Drugs of the Future 2009, 34(8): 681-692

CCC: 0377-8282/2009

NEW THERAPEUTIC DIRECTIONS: PRESENTATIONS FROM THE MOVEMENT DISORDER SOCIETY'S 13TH INTERNATIONAL CONGRESS OF PARKINSON'S DISEASE AND MOVEMENT DISORDERS

P. Cole

Prous Science, Provenza 388, 08025 Barcelona, Spain

CONTENTS

ABSTRACT

The 13th International Congress of Parkinson's Disease and Movement Disorders, held in Paris on June 7-11, 2009, was attended by 5,000 people from around the world. Over 1,700 posters were presented in addition to the 6 plenary sessions, 8 teaching courses and 19 parallel sessions, as well as the 20 video sessions and skill workshops. Many of these presentations highlighted the strategies being investigated to overcome the drawbacks to and limitations of the treatment of Parkinson's disease (PD) with levodopa, as well as the controversies surrounding that drug's proper implementation. Some of the questions addressed were: When should treatment be initiated? How should early PD be treated? How should motor complications be managed – how can we deal with the noncontinuous dopamine stimulation achieved with levodopa? What is the role of surgical interventions? How can we inhibit disease progression? What new therapies are being tested? The findings of recent clinical trials on new pharmacological therapies were presented, and while these were sometimes surprising and sometimes disappointing, all provided important information on these strategies. Corporate symposia held at the congress also covered a variety of topics, including 24-h symptom control (or the lack of it), the role of dopamine agonists and continuous delivery systems. Also highlighted here are a selection of poster presentations describing recent studies of drug candidates for PD. The Movement Disorder Society (MDS) congress also focuses attention on diseases other than PD, and a session providing an overview of the nature and management of Gilles de la Tourette's syndrome is detailed here.

INTRODUCTION

The existence of a very effective but imperfect treatment for Parkinson's disease (PD) places patients and clinicians in an ambivalent position characterized by a mixture of gratitude and dissatisfaction. The story of PD treatment is, of course, intimately tied to that of levodopa. Levodopa has enlightened scientists on the causes of the disease and tantalizingly offered dramatic improvement in symptoms. However, its drawbacks, such as wearing-off phenomena due to its short half-life, and questions about how it is best administered have generated confusion in the minds of patients and enthusiasm for the development of revised treatment algorithms, novel formulations and methods of levodopa delivery, as well as entirely new treatments.

The Movement Disorder Society's (MDS) 13th International Congress of Parkinson's Disease and Movement Disorders addressed these issues in great detail. As highlighted here, the congress presentations reviewed the shortcomings of current pharmacological treatment modalities and the corresponding strategies being investigated to overcome them. The results of some of the latest trials were not necessarily those expected, but nevertheless yielded important information on which to build.

As the title of the congress indicates, not only PD is covered at each year's meeting, and an oral session discussing the features and treatment of Gilles de la Tourette's syndrome was also held. This disease has often captured the general public's attention, becoming the focus of books and films. The reality of Tourette's syndrome, including the encouraging (e.g., improvement with age) and the difficult (e.g., disabling comorbidities), were described and are reported here.

PARKINSON'S DISEASE TREATMENT

This year's congress began with a series of therapeutic plenary sessions that were not sponsored by industry. The first of these dealt with the early management of PD, with Regina Katzenschlager's talk entitled simply: When? (1). This talk underscored a theme which

recurred throughout the congress, one which points to the fundamental strangeness of our current situation in facing the disease, based on a limited understanding of it: although treatments for PD are available, it is not clear when they should be initiated.

Parkinson's disease is a relentlessly progressive disease, as pointed out by Dr. Katzenschlager, and one for which the focus of treatment is on the dopaminergic deficit. Essentially, there are two management strategies for early PD: watch and wait or the initiation of treatment. The immediate initiation of treatment upon diagnosis has the advantage of improving motor and nonmotor symptoms and quality of life, but other questions revolving around adverse effects, the potential to delay motor complications, the delaying of disease progression —this last being the great unmet clinical need— remain open with this strategy. There is a great need for biomarkers to better understand treatment effects.

In the TEMPO (TVP-1012 [rasagiline] in Early Monotherapy for Parkinson's Disease Outpatients) study, which featured a delayed-start design, outcomes were better when PD patients received **rasagiline mesilate** treatment from the beginning instead of after a delay. Follow-up for over 6 years showed that patients begun on placebo and later switched to rasagiline never caught up to patients given rasagiline from the beginning in terms of improvement. Dr. Katzenschlager added results from the ADAGIO (Attenuation of Disease progression with Azilect GIven Once-daily) study, which also showed greater worsening at 18 months in patients not given rasagiline for the first 9 months; these patients and those given the active treatment from the beginning showed no signs of converging on outcomes over weeks 48-72. There was also a benefit in nonmotor symptoms when treatment was not delayed. Another delayed-start study, PROUD (assessment of potential impact of PRamipexole On Underlying Disease), will help to answer the question of whether **pramipexole hydrochloride** treatment has a disease-modifying effect (see Box 1 for separately presented pramipexole study results).

Another factor requiring more study to further the discussion about early treatment for PD concerns the compensatory mechanisms that are activated in the brain when PD develops. Early treatment may affect these mechanisms in good or bad ways; this is not known at present.

Finally, the equation is further completed by the patients themselves, with their own social and psychological background, perceived needs and support systems. There is some evidence of better patient-reported health status when treatment is initiated early.

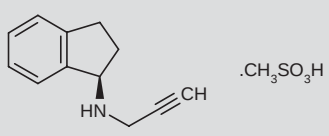
Dr. Katzenschlager closed by stressing these patient preferences and circumstances, as well as the fact that progression is fastest in the early years. An area of study for the future concerns the possibility of initiating treatment even before the development of motor symptoms.

Following Dr. Katzenschlager's talk was Stanley Fahn's discussion of how to treat early PD. Dr. Fahn began by quickly noting the role of exercise in this treatment (2). It should be made clear to patients that both physical and mental exercise is necessary, and patients should be encouraged to play an active role in treating their disease. An animal study using the MPTP model showed a reduced loss of dopaminergic neurons in animals made to exercise.

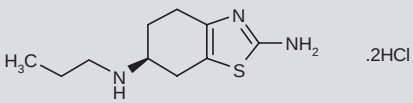
BOX 1

Extended-release pramipexole studied in early and advanced Parkinson's disease.

The immediate-release (IR) formulation of the dopamine receptor agonist pramipexole has demonstrated efficacy in early and advanced Parkinson's disease (PD), but two new studies indicate that a new extended-release (ER) formulation can be used in its place. A study in patients with early disease included patients with idiopathic disease diagnosed within the previous 5 years (N = 539) who were randomized in double-blind fashion to pramipexole ER 0.375-4.5 mg/day, pramipexole IR 0.125-1.5 mg t.i.d. or placebo for 33 weeks. Levodopa was permitted only as rescue medication. Pramipexole ER demonstrated superiority to placebo at week 18 in a subset of the study's first randomized patients according to the improvement in the United Parkinson's Disease Rating Scale (UPDRS) Part II+III score, which decreased an adjusted mean −8.1 and −5.1, respectively. Mean changes in this measure at week 33 were −8.6 and −8.8, respectively, with pramipexole ER and IR, indicating noninferiority. Safety was similar between the formulations. The study in advanced PD patients (N = 517) was likewise randomized, double-blind and placebo-controlled, with pramipexole doses of 0.375-4.5 mg/day administered for 33 weeks. The adjusted mean decrease in UPDRS Part II+III at week 18 was −6.1, −11.0 and −12.8, respectively, with placebo, pramipexole ER and pramipexole IR, with both pramipexole formulations significantly superior to placebo. At week 33, these figures were −7.0, −11.1 and −11.3, respectively, which again were significant for pramipexole versus placebo. Off time during waking hours was also significantly improved with the pramipexole formulations at 18 weeks. Adverse events were similar between similar dose levels of pramipexole. The pramipexole ER formulation thus appeared to offer enhanced convenience and potentially improved compliance in PD patients. The dopamine D_3 receptor agonist pramipexole was first launched in 1997 by Boehringer Ingelheim for the treatment of PD. In 2006, it was approved for the treatment of restless legs syndrome (26, 27).



Rasagiline mesilate



Pramipexole hydrochloride

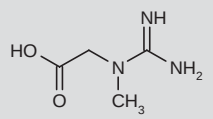
The pharmacological treatment of newly diagnosed patients centers on levodopa, an agent about which patients frequently worry. It is important to explain that levodopa works and does not stop working; increased symptom severity over time is due to worsening of the disease. Dr. Fahn recommended the use of "protective" therapies, those with effects documented in randomized, controlled trials. Notable among these are the monoamine oxidase B (MOA-B) inhibitors, including rasagiline and **selegiline hydrochloride**, for which numerous successful trials have been conducted. The DATATOP (Deprenyl [selegiline] And Tocopherol Antioxidative Therapy Of Parkinsonism) and BLIND-DATE studies indicated that selegiline is an appropriate treatment and may be neuroprotective in early patients. Other drugs have shown some efficacy, such as coenzyme Q10 (**ubidecarenone**), although this has not been successful in all studies. New results on coenzyme Q10 are awaited. **Creatine** is another agent that is currently being studied in a large trial.

For the treatment of symptomatic patients, studies have shown that levodopa is superior to dopamine agonists, although there may be more complications with this treatment. Anticholinergics and amantadine are not as important as treatment options. Dr. Fahn also stressed the importance of individualizing treatment. This theme was taken up again during the panel discussion and question session. Also arising again as a matter of concern was what has been described as "L-DOPA phobia", or the resistance patients have to taking levodopa for fear of it wearing off when they would benefit from it.

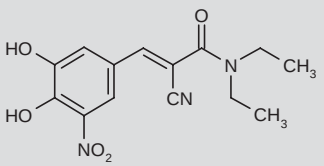
The medical and surgical management of motor complications was discussed in the following plenary session, with Heinz Reichmann leading off (3). When discussing pharmacological therapy, Dr. Reichmann naturally spoke of levodopa, the most effective drug for treating symptoms, and one which has been found to increase survival and quality of life in patients. Almost all patients receive it at some point, including those given dopamine agonists. The short plasma half-life of the drug, however, leads to the phenomenon of wearing off, a lack of continuous dopaminergic stimulation resulting in motor complications. Unfortunately, an obvious means of overcoming this limitation with continuous oral levodopa administration was found to still result in peaks and troughs of stimulation. A similar risk of motor complications was seen with controlled-release levodopa.

The problem affects many patients. In the ELLDOPA (Earlier versus Later Levodopa Therapy in Parkinson Disease) study in early patients, 17% had dyskinesias after 6 months and 30% had wearing off. Patients rated wearing off as the biggest problem related to levodopa therapy.

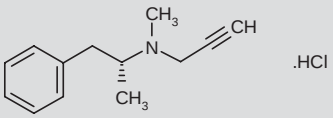
Other options exist, including the use of **entacapone**, which has been found to increase levodopa levels, and **tolcapone**, which can improve motor complications. These dopamine agonists are associated with a lower risk of dyskinesia development. Other approaches to avoiding or lessening wearing off in the future may involve the use of oral dopamine agonists with long elimination half-lives, subcutaneous infusion of apomorphine and transdermal drug administration. Amantadine also has antidyskinetic activity, but its efficacy lessens over time. The levodopa pump can provide stable levodopa blood concentrations and is associated with decreased off hours and decreases in dyskinesia. The apomorphine pump may be utilized in patients not suitable for deep brain stimulation (DBS), but the treatment becomes intolerable after 2-4 years. The apomorphine Penjet is also a means of providing intermittent therapy.



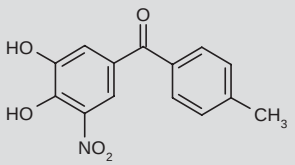
Creatine



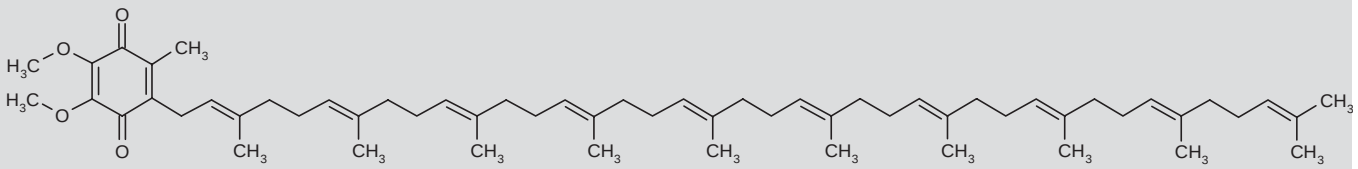
Entacapone



Selegiline hydrochloride



Tolcapone



Ubidecarenone

Dr. Reichmann summed up by saying that the early use of dopamine agonists may reduce, postpone or avoid motor complications. In the presence of motor complications, levodopa can be decreased and other treatments attempted.

Addressing surgical approaches was Patricia Limousin-Dowsey, who began by describing the positive effects of subthalamic nucleus deep brain stimulation (STN DBS) (4). These include major decreases in symptoms, decreases in dyskinesia, improved quality of life and improved physiological assessments. Although more data are needed, there have also been effects on nonmotor symptoms, such as bladder symptoms, sleep, sweating, hypotension and smell. Effects on depression have been seen, but Dr. Limousin-Dowsey hastened to add that mood can also deteriorate and apathy can worsen after STN DBS, leaving some patients at an increased risk of suicide. A range of side effects can occur, the most common of which are speech impairments and weight gain.

STN DBS is limited primarily by the fact that the positive results are seen only in a very select group of PD patients. There is also variability in responses, as well as fluctuations. Fine motor function can worsen, and the occurrence of tremor after DBS is indicative of the treatment having a disease-changing effect.

Dr. Limousin-Dowsey also discussed other targets that have been evaluated for DBS, including the ventral intermediate nucleus (VIM) of the thalamus and the globus pallidus internus (GPi). Although less common, these may be appropriate in some patients. VIM DBS may be useful in older patients with tremor, while GPi DBS may be appropriate for patients with severe dyskinesia.

Selection criteria are obviously of tremendous importance for the proper use of these techniques. Among other things, the prospective patient must have some chance to benefit with little risk. He or she should have symptomatic PD, some disability, compromised quality of life and should have attempted treatment with medication. Dr. Limousin-Dowsey emphasized the importance of making sure the patient's expectations for outcomes are reasonable.

Interestingly, the panel discussion following this speaker found by an informal survey of the audience not only that there is variability in the availability of pumps and DBS around the world, but that pumps are used perhaps less than they could be. An algorithm of treatment starting with oral medications and progressing through pumps and ending in surgery is therefore not always utilized. The views on these treatment modalities are also limited by the lack of a head-to-head comparison of pumps and surgery.

The second therapeutic plenary session on the second day of the meeting was titled "What's new in Parkinson's disease therapeutics", and provided access to clinical trial results not yet published, as well as an overview of ongoing clinical studies for new therapies in development. C. Warren Olanow discussed the completed trials, the results of two of which were not those hoped for, while the results of the third were also surprising (5). In the case of treatments failing to meet their primary objective, insight has been gained and the utility of these new modalities has still not been ruled out.

The first study dealt with CERE-120, a gene therapy consisting of an adeno-associated virus type 2 (AAV2) vector delivering neurturin, a member of the glial-derived neurotrophic factor (GDNF) family of trophic factors, in advanced PD patients. The double-blind, 12-month study compared the active gene therapy to a sham control treatment in patients with motor complications who were levodopa-responsive and had dopaminergic lesions. The primary endpoint was the change in Unified Parkinson's Disease Rating Scale (UPDRS) motor score at the final visit, in the practically defined off state. Improvement was seen with CERE-120, but also with placebo, and the active treatment did not have a significant effect on the primary endpoint. A trend towards a greater reduction in off time was seen with the gene therapy, as well as a significant improvement in quality of life. Adverse events with CERE-120 were consistent with a surgical procedure, and there were no serious adverse events attributed to CERE-120. Intriguingly, an analysis at 18 months in 14 patients did find a significant difference in the primary endpoint favoring CERE-120, as well as trends in other outcomes. Future studies are being planned to target the striatum and substantia nigra pars compacta.

The second study discussed was the STRIDE-PD (STalevo Reduction In Dyskinesia Evaluation) trial, an attempt to prevent levodopa-induced dyskinesia by using the catechol *O*-methyltransferase (COMT) inhibitor entacapone to prolong the half-life of levodopa, achieving something approaching continuous levodopa delivery. Entacapone has been found to extend the elimination half-life of levodopa from 90 min to approximately 3 h. In the double-blind, 134-week study, patients received Stalevo®, combining levodopa, carbidopa and entacapone, or standard levodopa/carbidopa given 4 times daily at 3.5-h intervals. The target daily levodopa dose was 400 mg and 745 patients were included. The primary endpoint was the time to onset of dyskinesia and a significant difference was seen favoring standard levodopa/carbidopa. The incidence of dyskinesia was also increased in the Stalevo® group. A post hoc analysis showed that patients in the Stalevo® group also taking dopamine agonists had a higher frequency of dyskinesia, a finding quite possibly related to the risk profile of these patients. The dyskinesia results of the study were perhaps due to the levodopa load. Stalevo® was associated with favorable trends in off time and UPDRS scores, while the adverse events of nausea, vomiting and diarrhea were more frequent in this group (see Box 2 for separately presented STRIDE-PD study results).

The last trial discussed was ADAGIO, which focused on the potential of rasagiline to prevent disease progression. The double-blind, 18-month study had a two-phase, delayed-start design. Untreated PD patients (N = 1,176) were first randomized to either placebo or rasagiline 1 or 2 mg for 9 months, after which those initially given placebo were randomized to one of the rasagiline doses for a further 9 months. The primary outcome measure was the mean change in UPDRS from baseline. Rasagiline 1 mg met the study endpoints. Patients initially given rasagiline 1 mg had a reduced rate of decline in the first phase of the study and better scores in the second half of the study compared to patients initially given placebo and later given rasagiline 1 mg. Importantly, these two treatment groups did not converge over time in the second half of the study; early treatment with rasagiline 1 mg maintained consistent superiority over delayed administration. Curiously, this was not seen with rasagiline 2 mg, as patients given delayed treatment started to catch up with the advantage of patients given early treatment. This may have been due to the benefit of rasagiline 2 mg being masked by the symptomatic effect of the drug. A long-term extension study is under way.

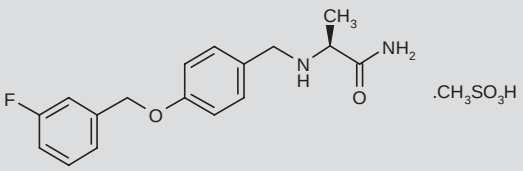
BOX 2

Can adding entacapone to levodopa delay dyskinesia onset? The STRIDE-PD study.

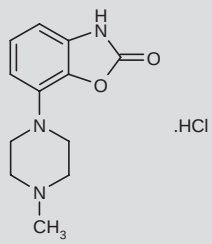
The Stalevo Reduction in Dyskinesia Evaluation (STRIDE-PD) study was conducted to determine if a catechol *O*-methyltransferase (COMT) inhibitor, entacapone, could increase the bioavailability of levodopa and delay the onset of dyskinesia in Parkinson's disease patients. STRIDE-PD was a randomized, double-blind, multicenter trial in which 745 patients requiring initiation of levodopa received either levodopa/carbidopa/entacapone (LCE; Stalevo®) or levodopa/carbidopa (LC), with a levodopa target dose of 100 mg q.i.d. The unexpected result was an earlier onset of dyskinesia in the LCE group compared to the LC group, with mean times to first occurrence of 74.2 weeks vs. 79.1 weeks. Dyskinesia developed in more patients in the LCE group during the first 134 weeks (41.7% vs. 32.4%; $P = 0.016$). Wearing off occurred in 45.6% and 48.3%, respectively, of the LCE and LC groups over the first 134 weeks, with time to wearing off not differing significantly between groups (150.6 weeks vs. 155.9 weeks). The mean difference in change from baseline in United Parkinson's Disease Rating Scale (UPDRS) total score (Part II+III), 1.1 points, favored LCE, but not significantly. Similar proportions of each treatment group experienced an adverse event (93.3% with LCE and 90.6% with LC) or a serious adverse event (24.4% with LCE and 22.6% with LC). The increased frequency of dyskinesia in the LCE group was possibly attributable to patients receiving a higher levodopa-equivalent dose, due to the effect of entacapone on plasma levodopa levels. It remains to be determined if continuous dopamine stimulation can be achieved with more frequent administration of LCE, resulting in a reduction in dyskinesia (28).

Following Dr. Olanow was Werner Poewe, who discussed new PD therapies in clinical development (6). Dr. Poewe began by pointing out the increase in recent years in trials targeting nonmotor symptoms and disease modification apart from those investigating treatments targeting motor symptoms. For the latter, several agents are presently in late-stage development, including the MOA-B inhibitor **safinamide mesilate**. A trial including 669 patients with fluctuating PD is evaluating the change in mean daily on time. Trials of the partial dopamine agonist **pardoprunox hydrochloride** have been conducted, and a new trial of adjunct therapy with pramipexole is set to commence this month. A phase III study (APEX-PD) of the novel extended-release carbidopa/levodopa formulation IPX-066 has been initiated. The formulation was associated with a greater reduction in off time compared to immediate-release levodopa and a longer duration of benefit in a phase II study. Another new levodopa patch formulation is also being studied. Finally, therapies aimed at enhancing endogenous dopamine synthesis under evaluation include **nitisinone**, which inhibits tyrosine metabolism in the liver, gene therapy and cell transplantation therapy.

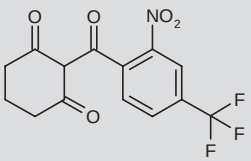
Many phase II studies are being conducted which are targeting motor complications. Agents in this area include **preladenant**, which targets the adenosine A_{2A} receptor. A phase III program including monotherapy and adjunct therapy is being initiated. Glutamate antagonism is being assessed with AFQ-056, with a proof-of-concept study also reported at the congress showing improved motor scores. A phase IIb study is about to begin. A phase IIb of **fipamezole hydrochloride**, which targets α_{2A}-adrenoceptors, is also ongoing (see Box 3 for separately presented fipamezole study results).



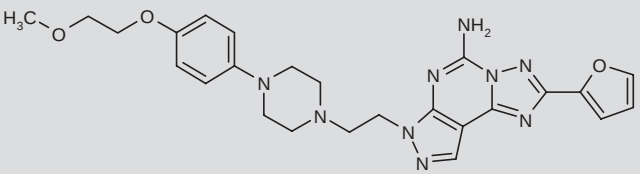
Safinamide mesilate



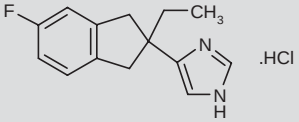
Pardoprunox hydrochloride



Nitisinone



Preladenant



Fipamezole hydrochloride

BOX 3

Fipamezole evaluated in proof-of-concept Parkinson's disease study.

α_2-Adrenoceptor blockade may be a means of ameliorating the motor complications seen with levodopa, according to the results of a randomized, double-blind study of monotherapy and adjunct therapy with fipamezole hydrochloride (Juvantia, Santhera). Treatment consisted of a placebo run-in phase followed by a randomized phase of five escalating doses of fipamezole (15, 30, 60 and 90 mg followed by the maximum tolerated dose or repeated 90 mg) or placebo administered as a buccal spray. The overall study duration was 3 weeks. Study subjects had relatively advanced idiopathic Parkinson's disease with levodopa-associated motor response complications. When given with steady-state levodopa infusion, fipamezole 60 and 90 mg significantly reduced the severity of dyskinesia (modified abnormal involuntary movements [AIMs] scores) by 23% and 31%, respectively, without reducing the antiparkinsonian response to levodopa. These doses also increased the duration of the response to levodopa, with the effect prolonged by 41 min with the dose of 90 mg. Fipamezole had no antiparkinsonian effect when given as monotherapy, as assessed by the United Parkinson's Disease Rating Scale (UPDRS) III. There were no serious adverse events in the study; 14 fipamezole-treated patients reported 204 treatment-emergent adverse events (TEAEs), while 13 patients reported 49 TEAEs with placebo. Most TEAEs were mild or moderate, and the most common seen with fipamezole administration were pallor (86%), oral hypoesthesia (64%) and nausea (64%). Adverse events led to discontinuation in one and two patients, respectively, in the placebo and fipamezole groups (29).

BOX 4

Long-term safety and low-dose efficacy of ropinirole PR studied in Parkinson's disease.

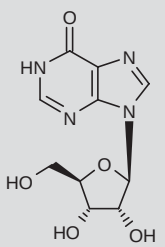
Data from clinical studies have been analyzed to assess the efficacy and long-term safety of prolonged-release ropinirole (ropinirole PR; GlaxoSmithKline), the extended-release formulation of the dopamine D_2 receptor agonist, in patients with Parkinson's disease (PD). The formulation was approved in the U.S. for PD last year. Data from the EASE-PD Adjunct and PREPARED studies, both double-blind phase III trials lasting 24 weeks in patients with advanced disease, were used to assess the relationship between dose and efficacy. In the EASE-PD study, a reduction in off time was seen in some patients given the lowest dose (2 mg/day), and a reduction of > 1 h from baseline was seen with doses of 6 mg/day and above. In PREPARED, 52% of patients achieved a reduction of at least 20% from baseline in off time with the dose of 6 mg/day; this figure was 63% in patients taking 24 mg/day. In both studies, treatment benefits increased with dose. The safety and tolerability of long-term treatment with ropinirole PR were evaluated in 502 patients with early or advanced PD who were initially enrolled in 1 of 5 studies and were then included in 2 multicenter, open-label extension studies. Flexible doses of 2-24 mg/day were administered, with 396 patients treated for over 1 year. With a mean dose of 15.9 mg/day and a total exposure of 50,807 days, ropinirole PR was well tolerated, with a dyskinesia rate of under 5%. Treatment-emergent adverse events (TEAEs) were experienced by 370 patients, with a similar amount receiving monotherapy or therapy as an adjunct to levodopa. The most commonly reported TEAEs were peripheral edema (11%), back pain (9%) and somnolence (9%). Serious TEAEs were reported in 16%, and TEAEs led to withdrawal in 13%. No new safety concerns arose with long-term treatment (30, 31).

Several small trials are investigating treatments for nonmotor symptoms, such as sleep disturbances, hypotension, urinary dysfunction, constipation and neuropsychiatric symptoms. Many of these studies involve agents used outside of PD.

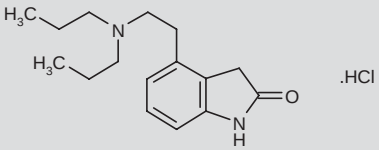
Lastly, a number of potentially disease-modifying agents are in clinical development. Pramipexole is in phase IV and the PROUD trial was recently completed. Results are expected this year. Coenzyme Q10 is in phase III, with study results expected in 2011. Phase II results for creatine are expected in 2014, and phase III data for green tea polyphenol should be available in 2012. Phase II data on **inosine** may also be available this year.

Corporate therapeutic symposia were also held during the congress. On Tuesday, GlaxoSmithKline sponsored a session entitled "Day and night treatment of Parkinson's disease", which highlighted the difficulty of managing PD symptoms a full 24 h each day, and the possible role of prolonged-release **ropinirole hydrochloride** (ropinirole PR) in meeting that need (see Box 4 for separately presented ropinirole study results).

Fabrizio Stocchi set the stage by breaking down PD symptoms into motor symptoms, nonmotor symptoms and motor and nonmotor



Inosine



Ropinirole hydrochloride

fluctuations (7). The disease is unpredictable, he noted, with a fluctuating nature and medications which are associated with side effects. Most patients have to organize their lives around the off period, which impacts their daily lives, their social lives and their work. The symptoms other than motor symptoms, such as sleep disturbances, neuropsychiatric problems, urinary incontinence, gastrointestinal problems and pain, also fluctuate, and symptoms also occur at night. Nocturnal symptoms increase as the disease progresses, and these symptoms are often not recognized.

To get a real-life picture of PD patients, a survey was conducted in approximately 3,000 patients. This revealed that over two-thirds feel they are not in control of symptoms over 24 h, that over half plan their day around the times they are taking medications and that approximately three-quarters have problems getting to sleep. Most also reported disrupted sleep. Dr. Stocchi underlined the dramatic difference between on and off states with film of patients in each state.

The assessment of nonmotor symptoms has advanced in recent years and now includes the Non-Motor Symptoms Questionnaire (NMSQuest), the Non-Motor Symptoms Scale (NMSS) and the new UPDRS. The current state of affairs, Dr. Stocchi concluded, points to the need for continuous 24-h treatment delivery.

Ray Chaudhuri elaborated on the tools available for the assessment of nonmotor symptoms in PD (8). He began with a case study of a patient with a UPDRS score of 12 suggesting early/mild PD. This same patient, however, had an NMSS score of 14 out of 30, indicating important difficulties. Pure motor assessments therefore miss major impacts on quality of life. This was demonstrated in the PDLIFE study, which concluded that quality of life deteriorates if treatment initiation is assessed by motor scores alone.

Dr. Chaudhuri reviewed the nonmotor assessment tools, starting with the NMSQuest. This tool is in widespread use and provides a snapshot view of a patient's nonmotor symptom profile. It can reveal things otherwise not declared, such as problems with sleep or sexuality. It is not a grade rating scale, however, which is the function of the NMSS, which complements and is correlated with the NMSQuest. It is also correlated with disease progression. Efforts are under way to use these scores to develop nonmotor staging of the disease.

The Parkinson's Disease Sleep Scale (PDSS) is used worldwide to assess nocturnal symptoms, which affect as many as two-thirds of patients. Fifteen separate items are gauged on a visual analog scale. Works in progress include attempts at validating individual items with other measures, identifying domain-based PDSS items and, importantly, identifying clinically relevant changes to judge interventions.

The discussion of treatment with a once-daily oral dopamine agonist, ropinirole PR, was led by Evzen Ruzicka, who discussed clinical trial data, as well as experience with patients in the clinic (9). Clinical study data came from EASE-PD (Efficacy And Safety Evaluation in Parkinson's Disease), a randomized, double-blind, placebo-controlled study in 391 advanced PD patients which lasted 6 months. In this study, ropinirole PR was associated with a significant decrease in off time compared with placebo, a significant improvement in depression and improvement in many aspects of quality of life. Ropinirole PR was also associated with an increase in dyskinesia and nausea.

The improved plasma concentration–time profile of ropinirole PR over immediate-release ropinirole (ropinirole IR) may mean that the former treatment can improve the sleep and wakefulness disturbances seen in PD. Indeed, in EASE-PD, PDSS scores improved from baseline in ropinirole PR-treated patients with a baseline PDSS under 100, signifying significant impairment.

Dr. Ruzicka described the efficacy of ropinirole PR in a case study of a patient who experienced improved nighttime sleep and early-morning akinesia with ropinirole PR 16 mg once daily. Sleep attacks during the day, which were present with ropinirole IR 5 mg t.i.d., also disappeared with ropinirole PR. A case series of 5 patients who switched from ropinirole IR to ropinirole PR was also presented. Here, sleep attacks also disappeared in the 4 patients initially affected. PDSS scores improved 10 and 20 points in 2 patients, while not changing in others. Epworth Sleep Scale scores declined in all patients.

The conclusions reached by Dr. Ruzicka were that the evidence suggests that ropinirole PR improves excessive daytime sleepiness and may improve sleep quality, as well as periodic leg movements in sleep, although these conclusions require further investigation.

On Wednesday, corporate therapeutic symposia included the UCB Pharma-sponsored session, "Parkinson's disease treatment – where do we go from here?" The discussion was begun by Anthony Schapira, who noted that, in terms of evidence-based treatment recommendations, several reviews have been done and guidelines and also several algorithms are available (10). Still, clinicians need to make individual decisions on what to start an early PD patient on. With progress, treatment gets more complex, and with advanced disease it is still more complicated, as it may require multiple therapies. The evidence base is critical, but it has to be applied in practice. At present there is no consensus for treatment initiation.

Eduardo Tolosa followed this introduction with a talk focused on whether second-generation dopamine agonists were fulfilling expectations (11). The difficulties in managing PD, Dr. Tolosa pointed out, cover various areas, with uncertainties in diagnosis, etiology, complications, symptoms and treatment. As for treatment, there are no preventive treatments or cures; treatment is symptomatic and only partially effective.

Levodopa is effective, but some patients are unresponsive and motor complications are common. Dopamine agonists were introduced to overcome the limitations of levodopa. These are characterized by a longer half-life, possible neuroprotective activity and direct stimulation of dopamine receptors, as well as the absence of metabolic conversion and absorption delay from competition with dietary amino acids. There are several dopamine agonists with different pharmacokinetic and pharmacological properties. All feature potent dopamine D_2 receptor stimulation and different, but long, half-lives. They can also affect other receptors.

The benefits of these agents in early PD and in advanced PD when used as an adjunct to levodopa include improved quality of life, improved comorbidities and potential neuroprotective effects. Double-blind trials comparing dopamine agonists with levodopa in early

PD revealed a slightly greater reduction in motor scores with levodopa and an increase in the number of patients with dyskinesia with dopamine agonist treatment. In one study comparing pramipexole and levodopa with 6 years of follow-up, imaging revealed a potential neuroprotective effect of the dopamine agonist.

Certain risks have been associated with dopamine agonists, including an increase in dopaminergic effects, although discontinuations due to adverse events have been similar to levodopa. Many long-term adverse events have been seen with dopamine agonists, including impulse control disorders. One study arrived at a figure of 4% with active disorders, with no difference among dopamine agonists. There is also a record of fibrotic reactions, which may be reduced with nonergot agonists.

These second-generation, nonergot dopamine agonists include new formulations for transdermal delivery and extended release. Continuous drug delivery may improve sleep, may delay motor complications and have the advantages of ease of use and titration with once-daily administration. At present, a phase III study is enrolling patients to compare ropinirole PR and ropinirole IR in patients with advanced PD receiving stable doses of levodopa (ClinicalTrials.gov Identifier NCT00823836). The PROUD study is also in progress, and may help answer the question of whether early treatment has long-term advantages over delayed treatment.

Summing up the outlook for second-generation dopamine agonists, Dr. Tolosa pointed out that levodopa is still needed, side effects with the agents are not uncommon and they do not treat most non-dopaminergic features of PD.

Heinz Reichmann followed with a discussion of the utility of continuous delivery (12). A repeated theme at the congress mentioned by Dr. Reichmann was that PD symptoms affect patients day and night. Compliance is also a very common problem. There is evidence that continuous delivery systems (CDS) improve motor function.

Focusing on the transdermal **rotigotine** patch, Dr. Reichmann outlined notable characteristics, such as its association with stable 24-h plasma concentrations, a low risk of accumulation, rapid metabolism and a low propensity for drug–drug interactions. In CLEOPATRA-PD (Clinical Efficacy of Pramipexole and Transdermal Rotigotine in Advanced Parkinson's Disease), transdermal rotigotine had a similar effect on off time as pramipexole. In another double-blind study, the patch improved on time without troublesome dyskinesias. An open-label study also found an improvement in sleep features, as assessed by the PDSS. While there is evidence of an increase in adverse events in elderly patients with the patch, in CLEOPATRA-PD discontinuations were the same among age groups. In an informal study of patient satisfaction, patients pointed to features they liked, including ease of use, once-daily application and no need to take medication in public.

A further advantage of continuous delivery may be its use in patients undergoing surgery. Dr. Reichmann described a study in which patients used the patch for surgery and switched back to other treatment afterwards. The patch was highly rated by neurologists, anesthesiologists and patients.

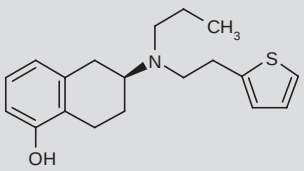
Possible new developments in continuous drug delivery include the lisuride transdermal patch, pramipexole ER, intranasal apomorphine and a levodopa transdermal patch.

POSTER HIGHLIGHTS

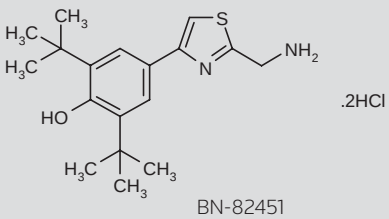
A number of posters were also presented at the congress which dealt with recent investigations into pharmacological treatment candidates for PD, and a few are highlighted here. The drawbacks to the use of dopamine agonists mentioned above led researchers at the Pennsylvania State University College of Medicine to seek a full dopamine D_1 receptor agonist with pharmacokinetic, safety and tolerance advantages over those thus far discovered for use in PD. Their efforts led to the identification of EFF-0311, which demonstrated high D_1 affinity, with a $K_{0.5}$ of 9.0 nM in rat striatal homogenates and a $K_{0.5}$ value of 325 nM for D_2 receptors. Selectivity for D_1 receptors over D_2 receptors and for dopamine receptors over most non-dopamine receptors was also demonstrated. EFF-0311 had an intermediate duration of action in rats of 8-10 h, which may mean that the compound has less potential for rapid tolerance, which has been seen with long-acting D_1 agonists. The antiparkinsonian effects of the drug are being evaluated in primates (13).

A primate model, the MPTP model of PD using macaques, has been employed to further the development of Ipsen's hybrid multitargeting agent **BN-82451**. The agent was previously found to significantly reduce dyskinesia in the 6-OHDA rat model of PD. BN-82451 was associated with a 35% decrease in the abnormal voluntary movements (AIMs) score after 5 days of treatment at 5 mg/kg s.c., without a reduction in spontaneous locomotor activity. All types of dyskinesias were affected, and a minor effect on choreas in different parts of the body was also noted. BN-82451 appeared to be more effective than amantadine, which did not affect the AIMs score in all treated animals. Acute injection of BN-82451 2 h before levodopa was associated with a greater reduction in the AIMs score (43%) compared to BN-82451 alone, while increasing spontaneous locomotor activity in 4 of 5 animals (14).

Statins have been found to have beneficial effects in many indications other than those for which they were initially studied. The possibility that a statin could reduce levodopa-induced dyskinesia was



Rotigotine



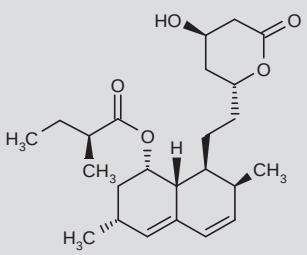
BN-82451

investigated in animal models and will also be studied in patients. In the 6-OHDA rat model of AIMs, **lovastatin** given prior to levodopa reduced locomotor, axial and orolingual, but not limb, AIMs. This effect was correlated with inhibition of the levodopa/benserazide-induced increase in pERK levels. In the MPTP model of PD in macaques, **simvastatin** treatment dose-dependently reduced levodopa-induced dyskinesia scores without affecting the antiparkinsonian activity of levodopa. Validation of the ERK pathway as a target for treating levodopa-induced dyskinesia with a statin will take a step forward later this year with the initiation of a crossover trial evaluating the effects of simvastatin. The trial is set to include 20 patients and may lead to the use of this agent in PD patients or to the search for a new, perhaps more brain-penetrant statin (15).

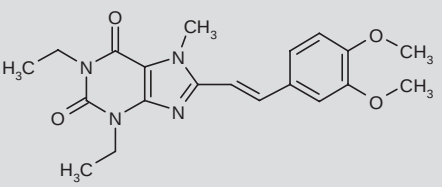
Among clinical studies was a trial revealing a significant improvement in daily off time with **istradefylline** (KW-6002) 20 and 40 mg/day compared to placebo in 363 Japanese patients with motor complications taking levodopa therapy. The drug is an adenosine A_{2A} receptor antagonist. The randomized, double-blind study was conducted at multiple centers and lasted 12 weeks. All patients were taking at least 300 mg/day levodopa and each had at least 2 h of off time per day. The change from baseline in daily off time was –1.31 and –1.58 h, respectively, on 20 and 40 mg istradefylline versus –0.66 h on placebo. Decreases in UPDRS III (on state) scores from baseline were also seen with istradefylline doses of 20 and 40 mg (–5.7 for both), which were significant compared to placebo (–3.7). The incidence and severity of treatment-emergent adverse events were similar between istradefylline and placebo; the most common such event was dyskinesia, occurring in 2.5%, 8.5% and 6.4%, respectively, of patients on placebo, istradefylline 20 mg and istradefylline 40 mg (16).

Asubio Pharma's 5-HT_{1A} receptor agonist **piclozotan hydrochloride hydrate** (SUN-N4057) had favorable effects on levodopa-induced motor complications, one of the most important limitations of PD treatment, in an animal model and in a study in patients. In 6-OHDA rats treated repeatedly with levodopa, wearing-off phenomena were seen, with a shortened duration of rotational behavior and dyskinesia-like forelimb hyperkinesia. These effects were significantly improved with piclozotan, which was also associated with significant recovery of the incidence of rotational behavior in rats that failed to show rotational behavior after levodopa administration. Piclozotan also modulated striatal dopamine release (17). The clinical study was a randomized, double-blind, placebo-controlled phase IIa trial including 25 PD patients with levodopa-induced motor complications (dyskinesia of at least moderate severity > 25% of the time). Patients received two 12-h i.v. infusions over 2 days. By day 2 of treatment, mean on time without dyskinesia doubled in the piclozotan group (reaching 41%) while it remained unchanged in the placebo group. Mean off time was halved in the piclozotan group. Also by day 2, 56% of the piclozotan group were classified as dyskinesia responders, compared to none in the placebo group. A trend towards an improvement in dyskinesia severity was seen on day 2. Treatment-emergent adverse events in the piclozotan group included nausea, dizziness, hypertension, vomiting and headache. The most common treatment-emergent adverse events decreased between days 1 and 2, suggesting acclimation to the drug. This and oral dosing may improve piclozotan tolerability (18).

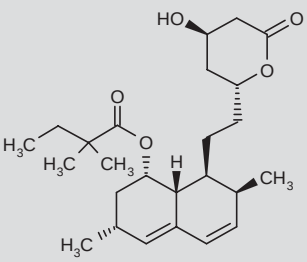
As discussed in the sessions above, continuous dopaminergic stimulation has been developed as a means of avoiding the disadvantages of pulsatile stimulation, such as wearing off, in PD patients. One option is duodenal infusion of levodopa/carbidopa gel. Whether this treatment could improve the psychiatric features of PD was addressed in a small open study in nine patients with advanced idiopathic disease followed for a minimum of 6 months. After 6 months, the Beck Depression Inventory (BDI) score was reduced from 15 to 9.6, the mean Montgomery-Asberg Depression Rating Scale



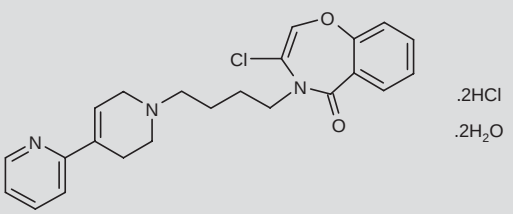
Lovastatin



Istradefylline



Simvastatin

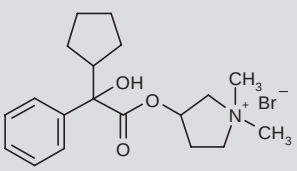


Piclozotan hydrochloride hydrate

(MADRS) score declined from 19 to 9.3, and anxiety and hallucinations/psychotic symptomatology were improved on the Neuropsychiatric Inventory (NPI). The Mini-Mental State Exam (MMSE) showed little change. While hypersexuality was improved in the one patient exhibiting that behavior, the Modified Minnesota Impulsive Disorder Interview (MIDI) did not detect the two patients with compulsive disorder. Motor symptoms and health-related quality of life were also improved with treatment (19). In 2008, the FDA granted fast track designation to Solvay's levodopa/carbidopa intestinal gel for the potential long-term treatment of motor fluctuations associated with advanced PD.

A study reported at the congress indicated that **glycopyrronium bromide** (Sciele Pharma) may represent a means of providing anticholinergic treatment for sialorrhea in PD patients, without the neuropsychiatric adverse effects seen with other anticholinergics. The possibility was assessed in a 4-week, randomized, double-blind, placebo-controlled, crossover study in 23 patients with idiopathic PD who received placebo and glycopyrronium bromide 1 mg t.i.d. given for 1 week each. The primary outcome, an improvement in sialorrhea score of at least 30%, was seen in nine and one patients, respectively, in the glycopyrronium bromide and placebo groups. A significantly greater improvement in this score was seen with glycopyrronium bromide, with a mean baseline score of 6.5 (severe sialorrhea) declining to 4.7 (moderate sialorrhea) on placebo and to 3.9 (mild to moderate sialorrhea) on glycopyrronium bromide. Adverse events were similar during the glycopyrronium bromide and placebo periods. A trend towards an increase in dry mouth, an effect related to the efficacy of glycopyrronium bromide, was seen in that group (20).

Finally, botulinum toxin treatment for cervical dystonia was examined in two studies. To help clarify the safety and efficacy of 500 U botulinum toxin type A (BoNT-A, Dysport®; Ipsen) in subtypes of cervical dystonia, 516 de novo patients were recruited for a study conducted at multiple centers in Germany and Austria. Treatment was individualized according to the muscles affected, taking into consideration shoulder elevation and tremor, evaluated using the Tsui rating scale. Of the patients, 78% had rotational torticollis, while the remainder had laterocollis. Four weeks after treatment, mean Tsui scores decreased –3.76 and –4.11, respectively, in rotational torticollis and laterocollis patients and –3.83 overall. These improvements in the symptoms of head deviation were significant, and there was no difference between these cervical dystonia subgroups. After 12 weeks, Tsui scores remained significantly below baseline levels. The treatment was well tolerated, with the expected adverse events of muscle weakness and dysphagia noted in 13.6% and 9.9% of patients, respectively, and overall treatment-emergent adverse events seen in 19.4%. Further evaluation of the results is ongoing (21).



Glycopyrronium bromide

Researchers at Solstice Neurosciences reported that botulinum neurotoxin type B (BoNT-B) was generally safe and well tolerated in patients with cervical dystonia included in a multicenter, open-label clinical study and followed for up to 7 years. The 502 patients enrolled were initially treated with a dose of 2500-5000 U, which could be increased to a maximum of 25,000 U; the mean was 16,159 U and the mean time between injections was 91 days. Patients were treated for a mean of 3.3 years, with a range of 28 days to 6.8 years. Subject-rated benefit was maintained for up to 7 years, and mean Treatment Assessment Scale scores of at least "slightly better" were maintained at all treatment sessions in BoNT-A-resistant and BoNT-A-responsive patients. Nearly all patients (98.4%) reported at least one treatment-emergent adverse event, the most common of which were dry mouth (69.3%) and dysphagia (40.4%). Most treatment-emergent adverse events were mild to moderate in severity; treatment-related adverse events led to withdrawal in 2.8% of subjects. Serious adverse events affected eight patients and there were no deaths due to treatment-related adverse events (22).

GILLES DE LA TOURETTE'S SYNDROME

The MDS congress naturally devotes a great deal of attention to PD, but other disorders are also explored. An example at this year's meeting was an afternoon oral session devoted to Gilles de la Tourette's syndrome, covering the clinical spectrum, pathophysiology, comorbidities and management.

Jonathan Mink described the clinical features of Tourette's syndrome, a neurobiological disease characterized by motor and vocal tics present for over 1 year and which change over time (23). There are also often symptoms of obsessive–compulsive disorder (OCD) or attention deficit hyperactivity disorder (ADHD), or both. Tics can be clonic (fast and abrupt) or dystonic/tonic (slow and sustained —lasting as long as 10-20 s). They can also be simple, looking and sounding purposeless, or complex, resembling purposeful movements or consisting of ensembles of simple movements. Tics are usually normal movements in an abnormal context. Tourette's syndrome begins in childhood, and the most common initial symptom is eye blinking, with vocal tics present in 12-37% of patients. The onset of the syndrome in childhood is often misdiagnosed as allergies. The severity of Tourette's in childhood is not predictive of the severity in adulthood and the severity is rarely greater in adulthood. Tics also wax and wane in severity. In one study, onset occurred at about age 5, with tic severity peaking at about age 10 and dropping off afterwards. Perhaps one-third of treated patients have tic resolution in adulthood.

Another curious aspect of Tourette's is the occurrence of premonitory feelings or sensations in 80% of patients, which contrast with the cognitive premonitory phenomena seen with compulsive behavior and which is linked to a logical idea relating a cause and an effect.

A neural circuit model is needed to explain the pathophysiology of Tourette's syndrome in order to improve treatment. Such a model must be able to explain the spectrum of tics to compulsions, provide a link to dopaminergic neurotransmission and account for the stereotyped nature of tics. Research indicates that basal ganglia

circuits are implicated in the syndrome, and the dominant hypothesis is that it is a result of overactive dopaminergic neurotransmission. Dr. Mink rounded up available data to hypothesize that tics result from multiple specific areas of focused facilitation in an otherwise normal inhibitor surround. Aberrant focal activation of striatal neurons due to loss of striatal inhibitor interneurons is also possible. Research into the origins of Tourette's may now be enhanced by a new, recently developed animal model and the body of consistent pathological data which is now available.

Jorge Juncos added detail to Dr. Mink's mention of comorbidities, pointing out that these are as important as tics and may have the greatest impact on quality of life (24). Comorbidities include sleep problems, ADHD, OCD (although not as evolved as that seen in other OCD patients), learning disabilities (in as many as 20% of patients) and nonspecific behaviors such as rage and self-mutilation. Motor, cognitive, social, limbic and oculomotor circuits are affected, and comorbidities, when misunderstood and treated inappropriately, can lead to increased symptom severity over time. While Tourette's syndrome rarely occurs in isolation of other behavioral problems, comorbidities are easily missed, and specific tools are needed to assess them. In addition, diagnosis in children is complicated by the fact that several behaviors start at the same age as tics, such as learning disabilities, ADHD and depression.

The prevalence of comorbidities was evaluated in a study in over 90,000 patients conducted by the Centers for Disease Control (CDC). The approximate numbers were 60% for ADHD, 40% for behavioral disorders, 40% for anxiety and 40% for depression. In another survey, 60% of patients had over two comorbidities and over 30% had over three comorbidities. A difference between boys and girls has also been detected, and Tourette's patients with ADHD have a higher rate of all other problems. Rage is common, perhaps affecting 20-30% of patients, although it may be much more prevalent, up to 70%. Self-injurious behavior is also common and is displayed by 17-22% of patients.

The management of comorbidities can benefit not only comorbidities but also tics, although evidence-based techniques are not always available. It is important to establish a hierarchy of impairing problems and treat the most impairing first. Tics may initially have to be ignored. The management of ADHD may improve tics. Stimulants are typically given to control ADHD, with α-adrenoceptor agonists added for tic and sleep control. If needed, atypical antipsychotics can be added or used in place of these treatments, and switching to neuroleptics is also possible. For rage and self-injurious behavior, parents have to be persuaded to stop behavioral reinforcement, while children undergo behavioral modification. Drug therapy is also available. For OCD, cognitive–behavioral therapy is recommended as a first approach, but a combined approach is also possible. Slow drug titration is necessary in patients with this comorbidity. Overall, treatment of comorbidities demands a systematic approach with close objective monitoring. Tics should be looked upon as a great opportunity to look for the presence of comorbidities.

On a visit to Paris one might visit the Pantheon, where the remains of the writer, historian and minister of culture André Malraux lie. Did he have Tourette's syndrome? Paul Krack's discussion of the pharmacological and surgical management of Tourette's syndrome made mention of Malraux as a patient and as an example to be given to patients and the parents of patients of how successful someone with Tourette's can be (25). Such encouragement is necessary, bolstered by the facts that Tourette's is a disease with good outcomes and for which treatments are available. Clinicians must also guide parents away from feelings of guilt arising from the notion that Tourette's in their child is a result of bad parenting. As in the previous talk, Dr. Krack pointed out the importance of screening for comorbidities and noted that disability does not necessarily correlate with the severity of tics.

As with the priorities laid out by Dr. Juncos, Dr. Krack stated that the treatment of tics comes last, after the treatment of comorbidities, and that the improvement of comorbidities can indirectly improve tics. Medical therapies are available for ADHD (e.g., stimulants), OCD (selective serotonin reuptake inhibitors, clomipramine with or without atypical neuroleptics, benzodiazepines) and tics (α_2-adrenoceptor agonists, dopamine D_2 receptor antagonists). Tics can be reduced, but not eliminated, with treatment. In addition, blinking and dystonic tics can be addressed with botulinum toxin. Targets for surgery and DBS include the frontal lobe (i.e., lobotomy), the limbic system, pallidothalamic fibers and the thalamus (e.g., thalamic DBS). Whatever the treatment option or options, therapy must address psychological issues such as self-esteem, as well as social aspects and other facets of disability.

REFERENCES

1. Katzenschlager, R. *Early management of Parkinson's disease. When?* Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
2. Fahn, S. *Early management of Parkinson's disease. How?* Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
3. Reichmann, H. *Management of motor complications: Medical and surgical. Pharmacological.* Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
4. Limousin-Dowsey, P. *Management of motor complications: Medical and surgical. Surgical.* Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
5. Olanow, C.W. *What's new in Parkinson's disease therapeutics. The major clinical trials of the past year*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
6. Poewe, W. *What's new in Parkinson's disease therapeutics. Promising new therapies in development*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
7. Stocchi, F. *Day and night treatment of Parkinson's disease. The challenge of managing Parkinson's disease during the day and night*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
8. Chaudhuri, R. *Day and night treatment of Parkinson's disease. Practical tools for assessing non-motor symptoms in Parkinson's disease*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
9. Ruzicka, E. *Day and night treatment of Parkinson's disease. Ropinirole prolonged release: An approach to managing day and night symptoms*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.

10. Schapira, A. *Parkinson's disease treatment - Where do we go from here?* Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
11. Tolosa, E. *Parkinson's disease treatment - Where do we go from here? Second generation dopamine agonists: Fulfilling expectations?* Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
12. Reichmann, H. *Parkinson's disease treatment - Where do we go from here? Continuous delivery: Optimized patient outcomes and beyond.* Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
13. Mailman, R.B., Murthy, V. *EFF0311, an antiparkinson full D1 dopamine agonist with longer duration and possible functional selectivity*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst We-152.
14. Badin, A., Brouillet, E., Spinnewyn, B., Auguet, M., Chabrier, P.E., Hantraye, P. *New treatment (BN82451) and assessment for L-dopa-induced dyskinesias in parkinsonian macaques*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst Mo-42.
15. Li, Q., Tison, F., Negres Pages, L., Rascol, O., Bezard, E. *The HMG-CoA reductase inhibitor simvastatin reduces severity of L-dopa-induced abnormal involuntary movements in the MPTP-macaque model of Parkinson's disease*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst We-151.
16. Mizuno, Y., Kuno, S., Yamamoto, M., Hasegawa, K., Kondo, T. *Clinical efficacy of istradefylline (KW-6002) in the treatment of Parkinson's disease: A randomized placebo-controlled study*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst Tu-198.
17. Tani, Y., Ogata, A., Koyama, M., Inoue, T. *Piclozotan (SUN N4057), a 5-HT1A receptor agonist, improves motor complications induced by repeated administration of levodopa without reducing levodopa efficacy in parkinsonian rats*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst Th-26.
18. Sage, J.I., Hauser, R.A., Cordon, M.E. et al. *Pilot study of the efficacy and safety of piclozotan in Parkinson's disease patients with L-dopa induced motor complications*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst We-197.
19. Fox, K., Fox, T., Dietrich, K. et al. *Effects of continuos application of L-dopa/carbidopa gel on psychiatric symptoms in advanced Parkinson's disease (PD).* Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst Mo-158.
20. Arbouw, M.E.L., Movig, K.L.L., Koopmann, M. et al. *Glycopyrronium bromide for the treatment of sialorrhea in Parkinson's disease*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst Mo-180.
21. Hefter, H., Benecke, R., Erbguth, F., Jost, W., Reichel, G. *Treatment of heterogeneous subtypes of cervical dystonia with botulinum toxin A (500 units Dysport®) – First aspects of a multicentre open study*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst Tu-403.
22. Birmingham, W., Salazar-Grueso, E. *Long-term (7-year) cervical dystonia safety study with Myobloc(R).* Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst Mo-57.
23. Mink, J.W. *Gilles de la Tourette syndrome. Clinical spectrum and pathophysiology*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
24. Juncos, J. *Gilles de la Tourette syndrome. Co-morbidities*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
25. Krack, P. *Gilles de la Tourette syndrome. Management: Pharmacological and surgical*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Oral session.
26. Poewe, W., Barone, P., Hauser, R.A. et al. *Pramipexole extended-release is effective in early Parkinson's disease*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst We-185.
27. Schapira, A., Barone, P., Hauser, R.A. et al. *Efficacy and safety of pramipexole extended-release for advanced Parkinson's disease*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst We-199.
28. Stocchi, F., Kakarieka, A., Kieburtz, K. et al. *The STRIDE-PD (Stavelo reduction in dyskinesia evaluation) study*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst.
29. Dimitrova, T., Bara-Jimenez, W., Savola, J.-M., Encarnacion, E., Mouradian, M.M., Chase, T.N. *Alpha-2 adrenergic antagonist effects in Parkinson's disease*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst Mo-199.
30. Stocchi, F., Giorgi, L., Earl, N., Pahwa, R. *Ropinirole prolongd release is effective in reducing "off" time in patients with advanced Parkinson's disease even at low doses.* Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst Th-182.
31. Szczudlik, A., Hunter, B., Statham, J., Earl, N., Hauser, R.A. *Safety and tolerability of long-term treatment with ropinirole prolonged release in patients with early or advanced Parkinson's disease*. Mov Disord [13th Int Congr Parkinson's Dis Mov Disord (June 7-11, Paris) 2009] 2009, 24(Suppl. 1): Abst Th-186.