodone and mirtazapine has been also reported [30]. Emotional incontinence is also treated with SSRIs at low doses [30].

### 4.7 Other Neuropsychiatric Symptoms

There is no pharmacological treatment for apraxia. Specifically for apraxia of eyelid opening, treatment with pretarsal injections of botulinum toxin has been used [9, 26]. Zolpidem can be used for insomnia because transient beneficial effects have been reported in the literature [26]. The classic treatment of RBD in MSA is the administration of low-dose clonazepam, a benzodiazepine, before sleep (0.5–2 mg/day) [33]. Melatonin (2 mg/day) can substitute clonazepam in patients with concomitant sleep apnoea [33]. The goal of treatment in RBD is to prevent self-injury or the injury of others, as RBD is otherwise usually not disruptive for the patient. Pharmacological treatment is therefore initiated when conservative measures (creating a safe sleeping environment, avoiding precipitating factors) are not deemed sufficient [38].

### 4.8 Urological Symptoms

Anticholinergic drugs are used to treat urinary frequency, urgency and incontinence, but have important side effects as they can worsen constipation, cognition and cause confusion [34, 39]. Commonly used anticholinergics include trospium (10–15 mg/2–3 times per day), tolterodine (2 mg two times per day) and darifenacin (7.5–15 mg once per day) as they have smaller effects on cognition than other substances of the same class, e.g. oxybutinin [34, 40, 41]. However, bear in mind that anticholinergic medication can increase urinary retention, and thus voiding ability should be assessed [39]. Mirabegron (25–50 mg once per day), a β3-adrenoreceptor agonist, can also benefit patients without promoting retention or influencing cognition [40, 41]. It must be noted that there are no studies in atypical parkinsonism with these drugs, and their use is only empirical. Botulinum toxin, injected to the detrusor muscle, has been suggested as an alternative to anticholinergic medications [42].

Urinary retention (post-void residual volume > 100 mL), on the other hand, can be treated with intermittent self-catheterization, but this practice has the potential to lead to urethral ulceration [34]. When ulceration occurs or when self-catheterization is no longer easy to perform due to disease progression, a permanent suprapubic catheter can be employed [33, 40]. α1-Adrenoreceptor antagonists that relax urethral smooth muscle (prazosin 1 mg TDS or moxisylyte 10 mg TDS) and cholinergic drugs, e.g. pyridostigmine, to promote detrusor contractility can supplement self-catheterization [34, 39]. When both retention and urgency/incontinence are present, anticholinergic medication and self-catheterization with α1-adrenoreceptor antagonists are used together [39]. Nycturia can be addressed with intranasal desmopressin (5 μg at night) [33]. If desmopressin is used, the possibility of emerging hyponatraemia and heart failure should be regularly assessed [39].

Erectile dysfunction can be addressed using phosphodiesterase-5 inhibitors, e.g. sildenafil (25–100 mg 1 h before sexual activity), or using alprostadil intracavernous injections. Note that α1-adrenoreceptor antagonists and phosphodiesterase-5 inhibitors can aggravate orthostatic symptoms, but cholinergic drugs and desmopressin might ameliorate them [34, 39].

### 4.9 Orthostatic Hypotension

The first steps to treating orthostatic symptoms is to assess concomitant medications, as many formulations have the potential to cause or exacerbate orthostatic hypotension, and to introduce conservative management [34, 43]. The list of medications that can exacerbate orthostatic symptoms includes, but is not limited to, levodopa and other dopaminergic substances, amantadine, phosphodiesterase-5 inhibitors, α1-adrenoreceptor antagonists, antidepressants (mainly TCAs) as well as the majority of drugs used to treat cardiovascular comorbidities [29, 43]. If possible, such medications should be discontinued, or their dosage revised. Conservative management refers to appropriate fluid and salt intake, exercise, refraining from sudden changes in posture, avoiding situations that can increase body temperature, such as hot baths or hot environments, sleeping with the head elevated relative to the feet to reduce supine hypertension and morning hypotension, using abdominal

and leg compression devices, eating frequent, smaller and low-in-carbohydrate portions of food, avoiding alcohol and addressing co-existing anaemia [34, 43]. Medications are added when conservative measures alone fail to provide sufficient symptomatic improvement or when symptom severity can endanger the patient [43]. Fludrocortisone (0.1–0.3 mg) is the classic treatment in MSA [44]. Other options include the sympathomimetic midodrine (2.5–10 mg TDS, at least 5 h before bedtime) and a prodrug of norepinephrine, droxidopa (100–600 mg TDS, at least 5 h before bedtime). All three drugs can worsen supine hypertension, and midodrine can exacerbate urinary retention [43]. Potential cases of neuroleptic malignant syndrome have been reported, so a high degree of suspicion is required when altering droxidopa dosage, or that of another associated medication, e.g. levodopa [45]. Pyridostigmine, an acetylcholinesterase inhibitor, might be appropriate for less severe cases [43]. It is not associated with supine hypertension, but can cause sialorrhoea, abdominal cramps, diarrhoea, excessive sweating and urinary incontinence [43].

In general terms, improving orthostatic hypotension takes precedence over supine hypertension because of the latter's interfering symptomatology in everyday life [43]. If supine hypertension is severe enough that pharmacological treatment is considered (systolic blood pressure > 180 or diastolic blood pressure > 110 mmHg), fludrocortisone should be best avoided and short-acting antihypertensive drugs could be employed [43]. Clonidine, captopril, losartan, hydralazine or transdermal glyceryl trinitrate at bedtime are recommended regimens [43]. If dietary modifications cannot satisfactorily address postprandial hypotension, caffeine, acarbose or octreotide before meals could be helpful [8].

### 4.10 Respiratory Involvement

Nocturnal inspiratory stridor and sleep apnoea are addressed with continuous or bi-level positive airway pressure devices [34]. Inspiratory stridor is highly specific for MSA [44]. In severe cases, unilateral botulinum toxin injection into the vocal cord adductors can be used after taking into consideration the possibility of aggravating dysphagia [8, 34]. Finally, in severe cases with daytime stridor, tracheostomy can be considered, but the risk of sudden death remains even after this procedure has been performed [44].

### 4.11 Other Symptoms

Dysphagia is not amenable to pharmacological therapy. A speech therapy approach is instead advised, with percutaneous endoscopic gastrostomy reserved for when there is a considerable risk for aspiration [34]. Drooling can be managed using topical or oral anticholinergics [29]. Drooling can be managed effectively by salivary gland injections with botulinum toxin [34]. This method carries a risk of worsening dysphagia in late disease stages [34], but is preferred over the use of anticholinergics (glycopyrrolate 1 mg TDS or topical 1% atropine drops, one drop TDS) due to their potential for cognitive side effects and for deteriorating concomitant urinary and orthostatic symptoms [29, 43]. Topical preparations can be used to treat eye dryness [29]. Constipation is handled conservatively by making dietary modifications, ensuring adequate fluid intake and using laxatives [8, 44].

## 5 Clinical Trials: Symptomatic Approaches and Disease Modification

The past few years have seen a surge of interventions aiming to alter disease progression in atypical parkinsonism. This is driven by the scientific community's increased understanding of these disorders [9]. Results for riluzole, tideglusib and davunetide in PSP and for riluzole, minocycline, lithium, rifampicin and rasagiline in MSA did not suggest a favourable effect on disease progression [9, 18]. On the other hand, administration of mesenchymal stem cells and the use of intravenous immunoglobulin, albeit uncontrolled, in patients with MSA slowed Unified MSA Rating Scale score progression and improved it, respectively [18, 46, 47]. Moreover, there are many ongoing trials on pharmacological interventions aiming at disease modification (Table 1). Most interventions designed for PSP aim to preserve normal tau function or halt the spread or formation of abnormal tau [9]. In a similar way, the spread and formation of abnormal conformations of α-syn have been targeted in MSA. In addition, substances aiming to modulate neuroinflammation in MSA have been also developed.

Among ongoing trials of symptomatic pharmacological interventions, particularly common are substances aiming to address neurogenic orthostatic hypotension in MSA, among other disorders (Table 2). The short-term effects on supine hypertension of many already in use substances, mainly antihypertensive medications, are also under study (NCT00223717). Non-pharmacological interventions to address supine hypertension in patients with orthostatic hypotension are also investigated. These include the use of continuous positive airway pressure (NCT03312556), abdominal compression (NCT02429557) and the application of heating pads (NCT02417415, NCT03042988). Direct current stimulation is another non-pharmacological intervention aiming to provide symptomatic benefits for ataxia or apraxia (NCT03120013, NCT00273897).

There are certain factors that could hinder the demonstration of an existing disease-modifying effect in clinical trials [9, 18]. First, the rarity of these diseases can lead to underpowered trials. Second, the clinical overlap

**Table 1** Ongoing or completed, but not yet published, studies of interventions aiming at disease modification

| ID | Conditions | Interventions | Action | Primary outcomes | Phase | Enrolment | Study design | Recruitment |
|---|---|---|---|---|---|---|---|---|
| NCT03403309 | MSA | Inosine 5′-monophosphate | Uric acid precursor, antioxidative properties | Serum uric acid elevation, safety and tolerability | 2 | 80 | | Not yet recruiting |
| NCT03265444 | MSA | Autologous bone marrow-derived mesenchymal stem cells (CS10BR05) | – | Safety and tolerability | 1 | 9 | Single group, open label | Not yet recruiting |
| NCT02388295 | MSA | AZD3241 | Myeloperoxidase inhibitor [18] | Microglia activation in the striatum | 2 | 59 | | Completed |
| NCT02315027 | MSA | Autologous mesenchymal stem cells | – | Safety and tolerability | 1 | 30 | Single group, open label | Active, not recruiting |
| NCT02270489 | MSA | AFFITOPE® PD01A or PD03A | Active immunization against α-syn [18] | Safety and tolerability | 1 | 30 | Randomized, single blind, placebo controlled | Completed |
| NCT02008721 | MSA | Epigallocatechin gallate | Inhibition of abnormal α-syn formations | Unified MSA Rating Scale | 3 | 92 | | Completed |
| NCT01146548 | MSA | Fluoxetine | Selective serotonin reuptake inhibitor | Unified MSA Rating Scale | 2 | 87 | | Completed |
| NCT02985879 (extension in NCT03391765) | PSP | ABBV-8E12 (C2 N-8E12) | Anti-tau monoclonal antibody [9] | PSP Rating Scale, safety and tolerability | 2 | 330 | | Recruiting |
| NCT02494024 (extension in NCT03413319) | PSP | ABBV-8E12 (C2 N-8E12), single dose | Anti-tau monoclonal antibody | Safety and tolerability | 1 | 32[a] | | Completed |
| NCT03068468 | PSP | BIIB092 (BMS-986168) | Anti-tau monoclonal antibody [9] | PSP Rating Scale, safety and tolerability | 2 | 396 | | Recruiting |
| NCT02460094 (extension in NCT02658916) | PSP | BIIB092 (BMS-986168) | Anti-tau monoclonal antibody | Safety and tolerability | 1 | 48 | | Completed |
| NCT02460731 | PSP | Plasma from healthy male donors < 30 years old | Rejuvenation [9] | Number of patients with drug-limiting toxicity | 1 | 10 | Single group, open label | Recruiting |
| NCT02422485 | PSP | Salsalate | Inhibitor of tau acetylation [9] | Number of patients with drug-limiting toxicity | 1 | 10 | Single group, open label | Recruiting |
| NCT01537549 | PSP | Alpha-lipoic acid and L-acetyl carnitine | Neuroprotection | Safety and tolerability | 1/2 | 11 | Single group, open label | Completed |
| NCT02133846 | PSP, CBS | TPI-287 | Microtubule stabilizer [9] | Safety and tolerability (maximum tolerated dose) | 1 | 44 | | Active, not recruiting |

ID refers to the clinicaltrails.gov identifier. Enrolment refers to actual enrolment for completed studies or otherwise to estimated enrolment. Study design is randomized, double blind, placebo controlled with parallel assignment unless otherwise mentioned

*α-Syn* alpha-synuclein, *CBS* corticobasal syndrome, *MSA* multiple system atrophy, *PSP* progressive supranuclear palsy

[a]Estimated enrolment

**Table 2** Ongoing or completed, but not yet published, studies of interventions for symptomatic treatment of atypical parkinsonism

| ID | Intervention | Pharmacological action | Condition | Target symptom | Primary outcome | Phase | Enrolment | Design | Recruitment |
|---|---|---|---|---|---|---|---|---|---|
| NCT03446807 | Droxidopa | Norepinephrine precursor | PD; MSA; PSP | Fatigue | Visual Analogue Fatigue Scale | 2 | 32 | | Not yet recruiting |
| NCT03325556 | Pimavanserin | Selective serotonin 5-$HT_{2A}$ inverse agonist [48] | Dementia-related psychosis (including frontotemporal degeneration spectrum) | Psychosis | Time to relapse | 3 | 356 | | Recruiting |
| NCT02839642 | Rivastigmine | Cholinesterase inhibitor | PSP | Motor, cognitive, behavioural | Number of falls and near falls | 3 | 106 | | Recruiting |
| NCT02796209 | Atomoxetine | Selective norepinephrine transporter blocker | MSA | Orthostatic hypotension | Orthostatic Hypotension Questionnaire score | 2 | 40 | Randomized, double blind, placebo controlled, crossover | Recruiting |
| NCT02705755 | TD-9855 | Norepinephrine and serotonin reuptake inhibitor [49] | Neurogenic orthostatic hypotension (including MSA) | Orthostatic hypotension | Seated systolic blood pressure | 2 | 30 | Randomized, single blind, placebo controlled | Recruiting |
| NCT02149901 | Pseudoephedrine + drinking water | Pressor response | MSA | Orthostatic hypotension | Peak increase in systolic blood pressure | 1 | 35 | Randomized, open label, placebo controlled, crossover | Active, not recruiting |
| NCT02071459 | Droxidopa | Norepinephrine precursor | MSA | Orthostatic hypotension | Orthostatic Hypotension Symptom Assessment score | 2/3 | 108 | | Recruiting |
| NCT02064166 | Intranasal insulin | Regional changes in cerebral perfusion [50] | PD, MSA | Motor, cognitive, behavioural | Brief Visuospatial Memory Test-Revised | 2 | 16 | | Completed |
| NCT02586623 | Droxidopa | Norepinephrine precursor | Symptomatic neurogenic orthostatic hypotension (including MSA) | Orthostatic hypotension | Time to intervention | 4 | 482 | Randomized withdrawal, double blind, placebo controlled | Recruiting |

ID refers to the clinicaltrails.gov identifier. Enrolment refers to actual enrolment for completed studies or otherwise to estimated enrolment. Study design is randomized, double blind, placebo controlled with parallel assignment unless otherwise mentioned

*MSA* multiple system atrophy, *PD* Parkinson's disease, *PSP* progressive supranuclear palsy

leads to recruitment of a more heterogeneous group of patients than desired. Third, avoiding the repercussions of this overlap can currently be achieved only at the expense of recruiting patients at later stages of disease progression, i.e. when specific features of the disease under study have become apparent. Unfortunately, at these stages, the effects of a potential treatment might be less pronounced or not present. Improving the sensitivity and specificity of diagnostic criteria and most importantly identifying early biomarkers of these diseases are the proposed and actively sought after solutions to these problems [9, 18].

## 6 Conclusions

MSA, PSP and CBD account for 10% of neurodegenerative parkinsonism. Neuropathologically, these disorders are characterized by the accumulation of abnormal forms of proteins that might exhibit prion-like properties. The type of the accumulating protein, α-syn or tau, its distribution and that of the associated degeneration differs among the disorders, but substantia nigra degeneration is present in all. Neuropathology provides the only way to a definite diagnosis. Considerable clinical overlap exists that extends to features considered characteristic of each disease. As a result, final clinical diagnoses often differ from initial impression and from definite diagnosis. Clinical diagnostic criteria have highlighted this clinical overlap and attempt to increase the accuracy of clinical diagnosis.

Accurate diagnosis is necessary to inform prognosis and to facilitate the recognition of disease-modifying treatments. Currently no such treatment exists. Nevertheless, many clinical trials aiming to change the natural history of these diseases are ongoing. The spread and accumulation of abnormal proteins are among the pathophysiological mechanisms targeted. For the time being, however, only symptomatic treatment with limited efficacy is available. Levodopa is used to treat parkinsonism, but patients usually show a poor or transient response. Amantadine is also used in practice for the same indication. Botulinum toxin can alleviate focal dystonic manifestations. Addressing non-motor manifestations is limited by the potential of available drugs to impact on other aspects of the disease. Most of the new symptomatic formulations under study are focused on orthostatic hypotension in MSA. Exercise, occupational, physical, and speech therapy and psychotherapy should always accompany pharmacological approaches.

### Compliance with Ethical Standards

**Funding** No funding was received for this article.

**Conflict of interest** Nikolaos Giagkou and Maria Stamelou have no conflicts of interest to disclose.

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