



Update on Therapeutic Strategies for Atypical Parkinsonian Syndromes

Atipik Parkinson Sendromları için Yeni Terapötik Stratejiler

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Abstract

Atypical Parkinsonian syndromes include multiple systems atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB). These conditions show signs of dopamine deficiency, but unlike Parkinson's disease (PD), they do not respond to dopaminergic treatments and usually have a worse outcome compared with idiopathic PD. The Atypical Parkinsonian syndromes have no specific treatment or cure. Up to now, there are just a few therapeutic approaches that place emphasis on symptomatic and supportive therapies. These approaches are based on palliative care, physical or occupational therapy, neuropsychology, speech pathology, psychiatry, and social works. Pharmacotherapy with levodopa, dopamine agonists, amantadine, co-enzyme Q10, botulinum toxin, cholinesterase inhibitors, and selective serotonin reuptake inhibitors may improve some symptoms of PSP and CBD. In this review, we categorize some of the recent studies on therapeutic strategies as follows: autologous transplantation of stem cells, deep transcranial magnetic stimulation, intravenous immunoglobulin, intranasal insulin, and pimavanserin. By classifying and comparing the most recent advances in treatment strategies of the atypical parkinsonian syndromes, we provide a benchmark for further studies to introduce new effective therapeutic methods.

Keywords: Atypical Parkinsonian syndromes, treatment, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, dementia with Lewy bodies

Öz

Atipik Parkinson sendromları arasında multisistem atrofi (MSA), progresif supranükleer palsi (PSP), kortikobazal dejenerasyon (KBD) ve Lewy cisimcikli demans bulunur (DLB). Bu hastalıklar dopamin eksikliği belirtileri gösterir, ancak Parkinson hastalığının (PH) aksine dopaminerjik tedavilere cevap vermezler ve genellikle idiyopatik PH ile karşılaştırıldığında daha kötü bir sonlanıma sahiptir. Atipik Parkinson sendromlarının spesifik bir tedavisi yoktur. Şimdiye kadar, semptomatik ve destekleyici tedavilere vurgu yapan birkaç terapötik yaklaşım vardır. Bu yaklaşımlar palyatif bakım, fiziksel veya mesleki terapi, nöropsikoloji, konuşma patolojisi, psikiyatri ve sosyal çalışmalar temellidir. Levodopa, dopamin agonistleri, amantadin, koenzim Q10, botulinum toksini, kolinsterez inhibitörleri ve selektif serotonin geri alım inhibitörleri ile farmakoterapi, PSP ve KBD'nin bazı semptomlarını iyileştirebilir. Bu derlemede; kök hücrelerin olog transplantasyonu, derin transkranial manyetik stimülasyon, intravenöz immünoglobulin, intranazal insülin ve pimavanserin gibi terapötik stratejiler üzerine yapılan son çalışmalardan bazılarını kategorize ettik. Atipik Parkinson sendromlarının tedavi stratejilerindeki en son gelişmelerin sınıflandırılması ve karşılaştırılması; yeni ve etkili terapötik yöntemlerin geliştirilmesi için yapılacak ileri çalışmalara kriter sağlar.

Anahtar Kelimeler: Atipik Parkinson sendromları, tedavi, progresif supranükleer palsi, multisistem atrofi, kortikobazal dejenerasyon, Lewy cisimcikli demans

Introduction

Parkinsonism is a clinical syndrome that manifests through the combination of bradykinesia and resting tremor, rigidity, freezing, and postural instability. Aside from many secondary or acquired causes of the parkinsonism, the most common neurodegenerative cause of parkinsonism is Parkinson disease (PD). Atypical Parkinsonian syndrome (APS) is a group of neurodegenerative disorders characterized by parkinsonian signs and special features that distinguish them from PD (1). The most

common APSs include progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB) (2). These are also classified as 'Parkinson-plus syndromes.' APSs are identified by abnormal deposition of proteins such as α -synuclein and tau in brain tissue. PSP and CBD are tauopathies, whereas MSA and DLB comprise the main synucleinopathies (as well as PD). Differentiation of these atypical syndromes from idiopathic PD is critical, because of the poor response to dopaminergic and standard PD treatments,

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and their worse outcome. There are some features that help to distinguish between APS and PD (3). These consist of rapid progression, cerebellar ataxia, autonomic dysfunction, oculomotor abnormalities, early postural instability, and falls, along with a poor response to levodopa, severe dysarthria, myoclonus, apraxia, and early dementia. This review article focuses on therapeutic advances in the most common APSs (4).

1. Progressive Supranuclear Palsy

PSP (Steele-Richardson-Olszewski syndrome) is a progressive clinical syndrome that presents with typical features including early postural instability, even leading to falls during the first year after the beginning of the symptoms, supranuclear vertical gaze palsy and parkinsonism that does not respond to levodopa, pseudobulbar palsy, and mild dementia (5). Abnormal tau protein (tauopathy) is deposited in the basal ganglia, brainstem, prefrontal cortex, and cerebellum. There are several variants of the PSP such as PSP-parkinsonism, PSP-pure akinesia with gait freezing, PSP-corticobasal syndrome, PSP-behavioral variant of frontotemporal dementia (FTD), PSP-primary lateral sclerosis, and PSP-cerebellar variant (6).

Therapeutic Strategies

1.1 Supportive Therapies

It is well known that there is no effective treatment for PSP. Current therapeutic approaches have been focused on symptomatic improvement based on neurotransmitter replacement and supportive therapies such as rehabilitative services and allied healthcare. Physical therapy is used for gait disturbances, postural instability, and fall prevention. Speech therapy is required for patients with speech apraxia. Periodic assessment of swallowing with fluoroscopy (every 6-month) to detect dysphagia and aspiration together with a modified diet is lifesaving. Feeding tubes or percutaneous gastrostomy tubes can be used in the later stages of disease, but the decision should be made very carefully in view of quality of life (7).

1.2 Symptomatic Pharmacotherapy

To assess the parkinsonism responsiveness to levodopa (specifically bradykinesia and rigidity), a trial with 1200-1500 mg/d levodopa is suggested for one month. Existing evidence suggests that response rates ranging from 25 to 38% with mild-to-modest but transient beneficial effects of levodopa on akinesia and rigidity. PSP-P, initially, is the most responsive to this trial among other variants of PSP; however, secondary resistance is to be expected within a few years from symptom onset (8). Most of the time, dopamine agonists have limited benefits. In one study, rotigotine (6 mg/day) resulted in a marked benefit in patients with Restless Legs syndrome, especially in PSP-P variant (9). Amantadine (N-methyl-D-aspartate-antagonist) has been declared as an effective choice for gait and dysphagia. Despite reported doses up to 600 mg/day, it rarely exceeds 400-450 mg/day dosage in practice, due to either lack of efficacy or intolerance (irritability or agitation) (10). Zolpidem has been reported to show transient improvement in voluntary saccadic eye movements (11). Furthermore, using gabapentin over 5 weeks led to some benefits in deficits of voluntary saccade inhibition and anti-saccade task.

Balance and eye movement therapy may be helpful in better control of downward saccades. Ophthalmic lubricants for dry eyes, sunglasses for photosensitivity, and prisms for diplopia are used (12).

Regarding sialorrhea, anticholinergic (glycopyrrolate, scopolamine) drugs can deteriorate cognition. Moreover, injection of botulinum toxin in the parotid and submandibular glands could worsen dysphagia. Ophthalmic atropine (1%) drops are prescribed sublingually for palliative treatment. Anticholinergics are not prescribed because of their potential for confusion (13). Botulinum toxin is used in cases of painful dystonic posturing, blepharospasm, and eye opening apraxia, and muscle relaxants (baclofen) are recommended for spasticity and contractures. For cognitive decline, cholinesterase inhibitors such as rivastigmine and donepezil have minimal benefit. Donepezil was tried in a randomized, placebo controlled and double-blind study. A crossover trial in 21 patients revealed improvements in memory but made motor function worse. As another cholinesterase inhibitor, rivastigmine was used in five patients with PSP and had positive effects on memory versus decreased motor function (14). Depression, anxiety and irritability had been managed with antidepressants such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) (15). Among tricyclic antidepressants, amitriptyline has shown the highest overall improvement, whereas desipramine had a greater effect on apraxia of lid opening. The recommended antidepressants for apathy include bupropion, venlafaxine, sertraline, and fluoxetine (16). For a pseudobulbar effect, dextromethorphan and quinidine, as tricyclic antidepressant or SSRIs might be useful (17). For the treatment of urinary frequency, agents such as tolterodine, trospium, solifenacin, and darifenacin are preferred over antispasmodics, due to central nervous system adverse effects such as beclouded dementia (18). Table 1 summarizes symptomatic pharmacotherapies that are used in APS.

1.3 Disease-modifying Treatments

Recently, research has focused on identifying novel disease-modifying treatments for PSP, targeting mainly tau dysfunction and mitochondria dysfunction (19). Table 2 includes disease-modifying treatments for categorized Parkinson-plus syndromes.

1.3.1 Tau Dysfunction

PSP is known as a tauopathic neurodegenerative disease. When tau aggregates, it may be toxic for cells. Hyperphosphorylation of tau may increase deposition of insoluble tau and decrease binding to microtubules, leading to loss of function. Hence, new therapeutic strategies have aimed to inhibit aggregation or phosphorylation, diminish tau levels, and provide microtubule stabilization. Glycogen synthase kinase-3 (GSK-3) is an important enzyme in tau hyperphosphorylation and thus, its inhibition may lead to reduction of tau phosphorylation *in vitro* and *in vivo*. In recent double-blind, placebo-controlled studies, lithium and tideglusib, two types of GSK-3 inhibitors, both failed to show efficacy (20). However, in a small subgroup of patients, there were some differences in progression of brain atrophy in serial magnetic resonance imaging. Methylene blue, through inhibition of the tau aggregation, and by reduction of tau levels by way of promoting autophagy or other mechanisms, is currently being investigated

Table 1. Symptomatic pharmacotherapies in atypical parkinsonian syndromes				
Symptoms	Treatment options			
	PSP	CBD	MSA	DLB
Parkinsonism/ rigidity	Levodopa Dopamine agonists Amantadine	Levodopa/carbidopa dopaminergic agents, benzodiazepines anticholinergics	Levodopa (MSA-P) Dopamine agonists, dopamine reuptake inhibitors SSRIs (paroxetine)	Levodopa Dopamine agonists
Cerebellar ataxia			Clonazepam, propranolol, baclofen and amantadine buspirone, gabapentin, protirelin tartrate physiotherapy	
Dysphagia	Modified diet, feeding tube or percutaneous gastrostomy			
Dysarthria	Speech therapies			
Gait disturbance	Physical therapy			
Dystonia, spasticity, contractures	Botulinum toxin muscle relaxants (baclofen)	Botulinum toxin benzodiazepines, anticholinergic agents muscle relaxants	Botulinum toxin anticholinergic, amantadine, dopamine agonists, muscle relaxants tetrabenazine.	
Cognitive impairment	Cholinesterase inhibitors	AChEIs Memantine (uncertain)		AChEIs/memantine Neuropsychiatric assessment Cognitive therapy/ neuropsychiatric assessment
Erectile dysfunction			Intracavernosal injection of papaverine or prostaglandin E1 sildenafil (limited)	
RBD			Clonazepam / sodium oxybate, temazepam, zopiclone, gabapentin and pramipexole donepezil / melatonin	Clonazepam/ melatonin
Orthostatic hypotension			Conservative approach fludrocortisone or desmopressin midodrine pyridostigmine droxidopa	
Behavioral disturbances	Tricyclic antidepressants SSRIs SNRIs ¹⁹ bupropion, venlafaxine, sertraline and fluoxetine	SSRIs behavioral therapy atypical neuroleptics trazodone (FTD)	SSRIs Electroconvulsion nursing care (ECT) and family education levodopa	SSRIs ECT atypical antipsychotics (psychosis)
Ocular symptoms	Anticholinergics/botulinum/ ophthalmic atropine zolpidem gabapentin (MAO)-B inhibitors balance and eye movement therapy			
Myoclonus		Clonazepam, levetiracetam, gabapentin, valproic acid		
Tremor		Propranolol		

PSP: Progressive supranuclear palsy, CBD: Corticobasal degeneration, MSA: Multiple system atrophy, DLB: Dementia with Lewy bodies, MSA-P: Multiple system atrophy parkinsonism, SSRIs: Selective serotonin reuptake inhibitors, AChEIs: Acetylcholinesterase inhibitors, RBD: REM sleep behavior disorder, FTD: Frontotemporal dementia, SNRIs: Serotonin norepinephrine reuptake inhibitors

Table 2. Disease-modifying treatments for categorized atypical parkinsonian syndromes

		Other strategies	Ongoing pharmacotherapies
Tauopathies	Tau dysfunction	-Riluzole (not effective)	-TPI-287 (microtubule stabilizer)
	-GSK-3 inhibitors	-GSPE	-salsalate (prevent acetylation of tau)
	-Methylene blue	-DTMS	-BM stem cells (stimulate neurotropic factors)
	-Davunetide (not effective)	-Intravenous and intrathecal infusions of autologous adipose tissue-derived mesenchymal stem cells (MSC) and bone marrow MSC	-ASOs and BMS-986168 (antibody against cerebrospinal fluid tau)
	-Microtubule stabilizers [GFAP, taxol derivatives (TPI-287), epothilones (mainly epothilone D)]		-Active or passive immunizations
	-ASOs		-Interfering RNAs and splice modifiers (decrease of 4R-tau isoforms)
	-Interfering RNAs		
	Mitochondrial dysfunction		
	-Coenzyme Q10		
	-Pyruvate		
	-Niacin amide		
	-Creatine		
Synucleinopathies	α-syn dysfunction	-Mesenchymal stem cells	-Neurotrophic factors (BDNF, GDNF)
	-Rifampicin	-Anti-glutamate drug (riluzole)	-Neurogenesis induction
	-Kallikrein-6 (neurosin)	-r-hGH (no significant effect)	-Cell therapy with stem cells
	-MMP9	-Estrogen (not confirmed)	-LRRK2 kinase inhibitors (sorafenib)
	-Cathepsin D	-DBS (not recommended)	-GW5074 and staurosporine for LRRK2
	Neuroinflammation		-Gene therapy for PARK2 and <i>GBA</i>
	-Intravenous immunoglobulin		-Neuroprotective products (DJ-1 glycolate and D-lactate)
	-Active Vaccination with AFFITOPE®		-Anti alpha syncline monoclonal antibodies
	-Nonsteroidal anti-inflammatory drugs (ibuprofen, indomethacin)		-Nilotinib (Abl tyrosine kinase inhibitor)
	-TNF α inhibitors (XPro1595)		-Passive immunization via 9E4
	-Immunomodulatory drugs		-Vaccine (AFFiRiS AG)
	-Antidepressants (fluoxetine)		-Lentiviral-mediated RNAi
	-Antioxidants (quercetin, curcumin)		-BS targeting nucleus basalis of Meynert (NBM)

GSK-3: Glycogen synthase kinase-3, GFAP: Growth factor activity dependent neurotropic protein, ASOs: Antisense oligonucleotides, GSPE: Grape seed-derived polyphenolic extracts, DTMS: Deep transcranial magnetic stimulation, r-hGH: Recombinant human growth hormone, DBS: Deep brain stimulation, BDNF: Brain-derived neurotrophic factor, GDNF: Glial cell-derived neurotrophic factor, *GBA*: β -Glucocerebrosidase, RNAi: RNA interference

in phase III clinical trials for Alzheimer's disease (AD) and behavioral variant frontotemporal dementia. Stabilization of the microtubules has been proposed as a mechanism to reduce tau function (21). Recently, davunetide did not show satisfying efficacy in a double-blind study. This peptide, extracted from the growth factor activity dependent neurotropic protein, was recommended as a microtubule stabilizer (22). Further microtubule stabilizers such as taxol derivatives (TPI-287), epothilones (mainly epothilone D), and others are currently considered as therapies for tauopathy disorders. Antisense oligonucleotides (ASOs) have also demonstrated great promise in reducing tau concentrations in animal models (23). Some experimental data demonstrated that small interfering RNAs for the suppression of expression of human tau could be another therapeutic choice in the future.

1.3.2 Mitochondrial Dysfunction

Mitochondrial dysfunction might be another target for therapeutic aims in PSP. Oral administration of coenzyme Q10 restored adenosine triphosphate (ATP) levels and reduced neuronal apoptosis in treated rats. In a small, double-blind, randomized trial, patients with PSP received coenzyme Q10 for 6 weeks. Compared with placebo, a significant increment of ATP/ADP (high-energy to

low-energy metabolites ratio) in magnetic resonance spectroscopy and slight improvement in cognitive function was observed (24).

Pyruvate is a free radical scavenger, niacin amide boosts the mitochondrial cofactor NAD⁺, and creatine is a rapidly accessible cellular energy buffer, all of them were explored as mitochondrial dysfunction agents and they showed neuroprotective properties in animal models (25).

1.3.3 Other Strategies

New studies revealed that grape seed-derived polyphenolic extracts potentially prevented tau neurotoxic aggregates and could be recommended as a potential novel botanical for the treatment of some forms of tauopathies including PSP (26).

Recently, treatment with intravenous and intrathecal infusions of autologous adipose tissue-derived mesenchymal stem cells (MSCs) and bone marrow (BM) MSCs in patient with PSP showed effects on delaying of neurologic deficit progression and functional improvement in the follow-up period. The trophic, anti-apoptotic, and regenerative effects of the stem cells can diminish neuronal loss. These findings suggest that repeated infusion of these autologous cells can be a novel candidate as a therapeutic tool in PSP, providing a new framework for further studies (27). Brain

deep transcranial magnetic stimulation (DTMS) is a new technique that uses a special coil, which is able to stimulate deeper regions of the brain. A few studies have evaluated the safety and efficacy of DTMS in PD and parkinsonism (28). However, the main limitation in identifying disease-modifying therapies for PSP is the lack of biomarkers, which are necessary for well-designed human trials.

1.4 Ongoing Medical Trials in PSP

Recent findings shone a light on new ways of therapeutic strategies in atypical PS. These include TPI-287 to stabilize microtubules, salsalate as one type of salicylate to prevent acetylation of tau, BM stem cells to stimulate neurotrophic factors, ASOs, and BMS-986168 as an antibody against cerebrospinal fluid tau to reduce its extracellular concentrations. Using active or passive immunizations have been performed, albeit only experimentally, to reduce extracellular tau levels. In addition, small interfering RNAs and splice modifiers are currently studied, which ensue to decrease tau isoforms with four microtubule-binding repeats (4R-tau isoforms) via tau splicing reduction. 4R-tau isoforms are more prone to aggregation than tau isoforms with three repeats (3Rtau) (29).

2. Corticobasal Degeneration

CBD is a neurodegenerative disease characterized by asymmetric extrapyramidal symptoms including rigidity, apraxia, dystonia, myoclonus, tremor, and cortical disorders such as alien limb phenomenon and sensory loss, motor speech disturbance, and cortical dementia. CBD may present with a wide range of clinical syndromes, such as oculomotor dysfunction (gaze palsy, impaired convergence), bulbar palsy, postural instability, gait difficulty, hyperreflexia, and extensor plantar response. Four-repeat tau is the main protein that aggregates in astrocytes and plays a principal role in the pathogenesis of CBD (30). Many of the clinical features of CBD overlap with other neurodegenerative diseases, including MSA and FTD (behavioral variant FTD and primary progressive aphasia), AD, posterior cortical atrophy, and PSP. Due to rarity of CBD, the lack of specific biomarkers and overlapping clinical picture with other neurodegenerative disorders, its diagnosis may be very difficult.

Therapeutic Strategies

2.1 Symptomatic Pharmacotherapy

Similar to PSP, CBD has no effective pharmacologic treatment or cure, and current therapeutic approaches remain mainly supportive. Medications for symptomatic treatment are developed for other diseases such as PD, which could help to decrease disability and related problems such as pain, particularly in association with dystonia. Critical considerations include physical therapy for fall prevention and general supportive care strategies for sores related to dystonia or immobility, assessment of swallowing difficulties, and identifying needs for palliative care service. Published reports in patients with CBD showed that levodopa-resistant symptoms do not respond to deep brain stimulation (DBS) surgeries. Hence, DBS should not be used for CBD (31). Physical, occupational and speech therapies are important aspects of favorable management in patients with CBD. For a parkinsonism a trial with levodopa/

carbidopa (3-4x100-200 mg) led to moderate and transient improvement of akinesia and rigidity in about 35% of patients. Dyskinesia rarely occurs. If the total daily dosage of 1000 mg or more does not lead to improvement, the drug should be gradually discontinued. Botulinum toxin injections (toxin A: 100-400 units; botulinum toxin B: 5000-25.000 units) was used for focal limb dystonia, which could reduce pain, improve hygiene, and prevent secondary contractures. Other agents such as benzodiazepines, anticholinergic agents, or muscle relaxants (Baclofen) are rarely effective (32). Clonazepam (2-6 mg/day) and levetiracetam (250-1500 mg twice daily) are the treatments of choice for myoclonus. Other agents such as gabapentin and valproic acid may be helpful (33). Acetylcholinesterase inhibitors (AChEIs) are sometimes used in CBD, it seems likely that the response to AChEIs in patients with CBD is related to phenotypes. Accordingly, some patients respond to these drugs and others do not. For example, donepezil led to worsening in four of 12 patients with FTD treated with the AChEI (34). In a small study, galantamine showed some efficacy in the primary progressive aphasia subgroup (35).

- The efficacy of memantine in CBD is uncertain. Several studies of memantine in patients with FTD showed no benefit (36). However, some CBD-presenting patients with AD as an underlying pathology, might benefit from memantine. Currently, depression in CBD is treated with SSRIs and cognitive behavioral therapy. It should be noted that SSRIs may sometimes exacerbate apathy. In addition, anxiety and obsessive-compulsive features are treated with SSRIs (37,38). Atypical neuroleptics or mood-stabilizers are used for inappropriate behavioral symptoms, but parkinsonism should be considered (39). Trazodone (150-400 mg/daily) was useful for behavioral symptoms in patients with FTD (40,41). Propranolol (80-120 mg/day, maximum dosage 320 mg/day) is commonly used for tremor.

2.2 Disease-modifying Treatments

Disease-modifying treatments have focused on tau pathology similar to PSP.

3. Multiple System Atrophy

MSA is a rapidly progressive sporadic neurodegenerative disorder with clinical features of parkinsonism with poor response to levodopa, cerebellar ataxia, pyramidal signs, and severe autonomic dysfunction (urinary incontinence and orthostatic hypotension) (42). MSA has been classified into two different phenotypes including MSA-parkinsonism type (MSA-P) and MSA-cerebellar type (MSA-C) (43). MSA-P often presents with bradykinesia, rigidity, and tremor, and patients with MSA-C exhibit gait disturbance, limb ataxia, and staccato speech or dysarthria. Oculomotor symptoms (nystagmus, jerky pursuits, and hypo or hypermetric saccades) can be presented (44). In advanced stages of MSA, dysarthria (combination of spastic, hypokinetic dysarthria or dysphonia), respiratory or laryngeal stridor and dysphagia often occur. Focal dystonia, postural instability and rapid eye movement (REM) sleep behavior disorder are also usual and later features (45). The major cause of death is nocturnal sudden death. Alpha-synuclein is the core protein that aggregates in oligodendrocytes (glial cytoplasmic inclusions), which triggers the progressive neuronal loss, neuroinflammation, and demyelination (46).

Therapeutic Strategies

Similar to other APSs, current treatments have been focused on symptomatic, supportive, and rehabilitation services. However, no effective treatment is yet available.

3.1 Symptomatic Pharmacotherapy

Treatment with levodopa will decrease parkinsonism signs such as hypokinesia and rigidity in approximately one-third of patients with MSA-P, but dyskinesia is also possible. Levodopa-induced orofacial dystonia, which may occur in half of all patients, is a red flag for MSA-P. Delirium and hallucinations with levodopa occur in MSA, less commonly than in PD, and it may be accompanied by pathologic hypersexuality (47). A trial of levodopa up to 1000-1200 mg/d for a period of three months is required to assess levodopa unresponsiveness (48). Domperidone is helpful to prevent dopaminergic adverse effects such as nausea and vomiting. Dopamine agonists (ropinirole, pramipexole) could not be recommended as a first-line therapy because of their adverse effects, particularly the worsening of autonomic dysfunction, and the lack of controlled studies on their efficacy (47). Dopamine reuptake inhibitors (amantadine 100-200 mg×3) are also beneficial in symptomatic treatment. However, there was no improvement in motor symptoms in a placebo-controlled trial in eight patients with MSA (49). Serotonergic depletion in brainstem nuclei has been demonstrated in several postmortem studies (50). In terms of this evidence type, SSRIs such as paroxetine induced slight motor improvement in comparison with placebo in a small placebo-controlled, randomized trial (51). For cerebellar ataxia, low doses of clonazepam could be operative in intentional cerebellar tremor (52). Propranolol, baclofen, and amantadine have shown modest and transient effects in previous reports (53). Buspirone might be used to treat ataxia in upper limbs (54). Gabapentin had limited benefits on ataxia, oscillopsia or dysarthria, and protirelin tartrate had no clear effect in MSA (55). It should be noted that physiotherapy is the best approach for cerebellar ataxia in MSA.

For autonomic symptoms such as orthostatic hypotension, the first-line of treatment is a conservative approach including oral hydration, elastic stockings, raising the head of the bed during sleep, increasing salt intake, and using an abdominal binder (56). If symptoms persevere, pharmacologic treatment with fludrocortisone (1-3×0.1 mg) or desmopressin, by increasing blood volume, may be effective, but are contraindicated in heart failure. Midodrine (α -adrenoceptor agonist) could be used in moderate-to-severe orthostatic hypotension (2.5 to 30 mg daily). Blood pressure should be monitored in patients receiving midodrine due to the potential risk of supine hypertension (57). Furthermore, pyridostigmine could be used without supine hypertension (58). Recently, droxidopa (2×200-600 mg), which is a synthetic amino acid precursor for norepinephrine and epinephrine, was approved by the United States Food and Drug Administration for the treatment of orthostatic hypotension in patients with MSA (59).

Urologic complications can lead to lower urinary tract and kidney infections, which are the most common causes of morbidity in MSA (60). The first-line management is clean intermittent self-catheterization because of the increased incidence of detrusor contractility impairment and detrusor-sphincter dyssynergia. Antispasmodics or intra-detrusor injections of botulinum toxin A

are often effective for neurogenic bladder (61). Anti-cholinergic agents are mostly used for urinary urgency, frequency and urge incontinence, but in the absence of urinary retention risk. Alpha-blockers may reduce the residual urine volume in benign prostatic hypertrophy, but lead to orthostatic hypotension (62). Synthetic antidiuretic hormone desmopressin (10-40 μ g spray, 100-400 μ g tablets) decreases nocturia and morning hypotension; however, it may induce water intoxication. Another therapeutic strategy can be transurethral resection of the prostate for bladder outlet obstruction (63).

Intra-cavernosal injections of papaverine or prostaglandin E1 are used in erectile dysfunction in MSA (64). Use of sildenafil in MSA is limited depending on related cardiovascular adverse effects, especially severe blood pressure drops (65). Botulinum toxin injections are used to control focal dystonia (66). Some symptomatic improvements have been reported with anticholinergic, amantadine, dopamine agonists, muscle relaxants or tetrabenazine. Camptocormia is a dystonic posture with abnormal forward flexion of the trunk that presents during standing or walking and disappears in the supine position. Protirelin tartrate revealed dramatic improvement of camptocormia in one case report (67). Botulinum toxin injections in rectus abdominus muscles may be effective ultimately, as well as physiotherapy in combination with specific orthosis. REM sleep behavior disorder (RBD) is recorded in 69-100% of polysomnographic studies in patients with MSA (68). Clonazepam is offered as a first choice, but may exacerbate existing obstructive sleep apnea (69). In addition, sodium oxybate, temazepam, zopiclone, gabapentin, and pramipexole were effective in some investigations (70). RBD may reduce with donepezil (71). Melatonin may restore RBD-related disturbance of the circadian rhythms without considerable adverse effects (72). Regarding depression, SSRIs are the mostly used antidepressants with lesser risk of orthostatic hypotension than tricyclics. In patients with MSA with depression, electroconvulsive therapy may be effective (73). Despite all medical therapy, nursing care and family education are essential in quality of life improvement. Moreover, levodopa may slightly improve mood disturbance in MSA. In patients with MSA, verbal fluency, visuospatial, and constructional functions are impaired, but there is no confirmed treatment yet.

3.2 Disease-modifying Treatments

Despite recent advances, all clinical trials failed to prove any effective disease-modifying treatment for MSA. Current investigations are designed towards α -syn deposition in the brain as the basic target of disease-modifying strategies (74).

3.2.1 α -Syn Dysfunction

Regarding toxicity of α -syn aggregation in neuronal cells, recent studies have aimed to: (1) inhibit α -syn production, (2) block its aggregation, or (3) increase its degradation and clearance. Fonseca-Ornelas et al. (75) suggested that small molecules such as rifampicin might act as conformational stabilizers and inhibit aggregation of α -syn (75). Interestingly, recent findings indicated that autophagy inducers and enzymes such as kallikrein-6 (neurosin), cathepsin D or MMP9, could decrease both α -syn propagation and accumulation (76).

3.2.2 Neuroinflammation

Interaction of some pathogenetic factors including activation of microglia, stimulation of toxic cytokines secretion, complement and free radicals, lead to degeneration of myelin or neuronal death, and could be responsible for cognitive impairments observed during MSA disease. Novak et al. (77) showed that monthly infusions of the intravenous immunoglobulin (IVIG) (dose 0.4 g/kg, for six months) - according to its anti-inflammatory potential - may stop neuroinflammatory and degenerative events from further progression. Moreover, active vaccination with AFFITOPE® (AFF 1), which mimics the C-terminus region of α -syn, induces the production of specific anti- α -syn antibodies, which cross into the CNS and recognize the α -syn aggregations within glial cells of immunized mice. It resulted in decreased accumulation of α -syn and reduced neurodegeneration (78). Clinical trials using the AFF 1 for PD and MSA are currently under investigation.

Some of the anti-inflammatory compounds including nonsteroidal anti-inflammatory drugs (ibuprofen, indomethacin), TNF- α inhibitors (XPro1595, immunomodulatory drugs), antidepressants (fluoxetine), and antioxidants (quercetin, curcumin) can be prescribed as palliative treatment for synucleinopathies, and may possess disease-modifying properties (79). It is important to note that the majority of these anti-inflammatories do not reduce extracellular α -syn concentration and do not significantly decrease motor deficits (80).

3.2.3 Other Strategies

In one study on MSA, 11 patients received intra-arterial and three repeated intravenous injections of mesenchymal stem cells (MSCs) for 3 months. Their neurologic deficits were compared with 18 untreated patients. Functional improvement in the treated group was greater than in those with no treatment, demonstrating that MSCs have neuroprotective effects against dopaminergic neuronal loss because of their potential to produce several trophic factors and immunoregulatory properties (81).

Although an anti-glutamate drug, riluzole, led to postponing of neuronal loss in a rodent model of MSA (82), there was no positive effect in a prospective trial performed in patients with MSA (83). Also, there was a significant effect achieved with recombinant human growth hormone (r-hGH) during one year as a neuronal survival factor (84). Furthermore, the hypothesis of neuroprotective role of estrogen has not been confirmed (85).

3.3 Ongoing Pharmacotherapies

Over the late stages of MSA, obvious neuronal loss severely decreases the therapeutic efficacy of strategies that were effective in earlier stages. Therefore, in this stage, disease-modifying therapies are resorted to for the use of neurotrophic factors (brain derived neurotrophic factor, glial cell-derived neurotrophic factor) (86), neurogenesis induction, and cell therapy with stem cells. According to the possibility of PD developing due to mutations in genes other than Synuclein, namely *LRRK2*, *PARK2* (parkin), *PINK1*, *PARK7* (DJ-1), *ATP13A2*, *VPS35*, *EIF4G1*, *GBA* (β -Glucocerebrosidase) and *UCHL1*, these genes should be considered as potential therapeutic targets in this sense (87). Other genes such as *COQ2* for MSA and *PARK11*, *GBA* for DLB are identified as associated genes with synucleinopathies. Several therapeutic strategies have been recommended for mutations of

these genes such as *LRRK2* kinase inhibitors (sorafenib), GW5074 and staurosporine for *LRRK2*, and gene therapy for *PARK2* and *GBA* (88). Some neuroprotective products such as DJ-1 glycolate and D-lactate were also recommended (89). Mutations in the coenzyme Q10 encoding gene- *COQ2*- have been associated with susceptibility to MSA. Interestingly, mutations in these genes may be helpful as biomarkers for the detection of MSA in pre-symptomatic stages. Use of the mitochondrial and neuroprotective agents contribute to delaying the onset of the disease.

4. Dementia with Lewy Bodies

DLB is characterized by rapidly progressive dementia, parkinsonism concurrent with or following dementia, fluctuating cognitive performance, and recurrent visual hallucinations. Additional symptoms include deficits in verbal fluency, executive functions, transient loss of consciousness, delusions, depressed mood, REM sleep behaviour disorder (RBD), gait instability, and falls and neuroleptic sensitivity. Regarding the atypical or non-specific presentations in early stages, existence of co-morbid conditions and visuoperceptual features make the diagnosis very difficult. Pathologically, DLB is characterized by alpha synuclein aggregation in the brain stem and neocortical regions, and destruction of the substantia nigra and cholinergic nucleus basalis (90).

Therapeutic Strategies

Treatment of DLB is limited to symptomatic management and should consider all three components of the syndrome: cognitive decline, psychiatric symptoms, and movement problems.

4.1 Symptomatic Management

The main conflict is that levodopa often improves parkinsonism, but sometimes worsens the psychosis and hallucinations. Dopamine agonists should not be used for DLB. The initial dose of carbi/levodopa is 25/100 mg daily and increases over several weeks to three times per day, according to the clinical response (91). For cognitive symptoms, the first step is the elimination of agents such as monoamine oxidase inhibitors, amantadine, and anticholinergics, due to the potential for cognitive alteration and psychosis. Then, neuropsychiatric assessment and cognitive therapy are required to manage comorbid depression, apathy, and anxiety. Cholinesterase inhibitors e.g. donepezil (1x5-10 mg) and rivastigmine (6-12 mg/d, bid or tid) are approved for symptomatic treatment of cognitive decline in DLB. Rivastigmine has been shown to improve function in activities of daily living. It may also decrease psychiatric and motor symptoms, although its efficacy for visual hallucinations and delusions has not been established. This medication may lead to worsening cognitive performance, RBD, or parkinsonism, thus patients should be monitored carefully while receiving this drug (92).

The most recent trial was designed as a 48-center, case-control trial with donepezil in Japan. After 12 weeks, improvement in Mini-Mental State Examination was observed in patients who received 5 mg/day and 10 mg/day dosages compared with placebo (93). Cholinesterase inhibitor can also induce gastrointestinal adverse effects such as vomiting and diarrhea (minimized with the transdermal form of the drug). Abrupt discontinuation of these medications may cause deterioration of cognitive functions

and behavioral problems (94). Memantine (1x5-20 mg) indicated benefits on cognition, sleep and motor symptoms, but may exacerbate psychiatric symptoms.

Treatment of hallucinations and psychosis may be achieved with atypical antipsychotics such as quetiapine or clozapine. Quetiapine is helpful in controlling milder symptoms, especially hallucinations. It has been demonstrated that clozapine was effective although it required whole blood count monitoring due to the risk of agranulocytosis. These medications should be used carefully because of the risk of cardiovascular or infectious mortality related with antipsychotics in patients with DLB. Such patients may have sensitivity to neuroleptic agents, so conventional antipsychotics are often avoided. Pimavanserin, a selective 5-hydroxytryptamine, serotonin receptor 2 (5-HT) inverse agonist, has been studied and recommended to control psychosis without exacerbating extrapyramidal signs (95). SSRIs can be used in the management of anxiety and depression in DLB; moreover, electroconvulsive therapy has been shown to be effective in treating refractory depression. It is recommended to avoid benzodiazepines (except in RBD) due to worsening of cognitive impairment, gait disturbance, and paradoxical agitation, and as well as tricyclic antidepressants because of their anticholinergic adverse effects (96). If RBD is present, clonazepam (0.25 to 1.5 mg) or melatonin (3 mg) at bedtime can be effective.

4.2 Disease-modifying Therapies

Anti-alpha synuclein monoclonal antibodies have been illustrated to be operative in animal models of DLB. These findings present new approaches for disease-modifying therapeutic strategies in DLB.

Nilotinib is an Abl tyrosine kinase inhibitor used for the management of chronic myelogenous leukemia. It could decrease the level of α -synuclein, stimulate autophagic degradation of α -synuclein, and reverse dopaminergic neuronal loss in a mouse model with a mutation of A35T α -synuclein (97).

A few studies found that immunotherapy with recombinant human α -synuclein targeting extracellular α -synuclein reduced accumulation of α -synuclein and neurodegeneration. In a mice model, passive immunization via 9E4, which is an antibody targeting the C terminal of α -synuclein, led to a reduction of α -synuclein aggregation in the neocortex and hippocampus (98).

Recently, AFFiRiS AG, an Austria-based biotech company, developed a vaccine targeting synucleinopathies. This vaccine contains small peptides that stimulate just the α -synuclein-specific T cell response (99). It was used in transgenic mouse models with PGDF- α -synuclein and Thy1- α -synuclein, which caused a decrease of accumulation of α -synuclein, neurodegeneration, and improvements in motor and memory deficits in both models (100).

Another approach targeting the α -synuclein is RNA interference (RNAi). Direct infusion of RNAi led to the reduction of α -synuclein. Recently, lentiviral-mediated RNAi based on lentivirus delivery was used successfully (101).

Recently, DBS targeting nucleus basalis of Meynert (NBM) was performed in the treatment of DLB (102). NBM stimulation had positive effects on cognitive performance, personality features, and social activities. Targeting beta amyloid or tau may have clinical value in DLB treatment because its pathology has some overlap with AD including amyloid plaques and neurofibrillary tangles.

Conclusion

APs are a rare group of neurodegenerative disorders. The current treatment of AP is focused on symptomatic management. There is a critical need for identifying effective novel disease-modifying therapeutic alternatives in this field. Thus, there is a necessity for more investigations based on etiopathophysiologic aspects of APs. In this review, we categorized some of the recent relevant advances including autologous transplantation of stem cells, DTMS, IVIG with blockage of inflammatory response, and some kinds of pharmaceutical products such as pimavanserin (selective 5-hydroxytryptamine receptors-2 inverse agonist). Our study, as a review, has inborn limitations. We tried to present a systematic review and propose a strategy for each drug or therapeutic modality, separately. These studies enable us to make a practical guide for treatment. In other words, these encouraging findings can lead to the design of new trials for developing novel therapeutic strategies in APs.

Ethics

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Authorship Contributions

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