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MEETING REPORT

HIGHLIGHTS FROM THE 14TH INTERNATIONAL CONGRESS OF PARKINSON'S DISEASE AND MOVEMENT DISORDERS: FUTURE TREATMENTS

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SUMMARY

The 14th International Congress of Parkinson's Disease and Movement Disorders, held June 13-18 in Buenos Aires, once again provided the great variety of oral and poster presentations, teaching courses and corporate-sponsored symposia for which the annual congress is known. The present review is focused on recently and soon-to-be opened avenues of investigation into the treatment of Parkinson's disease (PD) and other movement disorders. An examination of sessions at the congress focused on new treatments for PD reveals a disorder with well-known symptoms (motor symptoms) and a range of other symptoms (nonmotor symptoms) which are underappreciated but the subject of increasing attention. Likewise, nondopaminergic pathways are the focus of greater interest. The use of both dopaminergic and nondopaminergic strategies to treat motor and nonmotor symptoms makes the picture of the current state of PD investigation both exciting and complex. Innovation is also notable in nonpharmacological approaches to this disease, such as gene therapy, cell therapy, deep brain stimulation and physiotherapy –the forms of which naturally vary, with presentations of physiotherapy at this year's congress even including the study of the Argentine tango in PD patients.

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INTRODUCTION

For the sheer number, variety and quality of presentations, the Movement Disorder Society's annual International Congress of Parkinson's Disease and Movement Disorders has become one of the most important meetings for clinicians, researchers and students in the field. The size of the meeting precludes the possibility of summarizing it in its entirety, and the report which follows focuses on the most recent data and ideas related to innovations in treatment. Numerous strategies for treating Parkinson's disease (PD) are being investigated, including pharmacological treatments, gene therapies, cell therapies, deep brain stimulation (DBS) and physiotherapy. How best to target dopaminergic pathways, and the involvement and targeting of nondopaminergic pathways, are matters of controversy and continued study. Both pathways are being investigated for how they relate to motor and nonmotor symptoms, with the latter symptoms having garnered attention in recent years for their impact on patient quality of life and for what they may reveal about disease processes. Below are summarized a selection of presentations covering the therapies that have generated the most interest in recent times, modalities and mechanisms of action that have shown early promise, and studies of treatments with potential that are under way and may soon produce results.

DEEP BRAIN STIMULATION

To those working in the field, it would not be surprising to see a talk entitled "How does DBS work?" in one of the opening therapeutic plenary sessions of this year's congress, a session dealing with what is new in the field of DBS (1). And those familiar with DBS would also not be surprised to find that the person giving that talk did not intend to provide an overview of how DBS works, but that he was genuinely posing the question. Such is the somewhat strange position of DBS: an important therapeutic option in treating movement disorders, but one whose functioning is not understood. As discussed by Erwin Montgomery, this is because we do not know what DBS has to correct, as we do not know what is wrong with the functioning of the basal ganglia. This in turn is due to faulty conceptual models.

The prominent theory of parkinsonism, the globus pallidus interna (GPi) rate theory, is not entirely correct. Experimental evidence

shows that overactivity in the subthalamic nucleus (STN) is not a sufficient cause for parkinsonism. There is a tendency to think in terms of localized effects (STN, GP), but this is not the case. It is perhaps time to think in terms of a systems effect and not a local effect with DBS, where improvements are seen with stimulation of various regions in the basal ganglia–thalamic system. Thus, we have a systems pathophysiology. Another area of misunderstanding concerns DBS frequency. It is now known that there are no differences in neuronal responses to different DBS frequencies. The GPi rate theory was false because it was not a physiological theory, but anatomical and neurochemical. Dr. Montgomery stressed the need for new metaphors beyond one-dimensional dynamics of current conceptual approaches. Thus, we find ourselves in the curious position where DBS can teach us how the brain works, leading to understanding of how DBS works.

Dr. Montgomery's talk was followed by an overview of the many issues facing DBS offered by Michael Okun (2). These included the need to address adverse events related to DBS implants, as these implants –and related adverse events– become more common in what Dr. Okun termed the bionic age. Protocols for emergency rooms will have to be devised for this age. The approach to DBS is also changing, as imaging allows direct targeting and intraoperative magnetic resonance imaging (MRI) facilitates electrode placement. Postoperative imaging may also come into its own, allowing DBS failures to be rescued. At least one study found the approach to be safe. How DBS compares to best medical therapy is also a question to be further addressed, although at least two studies have suggested greater benefit with DBS. The most appropriate target of DBS is an ongoing debate, with a recent study reported in *The New England Journal of Medicine* finding equivalent efficacy with STN and GPi targeting. Few studies have addressed differences in adverse events, however. How should DBS be tailored to individual patients? And should this include staging? These are also critical subjects of debate. The nonmotor issues seen with DBS, such as impulsivity, medication withdrawal and verbal fluency issues, need to be addressed in greater detail. Questions surround the use of low-frequency DBS. Dr. Okun noted that it could work for treating dystonia, with benefits continuing after 6 months, but which patients would benefit is not clear. Could STN DBS be used for dystonia, and could there be a trial comparing STN and GPi DBS for dystonia? Dr. Okun stated that such a trial will happen. The use of DBS for treating Tourette's syndrome also requires further exploration, with nonmotor features monitored, as well as motor and vocal tics. The use of multiple DBS leads may be appropriate. Another area for investigation is the use of pedunculopontine nucleus DBS for gait and balance disorders. Lastly, Dr. Okun echoed Dr. Montgomery in noting the need for greater neuropathological understanding, as we do not know how DBS works.

DBS can also be used for neuropsychiatric disorders such as depression, a topic addressed by Ziad Nahas (3). This is a valid approach due to the diminishing returns seen with pharmacological therapy in some patients. With DBS in this setting, it is not the effect of stimulation per se that is beneficial, but the response of the brain to it. Epidural cortical stimulation DBS might be used in patients who do not have treatment-resistant depression, but Dr. Nahas noted, as other speakers at the congress would later do, that this approach and others are tested in patients with treatment-resistant disorders, i.e., those least likely to respond. The rationale for using DBS in depression stems from the notion that depression is a manifestation of dyssynchronous neural networks. Different stages of depression may also require different approaches.

A proof-of-concept study was conducted in five patients who had failed other treatment and who underwent epidural prefrontal cortical stimulation DBS, with the rationale that the prefrontal cortex includes two complementary networks concerning cognition, executive control and integration of emotion. The treatment proved beneficial, with three of the five patients treated in remission at 7 months. Dr. Nahas closed by noting the need for a data registry for psychiatric surgery, an idea first proposed many years ago but not yet pursued.

EXPERIMENTAL THERAPEUTICS IN PARKINSON'S DISEASE

Deniz Kirik began a discussion of "Hot topics in experimental therapeutics in Parkinson's disease" by addressing the promise of gene therapy in treating PD (4). Gene therapies for PD have been in development for over 20 years, with genes delivered by direct injection of gene-bearing viruses into the brain. Neurotransmitters other than dopamine (DA) are involved in the disease, but there has been a bias toward DA in these approaches.

One of the goals of gene therapy for PD has been to provide neuroprotection, where the loss of DA neurons is inhibited, potentially modifying disease progression. In this area, there has been much excitement around trophic factors such as glial cell line-derived neurotrophic factor (GDNF). GDNF injection has been effective in experimental models, depending on where it has been injected (see Box 1 for separately presented GDNF gene delivery study results). It is not yet known, however, if it is possible to modify disease progression with viral vector GDNF delivery.

Another candidate therapeutic molecule for neuroprotection in PD is neurturin. CERE-120 is a gene therapy product that delivers the neurturin gene (*NRTN*) and which was associated with some improvement in PD patients in a phase I clinical trial. In a phase II study, the same improvement was seen in controls and the treatment group. This may have been due to inadequate dosing or the choice of a site of delivery that was not optimal. Can GDNF delivery work if neurturin delivery does not, given that the same receptor pathway is involved? This is not yet known, but is to be tested.

Restorative treatment for PD is also under investigation, with multiple approaches being tested. Three of these strategies are focused on reconstituting DA production. One approach is aromatic-L-amino-acid decarboxylase (*AADC*) gene delivery, which is being evaluated in a phase I study. Triple gene therapy with *AADC*, tyrosine 3-hydroxylase (*TH*) and GTP cyclohydrolase 1 (*GCH1*) is also being assessed in clinical trials (see Box 2 for separately presented ProSavin gene therapy study results). A third approach consisting of *TH* and *GCH1* gene transfer has been effective in experimental models. It may be possible to use [^{11}C]-raclopride PET to measure DA in the brain, but this has not yet been tested clinically.

Roger Barker started a discussion of cell therapy at the beginning, asking why PD is a good candidate for this approach (5). The answer was that PD is a common and disabling disease with no cure. Its core pathology is loss of the dopaminergic nigrostriatal pathway, and patients respond well to dopaminergic therapies. Still, there are

BOX 1

The safety and functional recovery seen with administration of AAV2-GDNF to rhesus macaques previously lesioned with MPTP support the initiation of a phase I clinical trial in patients with PD. AAV2-GDNF consists of an adeno-associated virus containing the human *GDNF* gene, which encodes glial cell line-derived neurotrophic factor. It is delivered using convection-enhanced delivery and is being developed by investigators at Georgetown University and the University of California, Oakland. AAV2-GDNF was delivered to the putamen of macaques, the right hemisphere of which was completely and the left hemisphere partially lesioned with MPTP. Motor defects were monitored for the following 24 months. There were no adverse effects and functional recovery was observed throughout this follow-up period. Dopamine production was noted in the partially lesioned putamen, with dopamine at near-normal levels at all time points after AAV2-GDNF delivery. Dopamine levels did not change in the fully lesioned hemisphere but an increase in dopamine metabolites was noted. Positron emission tomography (PET) imaging revealed enhanced dopaminergic function in both hemispheres, which was correlated with behavioral recovery, suggesting potential efficacy in early- and late-stage PD. Immunohistochemistry showed increased tyrosine hydroxylase staining matching *GDNF* expression patterns. Broad *GDNF* expression was seen not only in putamen but also in substantia nigra due to anterograde transport. No immune response or adverse pathologies were discovered after 24 months of *GDNF* expression (21).

BOX 2

Results from an ongoing phase I clinical trial of the dopamine replacement gene therapy ProSavin® (Lenti-TH-AADC-CH1) in patients with PD have been encouraging, with a double-blind, sham surgery trial needed to rule out a placebo effect. In the study, six patients received one of two ProSavin® doses, with the second dose double that of the first. The treatment was found to be safe, with no serious adverse events observed, no OFF state dyskinesias, immune responses to ProSavin® or surgical serious adverse events. A decrease in off-levodopa Unified Parkinson's Disease Rating Scale (UPDRS) III score was noted in all patients, with a maximum motor improvement of 52.9% at 6 months and mean improvements of 28% and 33.5% in the respective treatment groups (22). Developed by Oxford BioMedica, ProSavin® is a lentiviral vector derived from the equine infectious anemia virus (EIAV). It contains genetic information encoding human tyrosine hydroxylase, aromatic-L-amino-acid decarboxylase and GTP cyclohydrolase 1.

other pathological pathways, so dopaminergic therapy will never be curative. Also, a cell therapy approach may not be competitive with other approaches. Is there a patient group that may do better with cell therapy? There may be, but determining who they are is not a simple matter. All patients are different in terms of clinical features. Two possible major subtypes were identified in the Cambridgeshire Parkinson's Incidence from GP to Neurologist (CamPaIGN) Study, and using these findings it would appear that cell therapy is most appropriate in the subtype consisting of subjects with "subtle" frontostriatal cognitive impairment but localized nigral pathology.

Dr. Barker addressed the evidence that cell therapies can be beneficial. There has been success in some patients, including a well-known case treated in the 1980s ("Patient 4"), but the same treatment was not as effective in another patient. About a decade ago, the first double-blind, placebo-controlled trial of transplantation of embryonic DA neurons was published. Minimal benefit was seen at 1 year, although younger patients appeared to do better. There were, however, significant adverse events, with five patients developing severe dyskinesia. The technique used may have led to reduced survival of DA cells. Still, longer-term follow-up showed improvements in treated patients. After a second double-blind, placebo-controlled trial produced similar results, with 13 of 23 patients developing graft-induced dyskinesia, investigation in the field came to a standstill. Lewy bodies were also detected in grafted neurons. But to Dr. Barker, these results are not sufficient to give up investigation into cell therapies. Learning from them can inform the way forward: the first double-blind trials in organ transplantation also failed. The way forward should therefore involve select subtypes and stages of PD, and it may be better to include patients with an earlier stage of disease. The transplant procedure should also be changed to avoid dopaminergic hot spots. There is a possible problem with the tissue being transplanted as well. A better source of cells may be needed, such as stem cells –in which case the type of stem cells must be determined. Trial design has also been a problem, with small groups of patients included yielding a wide variability in response. The answer is not to increase patient numbers but to improve the trial design.

The symposium closed with an overview by Jonathan Brotchie of small-molecule drugs in development for PD that have novel mechanisms of action, and with targets validated at least in nonhuman primates (6). A novel therapy was defined as one which could provide antiparkinsonian benefit as monotherapy, replacing dopamine therapy; reduce dyskinesia, as an adjunct to dopamine replacement; extend the duration and/or improve the quality of ON time; reduce nonmotor problems such as psychosis, orthostatic hypotension and impulse control disorders; or modify disease progression.

The rationale for a novel antiparkinsonian therapy would be to avoid nonphysiological dopaminergic stimulation and to reduce the activity of the indirect striato–external globus pallidus (GPe) pathway, reducing parkinsonism while avoiding dyskinesia even if it is already established. Table I details possible strategies and corresponding drug candidates that might provide effective antiparkinsonian therapy. Other types of agents of potential utility are δ opioid agonists, NR2B NMDA antagonists and NOP antagonists.

A novel dyskinesia therapy was defined by Dr. Brotchie as one that could suppress the expression of established dyskinesia, prevent the development of dyskinesia or reverse the processes responsible for the development of dyskinesia. Possible approaches for attenuating established dyskinesia are laid out in Table II.

Table I. *Potential pharmacological strategies for antiparkinsonian therapy (6; supplementary information provided by Thomson Reuters Integrity℠).*

Mechanism of action	Drug candidate	Phase of development	Organization
Adenosine A_{2A} receptor antagonism	Istradefylline	Preregistered (U.S.)	Kyowa Hakko Kirin
	Preladenant	III	Merck & Co.
	Vipadenant*	II	Vernalis/Biogen Idec
	SYN-115	II	Synosia Therapeutics
	DT-1133	Preclinical	Domain Therapeutics
$mGlu_4$ receptor agonism/positive allosteric modulation	AMG-889436	Preclinical	
	VU-0155041	Preclinical	Ascent Scientific/Vanderbilt University
Dopamine transporter (±norepinephrine transporter) inhibition	SEP-226330	Preclinical	Sepracor
Dopamine D_2/5-HT_{1A} receptor agonism	Pardoprunox	III	Solvay

*Now discontinued; other agents are being explored by Vernalis and Biogen Idec researchers as part of an adenosine A_{2A} receptor antagonist program.

Table II. *Potential pharmacological strategies for reducing established dyskinesia (6; supplementary information provided by Thomson Reuters Integrity℠).*

Mechanism of action	Drug candidate	Phase of development	Organization
$mGlu_5$ receptor antagonism	AFQ-056	II	Novartis
	ADX-48621	II	Addex Pharmaceuticals
	Fenobam	Preclinical	Neuropharm
α_2-Adrenoceptor antagonism	Fipamezole	III*	Juvantia/Santhera/Biovail
Dopamine D_4 receptor antagonism	L-745870	Preclinical	Merck Sharp & Dohme/Neugen Pharma
μ Opioid receptor antagonism	ADL-5510	Preclinical	Atuka/Adolor
Histamine H_2 receptor antagonism	Famotidine	Launched**	Astellas Pharma/Merck & Co.
5-HT_{1A} receptor agonism	Piclozotan	II	Asubio
	Pardoprunox	III	Solvay
5-HT_{2A} receptor antagonism	Pimavanserin	III***	ACADIA/Biovail

*Phase III development of fipamezole as an antidyskinetic treatment is expected to begin in 2011; **famotidine is available for the treatment of gastro-esophageal reflux disease, peptic ulcers and heartburn; ***pimavanserin is in phase III development for therapy-induced psychosis in patients with Parkinson's disease.

For preventing the development of dyskinesia, dopamine D_3 receptor antagonists, adenosine A_{2A} receptor antagonists, NMDA receptor antagonists and mGlu receptor antagonists are potential agents. Here, the rationale is to reduce the activity of either the direct striato–GPi pathway or the indirect striato–GPe pathway, while allowing dopaminergic stimulation of the other. Table III lists possible strategies for preventing or reversing the development of dyskinesia.

Therapies that may extend ON time include α_2-adrenoceptor antagonists such as fipamezole and mixed monoamine uptake (dopamine transport [DAT] + serotonin transporter [SERT]) inhibitors such as SEP-226330 (Sepracor) or UWA-0121 (Atuka, the University of Toronto, Toronto Western Hospital Research Institute and the University of Western Australia), both of which are in preclinical development. Such agents may be able to regulate dopamine avail-

Table III. *Potential pharmacological strategies for preventing or reversing the development of dyskinesia (6; supplementary information provided by Thomson Reuters Integrity℠).*

Mechanism of action	Drug candidate	Phase of development	Organization
$mGlu_5$ receptor antagonism	AFQ-056	II	Novartis
	ADX-48621	II	Addex Pharmaceuticals
	Fenobam	Preclinical	Neuropharm
Adenosine A_{2A} receptor antagonism	Istradefylline	Preregistered (USA)	Kyowa Hakko Kirin
	SYN-115	II	Synosia Therapeutics
	Preladenant	III	Merck & Co.
	DT-1133	Preclinical	Domain Therapeutics
	Vipadenant*	II	Vernalis/Biogen Idec
Dopamine D_3 receptor antagonism	S-33084	Preclinical	Servier

*Now discontinued; other agents are being explored by Vernalis and Biogen Idec researchers as part of an adenosine A_{2A} receptor antagonist program.

ability in a more physiological manner. Table IV details nonmotor problems and possible approaches to treating them.

The mechanisms cited in Table V may have disease-modifying effects by supporting the regrowth and survival of neurons, reducing cytokine-mediated apoptosis and stimulating neurogenesis.

MOTOR/NONMOTOR SYMPTOMS, DOPAMINERGIC/NONDOPAMINERGIC TREATMENTS

As pointed out by Oscar Gershanik in the introduction to a symposium titled "Dopaminergic and non-dopaminergic systems: The tango of Parkinson's disease" and sponsored by Merck Serono, PD consists of more than just motor disorders and involves multiple brain systems (7). Not just a dopamine deficiency syndrome, PD involves the acetylcholine, noradrenaline and serotonin systems, with modifications resulting in a variety of symptoms.

In a discussion of antidyskinesia agents with nondopaminergic activity that are in the development pipeline, Robert Hauser highlighted the AMPA glutamate receptor antagonist talampanel (Teva), for which a phase II study was conducted but no results reported; the $mGlu_5$ receptor antagonists MTEP (Merck & Co.), which is in preclinical development and is hoped to reduce the unwanted effects of L-Dopa, and AFQ-056 (Novartis), in phase II development; the α_2-adrenoceptor antagonists idazoxan (Potomac Pharma, Pierre Fabre), which was evaluated in a phase II trial that was stopped early, and fipamezole (Juvantia, Santhera, Biovail), which, in the

BOX 3

Analyses of preclinical data and pharmacokinetics in individuals with PD indicate that PYM-50028 (Cogane™; Phytopharm) can be delivered to patients at therapeutically effective doses. The product has shown neurorestorative potential in animal models of PD, elevating the levels of trophic factors (brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor) in the brain and restoring motor function. PYM-50028 restores dopaminergic parameters in MPTP-lesioned mice and a dose of 10 mg/kg produces PYM-50028 levels of approximately 400 ng/mL and 4000 ng/g, respectively, in plasma and brain. In a standard model of PD, the MPTP-lesioned macaque, a dose of 20 mg/kg was associated with a C_{max} of 400 ng/mL and 4260 ng/g of the agent in brain, in addition to a significant reduction (43%) in the median parkinsonian disability. In patients with PD, 150 mg of PYM-50028 was well tolerated and associated with a plasma C_{max} of 546 ng/mL and an $AUC_{(0\text{-}24\ h)}$ of 6182 ng.h/mL, results similar to those seen in healthy volunteers. PYM-50028 exposure was higher with a 450-mg dose. Modeling of pharmacokinetic data to estimate values for different dose levels predicted that a plasma C_{max} of approximately 400 ng/mL would be reached with an oral dose of approximately 125 mg (23).

Table IV. *Potential pharmacological strategies for reducing nonmotor problems (6; supplementary information provided by Thomson Reuters Integrity℠).*

Disorder	Mechanism of action	Drug candidate	Phase of development	Organization
Psychosis	$5\text{-}HT_{2A}$ receptor antagonism	Pimavanserin	III*	ACADIA/Biovail
Impulse control disorder/dopamine deregulation syndrome	Opioid antagonism	Naltrexone	II	University of Minnesota
Daytime somnolence	CNS stimulation	Caffeine	II/III	McGill University Health Center/ University of Toronto
	Dopamine transporter inhibition	Methylphenidate	II	University Hospital Lille
Orthostatic hypotension	α_2-Adrenoceptor antagonism	Fipamezole	III**	Juvantia/Santhera/Biovail
	Norepinephrine precursors	Droxidopa	III	Chelsea Therapeutics

*Pimavanserin is in phase III development for therapy-induced psychosis in patients with Parkinson's disease; **phase III development for fipamezole as an antidyskinetic treatment is expected to begin in 2011.

Table V*. Pharmacological strategies with disease-modifying potential (6; supplementary information provided by Thomson Reuters Integrity℠).*

Mechanism of action	Drug candidate	Phase of development	Organization
Antioxidants	Coenzyme Q10	III	Cornell University
Calcium channel blockade	Isradipine	II	Northwestern University
Glucagon GLP-1 receptor agonism	Exendin-4	II	University College, London
	Liraglutide	III*	Novo Nordisk
AMPA receptor modulation	AMPAKINE® compounds	Preclinical	Cortex
	LY-503430	Preclinical	Lilly
Steroidal sapogenins	PYM-50028**	II	Phytopharm

*Liraglutide is in phase III development as a treatment for obesity; **see Box 3 for separately presented PYM-50028 gene therapy study results.

BOX 4

The FJORD study of fipamezole treatment included PD patients with dyskinesia receiving treatment with levodopa, 115 at U.S. centers and 64 at 7 centers in India. The randomized, double-blind study compared fipamezole 30, 60 and 90 mg t.i.d. to placebo given over 28 days. The primary endpoint of change from baseline to day 28 on a levodopa-induced dyskinesia rating scale (LIDS) was not significantly affected by fipamezole treatment in the overall study population. In the U.S. population, however, a significant effect on LIDS was seen with the fipamezole 90 mg dose, and a dose–response was noted. The effect of fipamezole on LIDS was not associated with worsening parkinsonism, and the drug demonstrated acceptable safety, despite a mild hypertensive effect (24).

BOX 5

The results of a phase III trial of safinamide mesilate in patients with PD were described at the congress, along with details of planned and ongoing trials.

In a 24-week, randomized, double-blind, multicenter study, patients with mid- to late-stage PD who were experiencing motor fluctuations (N = 669) were treated with safinamide 50 or 100 mg/day or placebo as add-on therapy to levodopa. In the cohorts receiving low- and high-dose safinamide, the mean change in ON time (ON time without dyskinesia plus ON time with minor dyskinesia, according to patient diaries) was 1.28 and 1.32 h, respectively, at week 24, with differences from placebo of 0.59 and 0.63 h, respectively. Significant improvements in overall motor function and levodopa-induced motor function were also reflected in UPDRS scores with safinamide. Treatment-emergent adverse events occurred with similar frequency with safinamide and placebo, with the exception of dyskinesia, which was generally transient and mild to moderate in severity (25). Subjects with depression were excluded from the study. The improvement in GRID Hamilton Rating Scale for Depression-17-item (GRID HAM-D) total score was significantly greater with safinamide 100 mg than with placebo in the treated participants, and GRID HAM-D item scores for early insomnia, work and activities, and somatic anxiety also improved significantly more with safinamide 100 mg than with placebo. Depression was also reported less frequently as a treatment-emergent adverse event in the safinamide groups than in the cohort receiving placebo (26).

The ongoing SafinamidE Treatment as add-on To LEvodopa in idiopathic PD (SETTLE) study is a 24-week, randomized, double-blind, placebo-controlled phase III trial in patients with mid- to late-stage PD and motor fluctuations. Safinamide is given in doses of 50 or 100 mg/day, with diaries used to evaluate ON time with and without dyskinesia and OFF time. At least 484 patients are to be randomized. Cognition and depression will also be evaluated, along with other nonmotor and patient-reported outcomes (27).

The safinaMide add-On To dopamine agonist in early Idiopathic ParkinsON's disease (MOTION) study is another randomized, double-blind, placebo-controlled, multicenter phase III trial but is focused on patients with early-stage PD. The study is to include at least 666 patients from different countries who will be treated with safinamide 50 or 100 mg/day or placebo for 24 weeks. The primary efficacy variable is the UPDRS III score change from baseline, and depression, cognition and other common nonmotor symptoms and patient-related outcomes will also be evaluated (28).

phase II FJORD study, did not achieve the primary outcome, although the highest dose significantly reduced dyskinesias compared to placebo (see Box 4 for separately presented FJORD study results) (8). The 5-HT_{1A} receptor agonist sarizotan (Merck & Co.), which also displayed dopamine D_2 receptor antagonist activity, did not have a significant effect in a placebo-controlled study and was discontinued. An agent with dopaminergic and nondopaminergic effects, safinamide (Merck Serono, Newron), has entered phase III investigation for PD (see Box 5 for separately presented safinamide study results). Other agents of interest include the cannabinoid CB_1 receptor agonists nabilone (Valeant) and rimonabant (sanofi-aventis), the dopamine D_4/5-HT_2 receptor antagonist clozapine and the dopamine D_2/5-HT_{2A} receptor antagonist quetiapine (AstraZeneca).

As yet unmet therapeutic needs in PD were addressed by Anthony Schapira, who included in this category the improvement of motor control, the treatment or prevention of motor complications, the treatment of nonmotor symptoms and treatments that slow or prevent the progression of the disease (9). These may involve dopaminergic and nondopaminergic pathways. Dr. Schapira detailed potential therapies for these needs, focusing on nondopaminergic strategies. These are summarized in Table VI. Dr. Schapira noted that some of these agents could be expected to enter clinical practice, most likely for use in conjunction with other therapies.

The role of dopaminergic treatments in the nonmotor symptoms of PD was discussed in the "Broadening Perspectives in Parkinson's Disease" symposium sponsored by UCB. Medhi Tafti pointed out the role of dopaminergic transmission not only in PD, but in cognitive, behavioral and motivational disorders including attention deficit hyperactivity disorder, schizophrenia, addiction, restless legs syndrome, fibromyalgia and sleep disorders (10). Alterations in vigilance/wakefulness and sleep may be markers of PD. Olivier Rascol noted that nonmotor symptoms, which are common, occur in all stages of PD, are underreported and significantly impact quality of life in PD patients, may also be markers of the risk for developing PD and may represent a premotor stage of the disease (11). Some of these symptoms include olfactory dysfunction, rapid eye movement sleep behavior disorder, constipation and depression. That some of the nonmotor symptoms can be treated with dopaminergic strate-

***Table VI**. Nondopaminergic strategies for meeting unmet needs in Parkinson's disease. Detail is added for agents not previously mentioned that are under development for nonmotor symptoms and dyskinesia (9; supplementary information provided by Thomson Reuters Integrity℠).*

Disorder	Treatment
Nonmotor symptoms	Istradefylline Vipadenant LuAA-47070 (adenosine receptor antagonist; Lundbeck; discontinued) Preladenant Safinamide Zonisamide (sodium channel and T-type calcium channel blocker; Dainippon Sumitomo Pharma; launched) FP-0011 (antiglutamatergic; Faust Pharmaceuticals) Pardoprunox Isradipine *Nonpharmacological treatments:* DBS, pallidotomy, fetal implants, GDNF, BDNF transfection, cell therapies
Dyskinesia	Fipamezole Perampanel (AMPA antagonist; Eisai; discontinued) Talampanel Eliprodil (NMDA antagonist; Pfizer, Alcon, sanofi-aventis) AFQ-056 Pimavanserin Safinamide
Depression and anxiety	Paroxetine Nortriptyline Sertraline Venlafaxine Duloxetine Pramipexole*
Cognition	Memantine Rivastigmine patch Donepezil Safinamide
Psychosis and hallucinations	Clozapine Quetiapine Pimavanserin
Sleepiness	Caffeine BF-2649
Impulse control disorders	Amantadine Acamprosate
Orthostatic hypotension	Droxidopa
Urge incontinence	Solifenacin
Gait disturbance	Methylphenidate

*See Box 6 for separately presented pramipexole ER study results.

gies was discussed by K. Ray Chaudhuri (12). Continuous dopaminergic stimulation has shown promise for treating nonmotor symptoms in studies of rotigotine, ropinirole XL, apomorphine SC and levodopa administered via intrajejunal infusion.

RECENT AND ONGOING CLINICAL TRIALS

In the plenary session "Clinical trials in movement disorders: Today and the future," Karl Kieburtz highlighted some of the most important clinical trials conducted in 2009-2010 (13). Among these was a randomized, partially blinded comparison of DBS and best medical therapy published in *JAMA* in 2009, where DBS was superior in terms of ON time and motor function, but was associated with increased adverse events, falls and gait disturbance. The randomized PD Surge study published recently in *Lancet Neurology* compared DBS with best medical therapy to best medical therapy alone for advanced PD. Quality of life and motor function were improved more in the DBS group. Another innovative study published in *The New England Journal of Medicine* in 2010 compared pallidal and subthalamic DBS, where a similar improvement in motor function was seen in each group, adverse events were similar and quality of life improved in both groups. Evidence of cognitive detriment was observed, however, which was greater in the STN group.

A trial evaluating delayed administration of rasagiline (ADAGIO) produced results that were difficult to interpret, with a 1-mg dose meeting all endpoints (based on UPDRS scores) and a 2-mg dose meeting only some endpoints. The results indicated that early administration of rasagiline slowed disease progression compared to administration delayed for 9 months, but the difference in effects with different doses leaves many questions open. *The Lancet* published a double-blind, placebo-controlled study in 2009 where memantine was evaluated in patients with PD dementia or dementia with Lewy bodies. Memantine appeared to be effective in these patients, improving Clinical Global Impression of Change (CGI-C) scores compared to placebo.

Earlier this year, *Lancet Neurology* published a study in which implementation of a community-based professional physiotherapy network did not change health outcomes for patients but did reduce costs compared with usual care. A 12-week, double-blind study reported this year in *Parkinsonism & Related Disorders* found istradefylline to be safe and well tolerated but not effective in improving motor symptoms compared with placebo in PD patients. Other adenosine A_{2A} receptor antagonists are undergoing clinical assessment, however.

Lastly, trials of import in Huntington's disease include one that evaluated dimebolin, published this year in *Archives of Neurology*. The treatment was well tolerated and improved Mini-Mental State Examination (MMSE) scores compared with placebo. Results from a phase III study of pridopidine (MermaiHD) were also reported this year, with the agent associated with significant improvements in voluntary and involuntary motor symptoms (see Box 7 for separately presented pridopidine study results). The exact mechanism of action of pridopidine is not yet known. Another trial is ongoing.

A phase III trial assessing dimebolin in Huntington's disease was among those mentioned by Wolfgang Oertel in his discussion of important clinical trials with results potentially available in 2011 (14). Two trials of pridopidine in this disease are under way, as is a trial of AFQ-056. Another trial of interest is a phase III study of pregabalin in restless legs syndrome. Data from the phase III MICONOS trial of idebenone in Friedreich's ataxia have been reported, showing no significant effect on the primary endpoint, the mean change in the

BOX 6

The efficacy and safety of the dopamine D_3 receptor agonist pramipexole hydrochloride as an extended-release (ER) formulation were evaluated in patients with advanced PD in a 32-week open-label extension of a double-blind trial lasting at least 18 weeks. In the double-blind study, patients received levodopa plus pramipexole immediate release (IR), pramipexole ER or placebo. For the extension study, the placebo and pramipexole IR groups were switched to pramipexole ER. Pramipexole ER doses were then optimized over a 6-week period. The extension included 139 individuals previously treated with pramipexole IR and 123 previously given pramipexole ER. Changes in UPDRS II+III scores showed the efficacy of pramipexole to be maintained from the open-label extension baseline (end of the double-blind treatment) through 32 weeks in participants continuing ER treatment (scores declined a mean of 1.0) or switching from IR to ER pramipexole (scores declined a mean of 2.7). Mean final pramipexole doses were 3.00 mg/day in subjects switched from IR to ER and 2.97 mg/day in patients continuing ER treatment. Adverse event rates were also similar in these two groups during the extension study, as were rates of serious adverse events and event-related withdrawals. The most common adverse events were dyskinesia and somnolence (29). An ER formulation of pramipexole (Mirapex ER®; Boehringer Ingelheim) was approved in the USA earlier this year.

BOX 7

Data from two double-blind trials have revealed some evidence of improvement with pridopidine (ACR-16) in patients with Huntington's disease, although the primary endpoints were not met in either study. The dopaminergic stabilizer received orphan drug designation in the USA and the EU and is currently in phase III development at NeuroSearch. In a phase II trial, 28 patients were randomized to treatment with once-daily pridopidine 50 mg and 30 to receive placebo for a 4-week period. The primary endpoint of change from baseline in weighted cognitive score, assessed by Symbol Digit Modalities, verbal fluency and Stroop tests, showed no significant difference between the groups. Secondary endpoint analyses showed a trend towards an improvement in affective symptoms with pridopidine, while voluntary motor symptoms were significantly improved from baseline with the drug; this latter effect was significant compared to that of placebo in more severely affected patients. Pridopidine was well tolerated and did not negatively affect involuntary movement (30). The MermaiHD (Multinational EuRopean Multicenter ACR16 study In Huntington's Disease) study, a 6-month, randomized, double-blind phase III trial, included 437 patients treated with once- or twice-daily pridopidine 45 mg or placebo. The primary efficacy endpoint was the change from baseline to week 26 on the mMS subscale of the United Huntington's Disease Rating Scale (UHDRS) total motor score, which consists of 10 items relating to voluntary motor function. On this endpoint, an improvement was seen with pridopidine versus placebo, but this did not reach the level of statistical significance set for the trial. The change in this endpoint was significantly different from that with placebo in the per-protocol population with twice-daily dosing. Secondary endpoint analysis also suggested that another 6 months of treatment would produce a significant effect on voluntary motor function. Pridopidine also slowed motor symptom progression in patients with longer CAG repeat lengths, and the effect of pridopidine on voluntary motor function was independent of concomitant use of antipsychotic medication. The adverse event profile of pridopidine was similar to that of placebo in this study (31).

Table VII. *Clinical trials in Parkinson's disease (PD) with results expected in the near future (14).*

Indication	Treatment	Phase
PD	CERE-120	I/II
PD	Isradipine	II
PD	Inosine	II
PD	Duodopa intestinal gel	III
Early PD	PYM-50028	II
Early PD	Coenzyme Q10	III
Advanced PD	Transdermal rotigotine	III
Levodopa-induced dyskinesias	ACR-325	I
Levodopa-induced dyskinesias	Safinamide	II
Levodopa-induced dyskinesias	AFQ-056*	IIb
Motor symptoms	Transdermal nicotine	II
Iron overload	Deferiprone**	II/III
Daytime sleepiness	Pitolisant	III
Cervical dystonia	Botulinum toxin	III

*See Box 8 for separately presented AFQ-056 study results; **see Box 9 for separately presented deferiprone study results in pantothenate kinase-associated neurodegeneration.

BOX 8

A proof-of-concept study presented at this year's congress showed that the metabotropic glutamate $mGlu_5$ receptor antagonist AFQ-056 (Novartis) can reduce levodopa-induced dyskinesia in patients with PD. The agent is also being developed for fragile X syndrome, Huntington's disease and anxiety. The randomized, double-blind, placebo-controlled trial included 28 patients with severe levodopa-induced dyskinesias. AFQ-056 was administered twice daily before dopaminergic therapy and titrated during days 1-16 at 25-150 mg b.i.d. or the highest tolerated dose, and then downtitrated. Of the 14 patients given AFQ-056, a total of 8 reached the maximum dose of 150 mg b.i.d. On day 16, significant antidyskinetic effects were seen with AFQ-056 on the Abnormal Involuntary Movement Scale, with reductions of 9.75 and 4.84, respectively, for AFQ-056 and placebo, and on the UPDRS IV 32-33, with respective reductions of 2.56 and 0.98. AFQ-056 was also superior to placebo, although nonsignificantly so, on the Lang-Fahn Activities of Daily Living Dyskinesia Scale and the UPDRS III. Adverse events were noted in 13 patients in the AFQ-056 group and in 11 in the placebo cohort, with dizziness and fatigue being the most common. Most adverse events were mild to moderate in severity. Two serious adverse events (psychotic disorder and dyskinesia) were seen in the cohort receiving AFQ-056 and were considered to be related to the study drug (32).

BOX 9

Iron-chelating agents may reduce brain iron accumulation in patients with the autosomal recessive disorder pantothenate kinase-associated neurodegeneration (PKAN), but this effect may not yield clinical benefit. This was the conclusion of a two-center phase II study in which nine patients with PKAN received oral deferiprone 25 mg/kg/day for 6 months. Measurement of iron concentrations in the globus pallidus on MRI revealed a significant reduction after treatment (median reduction of 30%) and reductions in all patients, but no changes in scores on the Burke-Fahn and Marsden Dystonia Rating Scale or health-related quality-of-life scales (SF-36 and Child Health Questionnaire [CHQ-PF50]) were observed. Deferiprone was well tolerated, with the most common adverse events being nausea and gastralgia, experienced by four patients. Two patients suspended treatment for 10 days due to febrile illness but no severe adverse events occurred. The lack of clinical effect may have been due to damage to neurons beyond the possibility of recovery of function, irreversible damage to connections and circuits, and/or the lack of an association between iron accumulation and disease process (33).

International Cooperative Ataxia Rating Scale (ICARS) score from baseline. Important ongoing trials in PD are detailed in Table VII.

PHYSIOTHERAPY

Lastly, while this report has focused mainly on pharmacological interventions for treating PD, followed by DBS, other options are also available. As mentioned in the Blue Ribbon Highlights session on the last day of the congress, physiotherapy is a poorly developed treatment modality for PD. Gunther Deuschl and Dennis W. Dickson nevertheless drew attention to posters they considered highlights of the congress that dealt with physiotherapy (15, 16). In one, 60 patients with mild to moderate PD were randomized to the Training BIG technique, Nordic walking or domestic, nonsupervised exercise. While an improvement in UPDRS motor scores was seen at week 16 (–5.05) with the BIG technique, mild deterioration was seen in the other groups (17). Large-amplitude movement exercise also improved motor function in a case series of 20 PD patients participating in the ThinkBig program. Mean improvements of 50% on UPDRS scores and of 26% on Tinetti scores (an evaluation of mobility and stability) were seen at 8 weeks (18).

Also highlighted in this session were studies of the Argentine tango, including one where the dance was associated with improved balance and backward gait in 36 PD patients. Improvements were seen regardless of freezing of gait or fall history (19). In a separate study, 10 PD patients and their partners followed a DVD program of Argentine tango 1 h per day, 5 days a week and received 2 h per week of sessions with an instructor over the course of 5 weeks. UPDRS measures of gait, posture and speech were improved in all patients (20).

DISCLOSURES

The author states no conflicts of interest.

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