Oruen – The CNS Journal | Review article

Treatment options for atypical parkinsonisms

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A B S T R A C T

Success in treating patients with atypical parkinsonisms remains exceedingly low. This finding probably relates to the widespread distribution of the pathological changes that account for the varied and complex spectrum of clinical manifestations. Dopaminergic drugs are regularly used for the parkinsonian features; however, these rarely result in more than modest benefit. A variety of other treatments have been used in these disorders, sometimes directed at other specific features such as dystonia or myoclonus, and these treatments will be reviewed. Greater success in treating these disorders will require advances in our understanding of their cause(s) or the pathogenetic mechanisms underlying the neurodegenerative processes. The similarities in the molecular pathology of these diseases suggest that important advances in the management of one will have a definite impact on the treatment of the other.

Key words: atypical parkinsonisms, treatment options, pharmacological intervention, deep brain stimulation.

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INTRODUCTION

Atypical parkinsonian syndromes (APSs) comprise mostly progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), Parkinson's disease with dementia (PDD), and dementia with Lewy bodies (LBD). PSP, CBD, MSA, PDD, and LBD are distinct pathological entities [1–4]. With the recent advent in genetics, these disorders are constantly increasing as demonstrated by frontotemporal dementia (FTD) associated with parkinsonian symptoms [5]. Despite decades of research, the cause and pathophysiology of atypical parkinsonian disorders are still unknown. As a consequence, therapeutic options are still limited. A major limitation to the use of dopaminergic agents in APSs is the high risk of inducing psychotic adverse events and behavioral disturbance [6–7]. Various therapeutical approaches have been tried with rasagiline, immunoglobulin, autologous mesenchymal stem cells, davunetide, lithium, and tideglusib [8]. Recently, transdermal rotigotine was proposed for the treatment of atypical parkinsonisms [9,10], as well as deep brain stimulation of the peduncolopontine nucleus (PPN) alone or combined with the globus pallidus internus (GPi) [11]. This study reviews the limited available literature reporting treatment trials [12]. The outcomes reviewed here highlight the need for the development of novel therapies directed at altering the underlying biological mechanisms involved in the disease process.

Clinical features

Atypical parkinsonisms were selected as follows: PDD (9 patients), MSA-P (11), MSA-C (4), PSP (7), CBD (10), LBD (9), and FTD-P (1). In this study, the subjects affected by PSP were all PSP-RS type. Diagnosis of atypical parkinsonism was performed according to the most diffuse guidelines and clinical criteria [13–20]. Briefly, the classical PSP phenotype is characterized by postural instability and early falls, early cognitive dysfunction, and abnormalities of vertical gaze; it is referred to as Richardson's syndrome (RS). PSP was recently divided clinically and pathologically into two main phenotypes: classical RS and PSP-parkinsonism (PSP-P), the latter characterized by an asymmetric onset, tremor, and moderate initial therapeutic response to levodopa. The classical CBD phenotype consists of asymmetric parkinsonism, cortical signs (e.g., apraxia, cortical sensory loss, alien limb), and possibly other signs such as dystonia and myoclonus; it is referred to as corticobasal syndrome (CBS). MSA is typically characterized by parkinsonism, autonomic dysfunction, and a combination of cerebellar and pyramidal signs; MSA is classified according to the predominant phenotype at onset into MSA-parkinsonism or MSA-cerebellar type, and up to 80% of the patients develop most of the characteristic features during the course of the disease. A diagnosis of clinical definite, probable, or possible Parkinson's disease was made according to previously published criteria [21]. In order to obtain a homogeneous population with a high diagnostic specificity for Parkinson's disease, only subjects with definite Parkinson's disease were included in the study. This required that a patient had resting tremor and at least two of the three other cardinal signs of akinesia, rigidity, and postural abnormalities. Unilateral onset and development of parkinsonism as well as a good-to-excellent response to a dopaminergic agent were also required. Patients who developed dementia more than 1 year after the onset of parkinsonism were included. In step with clinical directions of LBD diagnosis, patients with cognitive impairment developed in not up to 1 year from

the parkinsonian symptoms' appearance, repeated falls, hallucinations at sickness onset, or symptom fluctuations and vivid dreams had been incorporated in this group [22].

Current pharmacological treatment options for atypical parkinsonian syndrome

Although there are still no treatments available for the sporadic atypical parkinsonian conditions, important efforts have been made in recent years, which, even if not proven effective clinically, will certainly guide further research. A randomized, placebo-controlled clinical trial to assess the effects of treatment with the monoamine oxidase-B inhibitor rasagiline (1 mg/day) for 48 weeks in 174 patients with possible or probable MSA-parkinsonism type, in 39 sites in 12 countries, found no significant difference in progression in the total Unified Multiple System Atrophy Rating Scale (UMSARS) score between the verum and placebo groups [23]. A single-arm, single-center, open-label pilot trial evaluated monthly infusions of 0.4 g/kg intravenous immunoglobulin for 6 months in seven patients using an anti-inflammatory approach, and found significantly increased SBP and improved UMSARS part I (activities of daily living) and II (motor functions); verification in a controlled study was proposed [24]. A recent study compared 30–50 intraarterial or intravenous injections of autologous mesenchymal stem cells (MSCs) versus placebo in 33 patients with probable MSA-cerebellar type and suggested that the MSC group had a smaller increase in total and part II UMSARS scores from baseline throughout a 360-day follow-up period; as the mechanism of action of this intervention remains unclear, a careful experimental and clinical re-evaluation of these findings should be considered [25].

In regard to PSP, a multinational phase II/III randomized, double-blind, placebo-controlled trial enrolled 313 participants, to be treated with 30 mg davunetide or placebo twice daily for 52 weeks at 47 sites, and found no significant effect on the co-primary outcome measures, the Progressive Supranuclear Palsy Rating Scale (PSPRS) and the Schwab and England Activities of Daily Living (SEADL) (press release, December 18, 2012, by Allon Therapeutics, www.allontherapeutics.com). An open-label pilot trial of lithium, an inhibitor of glycogen synthase kinase-3 (GSK-3), in individuals with PSP or CBD (ClinicalTrials.gov Identifier NCT00703677) recruited 17 patients and was stopped prematurely because the majority of participants did not tolerate the study drug. A multinational, phase II, double-blind, placebo-controlled trial enrolled 142 patients with PSP, who were treated orally with tideglusib (600 or 800 mg p.d.), also a GSK-3 inhibitor, or placebo for 1 year. There were no significant differences between the high dose, low dose, and either dose groups versus the placebo group in the primary clinical outcome measures. A subset of 37 patients underwent baseline and 52-week MRI; this substudy demonstrated significantly reduced global brain atrophy in tideglusib-treated patients [26]. The effect of the GSK-3 inhibitor in PSP thus warrants further investigation [27].

As for the LBD, the cholinergic deficit seen in LBD makes cholinesterase inhibitor drugs the mainstay of treatment for cognitive impairment. This class of drugs has also shown therapeutic benefit in reducing hallucinations and other neuropsychiatric symptoms of the disease. Because of their relatively greater therapeutic window, cholinesterase inhibitors are also used as first-line therapy for the treatment of psychosis in LBD. Patients with LBD are extremely sensitive to the extrapyramidal side effects of neuroleptic medications. Thus, only atypical antipsychotic agents, such as quetiapine, should be considered as alternative treatment for psychosis. Anxiety and depression are best treated with selective serotonin re-uptake inhibitors, whereas REM sleep behavior disorder may be treated with low-dose clonazepam. Parkinsonism responds to dopaminergic agents; however, precipitation or aggravation of hallucinosis may occur. Levodopa is preferred to dopamine agonists (DAs) due to its lower propensity to cause hallucinations and somnolence. As the diagnostic criteria for LBD become more refined and validated by postmortem studies, it is hoped that rigorous, well-designed trials will be performed, aimed at alleviating the primary target symptoms of dementia, psychosis, and parkinsonism [28].

Transdermal RTG as a treatment option for atypical parkinsonian syndrome

Transdermal RTG seems to be effective and well tolerated in patients with APS. In a recent study [10], 61 subjects with diagnosis of atypical parkinsonian disorders were treated with transdermal RTG. Results showed significant improvement in UDPRS-III scores, maintained along the course of the 24 month follow-up. Moreover, only seven patients were dropped out from the study and 15 patients were affected by adverse events. These results confirm previous pieces of evidence obtained in patients with idiopathic Parkinson's disease showing positive effect on motor control [29–33]. A plausible explanation of the results is that the RTG transdermal patch was developed to provide steady dopaminergic stimulation, as this may be important in reducing the unwanted motor effects of dopaminergic therapies, and could provide more continuous control of symptoms. Our results also show a reduction of NPI scores, which became significant at the last follow-up evaluation (T18), confirming previous evidence in PD studies. It has been demonstrated that rotigotine was also efficacious in reducing morning motor symptoms, sleep disturbance, and other non-motor symptoms in patients with poor morning motor control despite current treatments (most were taking levodopa); this suggests that the drug may be of particular value in patients with sleep disturbances and/or breakthrough of motor symptoms (most were taking levodopa) [30–33]. Side effects of antiparkinsonian therapy, including symptoms of depression and anxiety, hallucinations, delusions, with prevalent paranoid symptoms, agitation, delirium, and sleep disorders, are common in patients with extrapyramidal disorders [34,35]. Furthermore, treatment with DAs is the main risk factor for developing impulse control disorders (ICDs). The most common ICDs reported are pathological gambling (PG), hypersexuality (HS), compulsive shopping, and compulsive eating [6–8]. Our study did not find behavioral or

psychiatric adverse events or ICDs. This could be explained by the particular mechanism of action of RTG. Rotigotine is a non-ergolinic dopamine agonist with direct actions at dopamine receptors (D1–5) [36]. Rotigotine has its highest affinity for and activity at D3 receptors [26]. D3 receptors are sparse in the caudate–putamen region, but densely populated within the ventral striatum and show up to have a modulatory influence on motor output and the affective state [36]. Rotigotine also has affinity to non-dopaminergic receptors, such as α2B-adrenergic receptors and serotonin 5-HT1A receptors, that could positively modulate mood and behavior. The duration of the therapeutic effect on both motor and behavioral symptoms until 18 months of follow-up could suggest a neuroprotective effect. Even though beforehand visible in animal models and in vitro studies [36,37], this aspect wishes to be carefully assessed. During the study, our patients did not suffer from congestive heart failure. Of note, RTG had low affinity for 5-HT2B receptors, which may be of clinical importance, as ergolinic dopamine agonists thought to cause cardiac valvular damage are full or partial 5-HT2B receptor agonists [38].

Deep brain stimulation in PSP

In a recent study [11], three patients with PSP were submitted to the deep brain stimulation of the peduncolopontine nucleus (PPN). A reduction of falls and an amelioration of postural balance were observed. The patients required less assistance for daily living activities. The clinical improvement was, however, not fully reflected in the evaluating scales. The mean PSPRS percentage decrease was 26.3% (SD = 8.3) at the 12-month follow-up visit for the three patients. The diversity between the reported improvement and the PSPRS might be due to the phenomenological diversity of PSP, not fully captured by the PSPRS, and repeated scheduled postoperative evaluations are necessary to capture objectively the overall clinical improvement. That the greatest PSPRS percentage decrease (35.7%) was seen in the double implanted GPi-PPN patient is possibly due to the improvement of the concomitant amelioration of his dystonic state. It remains of course speculative in light of a single case, if this better clinical outcome seen in the GPi-PPN patient is reflection of an increased synergic effect of PPN and GPi secondary to stimulation, bearing in mind the strong connectivity between the basal ganglia and the PPN [11]. An interesting observation was related to the stimulation parameters: we started with low-frequency stimulation, which was increased progressively to 130 Hz without noticing a significant change in clinical presentation.

Supportive therapies

The review of treatment for these disabling neurodegenerative disorders needs to at least briefly mention the utility of palliative therapies. A variety of physical, occupational, and speech therapies can be used in these patients. APSs represent a rather unique and difficult challenge, because the apraxia that often constitutes a major source of disability in these patients also compromises the likelihood of any useful benefit from these techniques. When postural instability is prominent with the risk of falls and self-injury, it is important to encourage the patient and family to accept the need for a wheelchair. This acceptance can be surprisingly challenging and difficult. Many families view the use of a wheelchair as a marker of the final loss of the ability to ambulate and remain independent. They need to be convinced that the wheelchair not only is necessary for the safety of the patient but also can provide a greater degree of freedom than the limited mobility provided by the patient's attempts to walk with or without aids. The combination of poor postural stability and frontal lobe dysfunction presents an additional major challenge whereby patients commonly attempt to stand and walk (often "shooting" or "rocketing" out of the chair too quickly) without calling for help even though they have repeatedly fallen and injured themselves in the past. Various methods can be used to try to prevent this behavior (e.g., trays or other obstacles in front of the patient and various forms of restraint in the chair); however, most patients resist the application of these. Finally, it is important to monitor and support the well-being of the caregiver. These diseases present the particularly difficult combination of severe and refractory motor disability with cognitive and behavioral disturbances; therefore, caregiver burden is typically quite profound [12].

Future treatment options

As indicated in the introduction, it is unlikely that successful "symptomatic therapy" will be developed for these complex neurodegenerative disorders. Whether "regenerative" or "restorative" treatments (e.g., trophic factors, stem cells) will provide useful benefit in the future remains to be determined. It is hoped that major therapeutic advances will eventually occur in the field of disease modifying therapy. This achievement will require further advances in our understanding of the cause(s) of these disorders and the basic mechanisms underlying the pathogenesis of the progressive neurodegeneration. Several different approaches can be proposed even now given what is known of the basic biology of these disorders (see other contributions to this volume) and trials of "neuroprotective" therapies are actively being planned or have been implemented (e.g., a trial of riluzole for PSP and MSA has been initiated in Europe). Further discussion and evaluation of the best endpoints for clinical trials in these disorders are an important priority. One of the major obstacles to the design of the necessary clinical trials is the accuracy of clinical diagnosis. This finding emphasizes the need for developing biological markers for these neurodegenerative disorders. The similarities in the underlying neuropathology and molecular biology of these disorders suggest that critical advances in this field will equally have an impact on the treatment outcomes [12].

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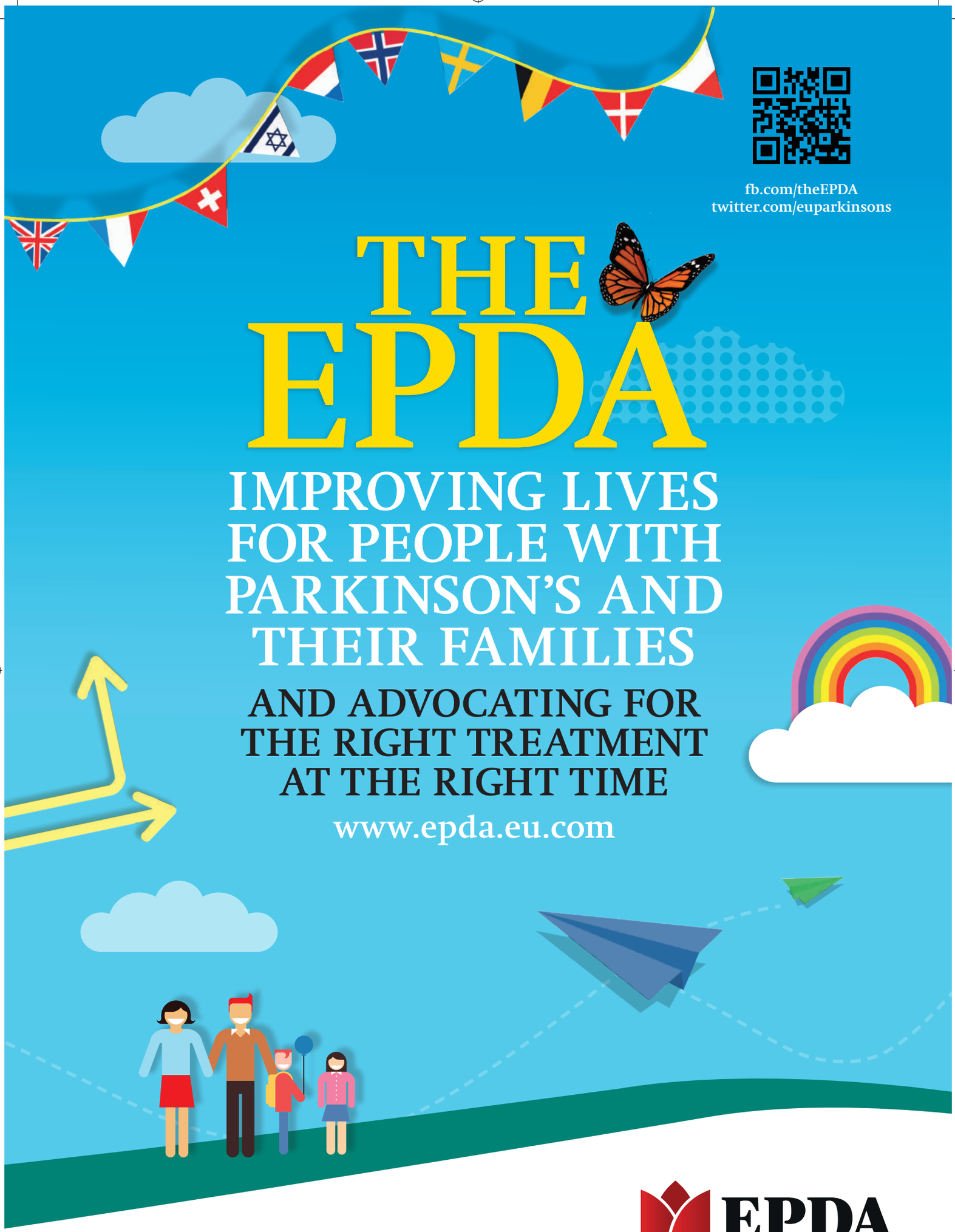
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