FEATURE

Learning From the Latest: Failures and Successes in Movement Disorders Trials

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In a session at the 18th International Congress of Parkinson's Disease and Movement Disorders, a panel of experts presented key findings from recent clinical trials on movement disorders and discussed challenges and methodological issues in current clinical trials.

CLINICAL TRIALS ON PARKINSON'S DISEASE

Christopher Goetz, MD, Rush University Medical Center, Chicago, Illinois, USA, presented an overview of findings from recently published clinical trials on Parkinson's disease (PD). He emphasized that there have been many new trials over the past year with a focus on both motor (Table 1) and nonmotor (Table 2) aspects of the disease, as well as a broad range of treatments, pharmacologic, surgical, and otherwise.

Dr. Goetz limited his discussion to randomized clinical trials with larger samples or particularly novel approaches, published since the 2013 International Parkinson and Movement Disorder Society (IPMDS) meeting in Sydney, through May 15, 2014, as well as studies being presented at the 2014 meeting. Dr. Goetz ended his presentation by highlighting that 383 active trials were underway as of May 15, 2014, with 335 in or near recruitment and 48 with recruitment completed. These trials are focused on old drugs for new indications, new drugs, novel interventions, and surgical therapies.

CLINICAL TRIALS ON OTHER MOVEMENT DISORDERS

Recent clinical trials on other movement disorders were presented by Werner Poewe, MD, Innsbruck Medical University, Innsbruck, Austria. Like Dr. Goetz, he limited his discussion to larger randomized trials published since the 2013 IPMDS meeting through May 27, 2014 (Table 3). These trials included patients with atypical parkinsonism (eg, parkinsonism due to multiple system atrophy, progressive supranuclear palsy, Huntington's disease, dystonia, and essential and other tremor disorders).

ONGOING TRIALS: CHALLENGES

The session ended with a presentation by Joaquim Ferreira, MD, PhD, University of Lisbon, Lisbon, Portugal, on what to expect from ongoing clinical trials, including current challenges and their influence on future trial design.

Prof. Ferreira emphasized that there is a gap in pharmaceutical interventions for PD, with no new licensed drugs specifically for PD since the United States Food and Drug Administration approved rivastigmine in 2007. Although most clinical trials underway since June 2013 are primarily examining the safety and efficacy of pharmaceutical agents, the number of clinical trials aimed at nontraditional interventions, such as physiotherapy and exercise, has increased substantially. The rationale behind this is reflected in the primary outcome used in most studies since June 2013: the effect of the intervention on gait, balance, and falls.

Those designing future clinical trials need to learn from prior clinical trials to improve design. Design elements that will validate the study have to be incorporated into the early stages of trials, such as the use of active controls, and trials must focus on more than just the type of intervention. Prof. Ferreira emphasized that when designing future clinical trials, researchers need to keep in mind what really matters most to the patient. What are the determinants of improving functional status, health-related quality of life, and perceived health status? As PD is a slowly progressive disease, there are further considerations of the different treatment goals for early versus later stages of disease.

Peer-Reviewed Highlights From the

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Table 1. Highlighted Clinical Trials With a Motor Focus

Trial	Findings/Conclusion
Disease modifying / neuroprotection	
Pramipexole on Underlying Disease [PROUD; Schapira AHV et al. *Lancet Neurol* 2013]; patients randomly assigned to pramipexole at study onset or placebo for 6 to 9 months and then pramipexole for both groups from 6 to 9 months.	No indication of disease-modifying effects seen with pramipexole.
Monotherapies	
IPX066: CD/LD bilayer short-acting, extended-release formulation in early PD in first exposure to LD [Pahwa R et al. *Parkinsonism Relat Disord* 2014]; patients with early PD randomly assigned to IPX066 (145, 245, or 390 mg TID) or placebo.	All doses of IPX066 superior to placebo for changes in UPDRS and quality of life. IPX066 is safe and efficacious as first LD exposure.
Adjunct therapies	
Exenatide as adjunct to dopaminergic medications [Aviles-Olmos I et al. *J Clin Invest* 2013]; patients previously treated for PD randomly assigned to subcutaneous exenatide or placebo.	Exenatide was well tolerated and associated with a significant improvement in early-morning UPDRS score. Chronic exenatide can be explored further for either symptomatic or disease-modifying therapy.
Progressive Resistance Exercise [Corcos DM et al. *Mov Disord* 2013]; patients on dopaminergic drugs randomly assigned to weight lifting (treatment group) vs stretching and balance (control group) twice weekly.	Both groups improved for first 6 months, with additional significant improvements after the first 6 months in the treatment group while the control group returned to baseline. Progressive resistance exercise is a useful adjunct to dopaminergic therapy and is superior to stretching.
Complications (fluctuations)	
Istradefylline [Mizuno Y et al. *Mov Disord* 2013]; patients with fluctuations randomly assigned to istradefylline (20 or 40 mg/day) vs placebo.	Both istradefylline doses significantly reduced "off" time compared with placebo. Istradefylline is approved in Japan and will again be tested in North America for motor fluctuations.
Safinamide [Borgohain R et al. *Mov Disord* 2014]; patients with fluctuations randomly assigned to safinamide (100 and 50 mg/day) vs placebo for 24 weeks.	Safinamide associated with significant mean improvement in "on" time without troublesome dyskinesia compared with placebo. Results suggest a role for safinamide to control motor fluctuations.
Continuous intrajejunal infusion of LD/CD gel [Olanow CW et al. *Lancet Neurol* 2014]; patients with fluctuations randomly assigned to oral LD/CD or intrajejunal infusion LD/CD for 12 weeks.	Infusion LD/CD associated with significant decrease in mean "off" time compared with oral LD/CD, as well as significant increase in "on" time without troublesome dyskinesia. Serious adverse events (mostly related to tubing apparatus) exceeded 10% of patients in both groups. Trial shows the benefit of continuous intrajejunal infusion for fluctuations but with serious adverse events.
Complications (dyskinesias)	
AFQ056 [Stocchi F et al. *Mov Disord* 2013]; patients with dyskinesias randomly assigned to AFQ056 (20 to 200 mg/day) or placebo.	AFQ056 showed dose-response decreases in dyskinesia, maximal improvement seen at 200 mg/day, with no worsening of parkinsonism on UPDRS measures. AFQ056 at 200 mg/day is ready for testing in a large clinical trial.
Surgery and stimulation	
Gene therapy: Cere-120 (AAV-NRTN) [Bartus RT et al. *Mol Ther* 2014]; moderately disabled patients with good response to LD were randomly assigned to gene placement in posterior putamen and substantia nigra vs sham.	No difference in UPDRS scores between groups. Results showed treatment failure but technical success in placing the gene therapy. Plans for future studies with this agent have stopped for this gene, but the protocol and techniques can be applied to future gene studies.
Deep brain stimulation: LF vs HF subthalamic nucleus stimulation [Khoo HM et al. *Mov Disord* 2014]; open-label study in which 14 patients were first optimized to LF rate (60 Hz), then HF rate (130 Hz), based on best UPDRS motor score, and then randomly assigned to LF followed by HF or HF followed by LF for 3 hours.	Optimal LF site was superior in improving UPDRS total motor score with improved akinesia and axial signs without compromising effects on tumor and rigidity. Optimal LF site was more ventral than optimal HF stimulation. LF was more effective than HF, but the stimulation site was directed further ventrally than HF standards.
Magnetic stimulation: Spinal stimulation and camptocormia (an abnormal flexion of the trunk that appears when standing or walking and disappears when lying flat) in PD [Arii Y et al. *J Neurol Neurosurg Psychiatry* 2014]; patients with camptocormia were randomly assigned to a single treatment of repetitive transspinal magnetic stimulation or sham.	Immediate effect with stimulation (patient's spine flexion angle improved by a mean of 10.9° vs no change with sham). Future studies need to look at continual therapy and persistence of benefit.

CD=carbidopa; HF=high frequency; LD=levodopa; LF=low frequency; PD=Parkinson's disease; UPDRS=Unified Parkinson's Disease Rating Scale.

Table 2. Highlighted Clinical Trials With a Nonmotor Focus

Trial	Findings/Conclusion
Cognition	
Hallucinations/psychosis: Pimavanserin [Cummings J et al. *Lancet* 2014]; patients with hallucinations randomly assigned to pimavanserin or placebo over 6 weeks.	Significant improvement in Parkinson's disease-adapted scale for assessment of positive symptoms with pimavanserin compared with placebo, with no significant safety concerns or worsening in motor signs.
Cognition: Cognitive speed-of-processing training [Edwards JD et al. *J Gerontol B Psychol Sci Soc Sci* 2013]; patients without dementia or fluctuations were randomly assigned either to 20 hours of self-administered speed-of-processing training (using InSight software) or to no intervention.	Useful Field of Vision as a cognitive index. Patients with mild to moderate Parkinson's disease could self-administer training and improve their cognitive speed of processing, as indexed by Useful Field of Vision, a robust predictor of driving performance in aging and Parkinson's disease.
Sleep	
Insomnia treatment [Rios Romenets S et al. *Parkinsonism Relat Disord* 2013]; patients with insomnia randomly assigned to doxepin vs placebo vs cognitive therapy plus bright light.	Both doxepin and cognitive therapy plus bright light therapy significantly improved insomnia compared with placebo, with no significant adverse effects. Drug and nondrug therapies both play a role in managing insomnia.
Orthostatic hypotension	
Orthostatic hypotension study [Hauser RA et al. *J Parkinsons Dis* 2014]; patients with orthostatic hypotension randomly assigned to droxidopa vs placebo.	Failed study. No difference seen in the Orthostatic Hypotension Questionnaire score between droxidopa and placebo, although droxidopa was associated with fewer falls and fall-related injuries. Further trials in development.

Table 3. Clinical Trials on Other Movement Disorders

Trial	Key Learnings
Multiple-system atrophy	
Rifampicin [Low PA et al. *Lancet Neurol* 2014]	This and several other trials have failed. Need to return to the drawing board with regard to defining targets, size, duration, and outcomes.
Progressive supranuclear palsy	
Tideglusib [Tolosa E et al. *Mov Disord* 2014; Hoglinger GU et al. *Mov Disord* 2014]; davunetide [Boxer AL et al. *Lancet Neurol* 2014]	Large randomized clinical trials are feasible. First trials of agents targeting Tau pathology. Good safety but no signals of clinical benefit. Consistent decline in Progressive Supranuclear Palsy Rating Scale and MRI volumes. Imaging and cerebrospinal fluid biomarkers may be sensitive to interventions.
Huntington disease	
Creatine Safety and Tolerability in Premanifest Huntington's Disease [PRECREST; Rosas HD et al. *Neurology* 2014]. Assessed feasibility of premanifest HD studies by including patients at risk for developing HD who have declined genetic testing.	Showed feasibility of prevention trials for HD and safety of high-dose creatine. Provided possible evidence of disease modification (MRI showed treatment-related slowing of cortical and striatal atrophy at 6 and 18 months). MRI measures may be potential surrogate progression markers in future clinical trials. There was a higher dropout rate of known carriers compared with at-risk patients.
Dystonia	
Deep Brain Stimulation [Schjerling L et al. *J Neurosurg* 2013]	Compared the subthalamic nucleus with the globus pallidus internus as a stimulation target for deep brain stimulation for medically refractory dystonia. Globus pallidus internus deep brain stimulation is effective for refractory cervical dystonia. The subthalamic nucleus may be a promising target in patients with dystonia.
Essential tremor	
Focused ultrasound [Lipsman N et al. *Lancet Neurol* 2013; Elias WJ et al. *N Engl J Med* 2013]; handheld device using ACT technology [Pathak A et al. *Mov Disord* 2014]	Nonmedical therapies (focused ultrasound and ACT devices) hold promise for essential tremor.

ACT=active cancellation of tremor; HD=Huntington's disease; MRI=magnetic resonance imaging.

Finally, Prof. Ferreira highlighted the need for researchers of future trials to consider the type of patients to recruit and the broad spectrum of issues needed to consider when choosing patients, including types of markers, stage of disease, and route of administration. As an example of the importance of properly selecting patients for future clinical trials, he noted that registries of ongoing fall-related clinical trials in PD patients show that patients with cognition problems are excluded from many of these trials, despite the fact that cognition problems and falls are often connected.