DISEASE BRIEFING:
PARKINSON’S DISEASE
AN ABBREVIATED ENTRY
IN THIS ISSUE

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FACTS ABOUT PARKINSON’S DISEASE

Parkinson’s disease (previously also known as paralysis agitans or shaking palsy) is a common, progressive, multicentric neurodegenerative disorder of insidious onset whose main features are bradykinesia, rigidity, tremor at rest, shuffling gait and postural instability. Parkinson’s disease is named after James Parkinson, who in 1817 described six patients with involuntary tremulous motion, decreased muscular strength and a propensity to bend the trunk forward. Today, the same clinical features first recognized by Parkinson characterize the disease bearing his name (Lees, A.J. et al (2009)).

The primary pathological feature of Parkinson’s disease is the death of dopaminergic cells in the substantia nigra and degeneration of the nigrostriatal pathway, as well as the presence of Lewy bodies (intracytoplasmic inclusion bodies) in residual dopaminergic neurons (Fritsch, T. et al (2012)). The gradual loss of dopamine-producing cells in the brain affects the nervous system in a way that progressively limits the patient’s ability to control the muscles. While symptoms of early disease tend to respond well to treatment, later-stage Parkinson’s disease becomes increasingly resistant to drug therapy, necessitating continuous drug dosing to maintain therapeutic effect (Worth, P.F. (2013)). Several characteristic nonmotor features are also included in the clinical description of Parkinson’s disease. These include impaired executive function, autonomic nervous system failure, sleep disturbances and a range of behavioral and neuropsychiatric changes (Fritsch, T. et al (2012)). Many of these nonmotor features are caused by misfolding and widespread distribution of alpha-synuclein, a major constituent of Lewy bodies (Jellinger, K.A. (2014)).
Normal control of movement and muscle tone is mediated by the extrapyramidal system, which relies most notably on the striatum. The striatum is under stimulatory control by the cortex (glutamatergic pathways) and the substantia nigra (dopaminergic pathways). At the same time, the striatum emits inhibitory signals to the thalamus, subthalamic nuclei, substantia nigra and globus pallidus through GABAergic, enkephalinergic and substance P-utilizing pathways. In Parkinson’s disease the dopaminergic nigrostriatal pathway is largely depleted, with more prevalent inhibition of the thalamus by the substantia nigra. This results in a loss of muscle movement and tone control, leading to the three cardinal symptoms of Parkinson’s disease: resting tremor, rigidity and bradykinesia.

While the condition usually develops after the age of 65, the National Parkinson Foundation says that 15% of those diagnosed are under 50. Several different distinctions are made. Early-onset parkinsonism refers to parkinsonism, regardless of cause, with onset before age 40 years. Juvenile parkinsonism is a subset of early-onset parkinsonism with an even earlier age of onset (21 years or younger). Finally, young-onset Parkinson’s disease (YOPD) is a subset of early-onset parkinsonism with onset at or above 21 years and a clinical phenotype similar to “typical” PD (Schrag, A. et al (2006); Rana, A.Q. et al (2012)).

Once it develops, Parkinson’s disease involves degenerative changes in the substantia nigra, a thin band of pigmented neurons wherein dopamine is produced. Dopamine is the main neurotransmitter controlling both smoothness of normal movement and balance through the nigrostriatal pathway to the caudate and putamen nuclei. The substantia nigra acts as a reservoir that buffers the supply of dopamine to the brain. Peaks and troughs are diminished as excess dopamine is stored or stored dopamine is released, so that continuous levels of dopaminergic stimulation are achieved. The disorder follows a highly variable, chronic, slowly progressive course. Clinical signs may not be appreciable until approximately 60% of the substantia nigra pars compacta dopamine neurons are lost, translating into more than 80% loss of dopamine (Feng, L.R. et al (2010)).
Although loss of dopaminergic neurons is the primary clinical feature of Parkinson’s disease, other neuronal fields and neurotransmitter systems are also affected and contribute to the development of the various nonmotor symptoms of the disease. Degeneration of non-adrenergic, serotonergic and cholinergic neurons manifests as symptoms of cognitive decline, depression, sleep disturbances, urinary and gastrointestinal abnormalities, among others (Schapira, A.H. et al (2006)).

The presence of Lewy bodies, a type of intracytoplasmic inclusion bodies found in pigmented brainstem neurons, is a hallmark pathological feature of Parkinson’s disease (Schapira, A.H. et al (2011)). Lewy bodies are typically present in the substantia nigra but may also be observed in the cortex, amygdala, locus ceruleus, vagal nucleus and peripheral autonomic nervous system. Lewy bodies are believed to contribute to the development of many nonmotor symptoms of Parkinson’s disease (Samii, A. et al (2004)).

**RISK FACTORS**

Current consensus is that Parkinson’s disease is a complex pathology that develops due to triple pressure from aging, genetic predisposition (discussed in the next section) and environmental exposure (Schapira, A.H. et al (2011)), although animal models are not sufficiently representative of human PD to test this theory. Large-scale geneticoepidemiological studies designed to test this hypothesis would provide the essential information needed to understand this complex disorder (Gao, H.M. et al (2011); Burbulla, L.F. et al (2011)).

Hypotheses regarding the process of dopaminergic neurodegeneration of the substantia nigra center on triggers of mitochondrial dysfunction, oxidative stress and protein mishandling (Burbulla, L.F. et al (2011)). Heavy metals including neonatal iron exposure, the herbicide paraquat (Peng, J. et al (2007)), pesticides, especially herbicides and insecticides (Tanner, C.M. et al (2009); van der Mark, M. et al (2011)), and dietary factors such as alcohol and dairy products are just a few of the potential environmental risk factors that have been studied (de Lau, L.M. et al (2006); Elbaz, A. et al (2008)). Suggested potential vascular risk factors for PD include Diabetes (Schernhammer, E. et al (2011)), Arterial Hypertension and high cholesterol (see Atherosclerosis) (Hu, G. et al (2008); Elbaz, A. et al
Epidemiological evidence suggests that different risk factors may contribute to PD in a gender-dependent fashion (Ragonese, P. et al (2006)). Investigators from the Mayo Clinic performed a two-step statistical analysis to study risk factors in PD and found that hereditary factors, specifically interaction between UCHL1 and alpha-synuclein genes, may play a greater role in the development of PD in women, while environmental factors may play a greater role in men (Maraganore, D.M. et al (2003)). Surgical removal of both ovaries has been found to nearly double the risk of developing PD and parkinsonism later in life, according to results of a general population study conducted by Mayo Clinic researchers. The study also showed that younger women who underwent oophorectomy prior to menopause had the greatest risk. These findings provide further evidence of the protective effects of estrogen in the brain, although further study is required to determine whether estrogen replacement therapy may alter the risk of parkinsonism after ovarian removal (Rocca, W.A. et al (2008)).

Diet is another factor affecting the etiology of Parkinson's disease. High intakes of mono- and disaccharides and animal fats may increase the risk of developing the disease, while high intake of vitamins D (Knekt, P. et al (2010)), C, and E and beta-carotene (pro-vitamin A) may be protective. Uric acid may be protective, but it may cause heart disease and gout and has been associated with an increased mortality rate. Flavonoids might also be excellent candidates for prevention of Parkinson's disease. High intake of iron, especially in combination with manganese, may also be related to risk for PD. A population-based case control study conducted among newly diagnosed cases of PD and controls revealed that subjects with an iron intake in the highest 25% had an increased ratio of PD compared with those in the lowest 25%. Dietary intake above median levels of both iron and manganese together nearly doubled the risk (Powers, K.M. et al (2003)). Dietary folate deficiency has been identified by NIH researchers as another important risk factor for PD. Dietary folate was shown in a mouse model to increase the vulnerability of dopaminergic neurons to environmental toxins (Duan, W. et al (2002)).

Northwestern University researchers, based on their study of the role of calcium channels in mitochondrial metabolic stress, have hypothesized that although genetic and environmental factors may affect its onset, Parkinson's disease has its basis in a series of neuronal design factors that are common to all humans, and development of the disease is thus just a matter of time (Surmeier, D.J. (2007)).

**GENETICS**

Based on epidemiological data and the results of case-control studies, a clear genetic factor in the pathogenesis of PD has been elucidated. Family history has been found to be a significant risk factor for PD in various large epidemiological studies. To date eleven gene loci (PARK1-PARK11) associated with familial Parkinson’s disease and five causative genes --PARK1 and PARK8 (dominantly inherited) and PARK2, PARK6 and PARK7 (recessively inherited)-- have been identified (Gao, H.M. et al (2011)). Most of these are implicated in oxidative stress and mitochondrial dysfunction, two biochemical abnormalities that are believed to underlie both familial and sporadic forms of PD (Schapira, A.H. (2008); Schapira, A.H. et al (2011)).

Members of an international research team announced in early 2005 the discovery of a particular mutation in the LRRK2 (PARK8) gene, said to be the most common genetic cause of inherited Parkinson's disease identified to date. Researchers at the Cincinnati Children's Hospital Medical Center and the National Institute on Aging located the gene on a region of chromosome 12, and found that it affects approximately 5% of all Parkinson's disease patients they studied. Interestingly, the gene appeared to be associated with a milder, more slowly progressing form of the disease. Given this high incidence, the investigators recommended that LRRK2 be included in future genetic testing tools for PD (Nichols, W.C. et al (2005)). Their findings have been replicated by other research teams (Di Fonzo, A. et al (2005); Gilks, W.P. et al (2005); Glasson, B.I. et al (2008); Healy, D.G. et al (2008); Cookson, M.R. et al (2010)).
Epidemiology

Parkinson’s disease is the second most prevalent neurodegenerative disorder after Alzheimer’s disease (Kowal, S.L. et al (2013)), affecting between four and six million people worldwide (National Parkinson Foundation, website consulted November 22, 2013). The prevalence of Parkinson’s disease in industrialized countries has been estimated at approximately 0.3% of the general population, including 1% of the population aged over 60 years and older (Samii, A. et al (2004); de Lau, L.M. et al (2006)), and increases sharply after age 85, when it affects 4-5% of the population (Rao, S.S. et al (2006)). According to the National Parkinson Foundation, there are approximately one million patients with PD in the U.S., as well as 50,000-60,000 new cases diagnosed each year (website consulted November 22, 2013). In American Indian and Alaskan Native populations, the age-adjusted prevalence of PD is 355.7 per 100,000, albeit with regional differences (Gordon, P.H. et al (2012)). PD prevalence in Buenos Aires, Argentina is approximately 394 per 100,000 in the over-40 population (Bauso, D.J. et al (2012)). In the U.K., the prevalence of PD is estimated to be 27.4 per 10,000 population, equivalent to 126,893 cases (Parkinson’s prevalence in the United Kingdom (2009) (Parkinson’s UK)). Furthermore, based on the aging of the world’s population, the prevalence of PD is expected to increase significantly in the coming years. A study of the world’s 10 most populous nations and of western Europe’s five most populous countries has concluded that the combined prevalence of PD in these 15 countries could reach approximately 9 million (range 8.7-9.3 million) by the year 2030, approximately double the current rate (Dorsey, E.R. et al (2007)).

The disease is less prevalent in Asian countries, where the age-standardized rate ranges from 51.3 to 176.9 per 100,000 in door-to-door surveys and from 35.8 to 68.3 per 100,000 in record-based studies (Muangpaisan, W. et al (2009)). The age-adjusted prevalence of PD in a community-based study in India was reported to be 52.85 per 100,000 (45.15 per 100,000 in men and 60.34 per 100,000 in women) (Das, S.K. et al (2010)). It is even less common in sub-Saharan Africa, where prevalence is reported to be in the range of 7-20 per 100,000 population (Blanckenberg, J. et al (2013)).

Crude incidence rates for PD are reported to be 4.5-19 per 100,000 population per year (Neurological disorders: Public health challenges (World Health Organization, 2006)). However, because onset before age 50 is rare and incidence rises rapidly after age 60 (de Lau, L.M. et al (2006)), age-adjusted rates provide a more realistic picture (Neurological disorders: Public health challenges (World Health Organization, 2006)). In a study of elderly Canadians, the age-standardized incidence rate (1991-2001) in men ranged from 208 to 396 per 100,000 person-years, and in women ranged from 127 to 259 per 100,000 person-years (Allyson Jones, C. et al (2012)).

Juvenile and early-onset forms of Parkinson’s disease are much more rare. The annual incidence of early-onset parkinsonism in the U.S. is 0.8 per 100,000 for the 0-29 age group, and increases to 3.0 per 100,000 in those aged 30-49 years. Although there are relatively few PD patients in this age group, the long life span in parkinsonian patients means that overall, as many as 3-5% of all patients at any time are younger than 40 years. In countries with a higher incidence of early-onset PD, this figure may be as high as 10% (Schrag, A. et al (2006)).

For more epidemiology information, consult the Incidence and Prevalence Database (IPD): IPD: Parkinson disease (PD).
MORBIDITY AND MORTALITY

Parkinson’s disease runs a relentlessly progressive course, although symptoms and rate of progression are highly variable from one patient to another. Gender differences in motor and cognitive symptoms of Parkinson’s disease have been described (Miller, I.N. et al (2010)). Symptoms may also vary in the same patient over time.

In the early stages, motor disability is generally not a significant problem, with symptoms being mild and focal in nature (Rodríguez-Oroz, M.C. et al (2009)). As the disease progresses, however, motor disability increases (correlating with loss of dopamine in the motor region of the striatum) and activities of daily living are affected, resulting in potential loss of independence and ambulation (Varanese, S. et al (2011)). Gait disturbances may result in falls and subsequent bone fractures. Communication may be impaired as a result of dysarthria and hypophonia. Deglutition disorders carry an increased risk of aspiration pneumonia. Side effects of drug therapy for PD are another important cause of morbidity in this patient group.


Mortality among Parkinson’s disease patients is reported to be approximately 1.52 times higher than in the normal population, although this represents a significant improvement over the pre-levodopa era, when mortality was three times greater in PD patients as compared to normal controls (Neurological disorders: Public health challenges (World Health Organization, 2006)). In the Spanish NEDICES study, the hazard ratio of mortality in PD patients was 2.29 times greater than in controls, with especially high risk of mortality among a subgroup of PD patients with dementia (Posada, I.J. et al (2011)). The detrimental impact of dementia on survival in PD has been confirmed in other studies (Willis, A.W. et al (2012)). Other causes of increased mortality include incidental complications stemming from motor disability (immobility, prostration, deglutition disorders) and autonomic dysfunction, which often leads to falls, fractures, pneumonia, urinary tract infections and other complications. An increased incidence of melanoma and other skin cancers has been reported in PD patients, although no recommendations can be made at this time regarding the need for periodic dermatological screening (Ferreira, J.J. et al (2010)).

According to WHO’s 2010 Global Burden of Disease (GBD) study, Parkinson’s disease was the cause of death of 111,100 (range 81,200-138,600) people worldwide in 2010, a 107.7% increase over the 1990 figure (53,500). The age-standardized death rate was 1.7 (range 1.2-2.1) per 100,000 (Lozano, R. et al (2012)). In 2011, 23,107 people died as a result of Parkinson’s disease in the U.S., making it the 14th leading cause of death in that country (Hoyert, D.L. et al (2012)). According to WHO’s 2010 GBD study, Parkinson’s disease was the cause of death of 7,300 (range 4,700-11,300) people in China that year, yielding an age-standardized death rate in that country of 0.5 per 100,000. This was a 73% increase over the number of deaths (4,100) reported in 1990 (Yang, G. et al (2013)). This rate is much higher when all information on death certificates is used, as shown in a U.K. study, where the age-standardized mortality rate for males and females with any mention of PD in 2006 was 11.7 per 100,000 and 4.9 per 100,000, respectively (Mylne, A.Q. et al (2009)).
In the United States, the national economic burden associated with Parkinson's disease in 2010 was estimated to be USD 14.4 billion, equivalent to approximately USD 22,800 per patient (Kowal, S.L. et al (2013)). Among individual patients diagnosed with the disease, Medicare expenditures during the first year after diagnosis are significantly higher for newly diagnosed PD patients than for non-PD controls (USD 7,423 and 5,024, respectively) (Kaltenboeck, A. et al (2012)).

The CDBE2010 Study Group has estimated that for the year 2010, the total cost of Parkinson’s disease in Europe (27 EU countries plus Iceland, Norway and Switzerland) was EUR 13.9 billion (Gustavsson, A. et al (2011)). This included EUR 7 billion in direct healthcare costs, EUR 5.5 billion in direct nonmedical costs, and 1.4 billion in indirect costs. The per-patient cost of PD in this study was estimated to be EUR 11,153 (Olesen, J. et al (2012)). In the U.K., the total annual cost of Parkinson’s disease has been calculated at between GBP 449 million and 3.3 billion, depending upon the cost model and prevalence rate applied. The most significant of the direct costs are inpatient and institutional care, while lost productivity and caregiver burden incur the greatest indirect costs (Findley, L.J. (2007)). The total direct costs associated with Parkinson’s disease in Sweden have been calculated, amounting to SEK 1.7 billion in 2009. The cost per patient was estimated at SEK 76,000. Inpatient care accounted for 52% of costs, while outpatient care and drugs accounted for 27% and 21%, respectively (Lökk, J. et al (2011)).

Among patients in a Danish study with Parkinson’s disease or atypical parkinsonism, annual mean healthcare-related costs were EUR 6,500 and EUR 9,771 greater than costs in randomly selected, matched controls. Increases in healthcare and employment-related costs could be identified as much as eight years prior to a clinical diagnosis of PD or atypical parkinsonism (Jennum, P. et al (2011)).

In other areas of the world, where access to health care and medications may be limited and life expectancy may influence disease burden, cost estimation is more difficult (Neurological disorders: Public health challenges (World Health Organization, 2006)).

On the individual level, the greatest economic impact of Parkinson’s disease is derived from loss of productivity and income, which in one analysis represented almost 50% of the total cost of the illness (Neurological disorders: Public health challenges (World Health Organization, 2006)), particularly for patients with young-onset disease. For patients diagnosed with PD at age 45, 55, 65 and 75 years, projected income losses (in 2009 U.S. dollars) were USD 569,393, USD 188,590, USD 35,496 and USD 2,451, respectively (Johnson, S. et al (2011)). Another significant indirect cost is that of uncompensated care (caregiver burden), which accounts for 18.8% of the total costs of PD. Inpatient and outpatient care (19.9 and 7.5%, respectively) and prescription drug costs (4.4%) make up the rest of the total cost of PD (Huse, D.M. et al (2005)). Medication nonadherence, which is a frequent problem limiting treatment efficacy in patients with Parkinson’s disease as well as those with other chronic diseases, has also been shown to incur significant medical and healthcare costs; although nonadhering patients may have lower prescription drug costs, these do not offset the increased medical costs directly associated with nonadherence (Davis, K.L. et al (2010)).

The potential economic impact of slowing disease progression is significant. Based on previous estimates that PD incurs average excess direct costs of USD 303,754, U.S. researchers have calculated that a treatment which slowed disease progression by 20% could result in net monetary benefits of USD 60,657 per patient. These savings reflect increases in quality-adjusted life years and reductions in direct medical costs, as well as income which would otherwise be lost (Johnson, S.J. et al (2013)).
At present, the diagnosis of Parkinson’s disease is made based on observation of clinical features, particularly bradykinesia; postmortem confirmation is required for a definitive diagnosis of PD (de Lau, L.M. et al (2006)). Parkinson’s disease is defined by the presence of at least two of the following cardinal signs: distal resting tremor, bradykinesia, rigidity and postural instability. Other features aiding in the clinical diagnosis of PD include reduced arm swing, difficulty rising from a seated position, stooped posture, shuffling or freezing gait, coordination difficulties, speech disorders, impaired olfaction and micrographia (Lees, A.J. et al (2009)). Another criteria for PD diagnosis is positive response to a therapeutic challenge with levodopa or apomorphine (Savitt, J.M. et al (2006); Lees, A.J. et al (2009)). Equally important is the absence of atypical features, which would suggest an alternative diagnosis. Specific procedures for diagnosing PD dementia have been presented (Dubois, B. et al (2007)).

Rating of disease severity is another aspect of diagnosis that also serves to determine the correct treatment strategy and treatment response, as well as to document disease progression. The standard scale used for this purpose is the Unified Parkinson’s Disease Rating Scale (UPDRS, available at unified Parkinson’s Disease Rating Scale (UPDRS)). The four-part scale measures mentation, behavior and mood; activities of daily living; motor function; and complications of therapy.

Although confirmation of diagnosis is not feasible until autopsy, evidence suggests that through conscientious application of these diagnostic criteria, an accurate clinical diagnosis of PD can be made between 80% and 90% of the time (Camicioli, R. (2002)). Nonetheless, a survey of patients in the community has shown that among those receiving antiparkinsonian therapy, a confirmed diagnosis of PD could be made in only 75% of them. Analysis of tissue samples obtained postmortem in Canada and the U.K. revealed a rate of diagnostic error of nearly 25%. Diagnostic accuracy is much higher, however, in units specializing in movement disorders (Tolosa, E. et al (2006)).
Imaging techniques such as PET (positron emission tomography) and SPECT (single photon emission computed tomography) are increasingly being developed to visualize and quantify dopaminergic neurons in the living human brain (Stephenson, R. et al (2009); Walker, R.W.H. et al (2009)). The first clinical method to detect changes in dopaminergic neurons used 6-[^18F]-fluoro-L-3,4-dihydroxyphenylalanine for PET studies, which demonstrated loss of uptake of[^18F]-dopa in the basal ganglia of Parkinson’s disease patients as compared to neurologically normal controls. However these procedures, while being highly sensitive and specific, are also very expensive and thus are not widely used (Stephenson, R. et al (2009)).

Another approach involves the use of radioligands with selective affinity for dopamine transporters (DAT), a class of membrane proteins that are highly specific for dopamine neurons. PET and SPECT used with[^11C]- and[^123I]-labeled cocaine analogues, respectively, showed a loss of striatal dopamine transporters in patients with Parkinson’s disease.

GE Healthcare’s[^123I]-labeled ioflupane (DaTSCAN), a cocaine analogue, was launched in the Netherlands in November 2000. DaTSCAN is used for SPECT imaging of dopamine transporters, as a diagnostic imaging agent for Parkinson’s disease and for the differential diagnosis of Parkinson’s disease, i.e., to distinguish between PD and other diseases such as essential tremor. The imaging agent was approved by the U.S. FDA for the same indication in 2011.

Magnetic resonance imaging (MRI) may also be used in the diagnostic workup of Parkinson’s disease and other neurological disorders. Conventional (T2-, T1-weighted) MRI is usually normal in PD patients but is useful to discard the presence of brain tumors, vascular lesions, multiple sclerosis and other potential causes of parkinsonism. Newer MRI methodology is being developed that may eventually enable greater sensitivity in diagnosing PD at the earliest stages of the disease (Hotter, A. et al (2009)). Structural MRI has also been suggested to be useful in detecting cortical atrophy leading to cognitive impairment in PD patients (Ibarretxe-Bilbao, N. et al (2009)).

The study of imaging agents for the diagnosis of Parkinson’s disease is an active area of research at this time, as indicated in the following table.
IMAGING AGENTS FOR PARKINSON’S DISEASE

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>ORGANIZATIONS</th>
<th>MECHANISMS</th>
<th>PHASE</th>
<th>STRUCTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>[^{[123]}]-E-1ACFT</td>
<td>Navidea Biopharmaceuticals</td>
<td>Drugs Acting on Dopaminergic Transmission; Signal Transduction Modulators</td>
<td>Phase III</td>
<td><img src="image1.png" alt="Structure" /></td>
</tr>
<tr>
<td>Florbenazine F18</td>
<td>Lilly</td>
<td>Signal Transduction Modulators; Vesicular Monoamine Transporter 2 (VMAT2) Ligands</td>
<td>Phase II/III</td>
<td><img src="image2.png" alt="Structure" /></td>
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<tr>
<td>NuroPro</td>
<td>Power 3 Medical Products</td>
<td></td>
<td>Phase I</td>
<td>Blood test</td>
</tr>
<tr>
<td>[^{[123]}]MNI-420</td>
<td>Inst for Neurodegenerative Disorders</td>
<td>Adenosine A2A Antagonists; Signal Transduction Modulators</td>
<td>Phase I</td>
<td></td>
</tr>
</tbody>
</table>

BIOMARKERS

In recent years, a number of biomarkers have been described that may indicate vulnerability to Parkinson’s disease, in some cases long before symptoms begin to emerge. Some of the more useful indicators identified to date include hyperechogenicity of the substantia nigra, PET and SPECT abnormalities and premotor symptoms such as olfactory dysfunction (Bohnen, N.I. et al (2010); Jones, R. (2010)), autonomic impairment, depression, REM sleep disturbances and neuropsychological impairment. Identification of patients in the early stages of disease is an important goal, given that early treatment can lead to significantly improved outcomes (Berg, D. (2008); Stephenson, R. et al (2009)).
DIFFERENTIAL DIAGNOSIS

Conditions that may also cause symptoms of parkinsonism, and which should be considered in the differential diagnosis of Parkinson’s disease, include Alzheimer’s Disease, Huntington’s Disease, essential tremor (Adler, C.H. et al (2011)), progressive supranuclear palsy, dementia with Lewy bodies, drug-induced or vascular parkinsonism, postencephalitic parkinsonism, normal aging and more (Lees, A.J. et al (2009); Suchowersky, O. et al (2006); Kalra, S. et al (2010)).

Symptoms suggestive of a diagnosis other than Parkinson’s disease include (Rao, S.S. et al (2006)):
- lack of response to a therapeutic challenge with levodopa;
- early postural instability (falling within one year of diagnosis);
- hallucinations;
- early-onset and pronounced dementia;
- upward gaze paralysis;
- severe and early-onset autonomic dysfunction; and
- involuntary movements other than tremor.
To date there are no definitively proven techniques for preventing or slowing the progression of Parkinson’s disease. It has been suggested that the identification of risk factors could assist researchers in developing preventive strategies. Investigators at the Department of Veterans Affairs in Honolulu, Hawaii analyzed data from a 30-year follow-up study of 8,004 Japanese American men (aged 45-68) enrolled between 1965 and 1968 in the prospective longitudinal Honolulu Heart Program to explore the association of coffee and dietary caffeine intake with the risk of PD. For what is believed to be the first time, the prospective study demonstrated a significant inverse relationship between coffee consumption measured during midlife and incidence of PD. During the follow-up period, 102 men were identified as having Parkinson’s disease, and the age-adjusted incidence of PD declined consistently with increasing amounts of coffee intake. After adjusting for age as well as cigarette smoking, the researchers found that the risk of PD was two to three times greater for non-coffee drinkers than it was for coffee drinkers. Based on data collected at the time of study enrollment, non-coffee drinkers had a risk of disease more than five times that of men who consumed 28 ounces or more of coffee per day. Similar relationships were observed with total caffeine intake and intake of caffeine from sources other than coffee (Ross, G.W. et al (2000)). Other studies have replicated these findings, and have also suggested a similar protective effect for tea consumption (Hu, G. et al (2007)).

A meta-analysis of eight case-control and five cohort studies has provided further epidemiological evidence that coffee drinkers have a reduced risk of Parkinson’s disease (Hernán, M.A. et al (2002)). Building on evidence that male but not female coffee drinkers have a lower risk of PD, researchers from the Harvard School of Public Health sought to determine the risk of PD in women according to the use of postmenopausal hormones. The study population included 77,713 women free of PD, stroke or cancer at baseline, who were postmenopausal at baseline or who reached menopause before the end of the study. After 18 years of follow-up, 154 cases of PD were documented. The results showed that while the risk of PD was similar in women who used hormones and those who didn’t, the risk was reduced in women taking hormones with low caffeine intake but was increased by four-fold in those taking hormones with high caffeine intake (six or more cups a day) (Ascherio, A. et al (2003)). Adenosine A2 receptor antagonism may be one mechanism underlying the antiparkinsonian effect of caffeine (Lees, A.J. et al (2009)).

An analysis of 44 case-control and four cohort studies has established a protective effect for cigarette smoking, although the biological mechanisms underlying these effects remain to be determined (Hernán, M.A. et al (2002)). A later pooled analysis of eight case-control and three cohort studies confirmed this observation, establishing a dose-dependent reduction in risk of Parkinson’s disease among cigarette smokers. This effect was, furthermore, more pronounced among current as compared to former smokers, and could possibly be extrapolated to other forms of tobacco use such as pipe smoking (Ritz, B. et al (2007)). To further elucidate the effects of smoking on PD risk, researchers at Harvard School of Public Health analyzed data from the Cancer Prevention Study II Nutrition Cohort, which included nearly 80,000 women and more than 63,000 men who were followed for up to 10 years. There were 413 cases of incident PD during the study follow-up period. All participants with were assessed according to smoking status and lifetime smoking histories. The results demonstrated a 30-60% decrease in the risk of PD among subjects who smoked in the period 15-24 years before symptom onset. Compared with those who had never smoked, former smokers had a relative risk (RR) of 0.78 and current smokers had an RR of 0.27. The risk of developing PD was lowest among study participants with a longer history of smoking, greater level of cigarette consumption, older age at quitting and fewer number of years since quitting. This relationship is strongly suggestive of an as-yet-undetermined biological effect (Thacker, E.L. et al (2007)).
A prospective cohort of 44,057 men and 98,845 women free from PD, stroke or cancer at baseline were evaluated to assess the relationship between the use of NSAIDs and decreased PD risk. Results showed that participants who were regular users of nonaspirin NSAIDs at the beginning of the study had a lower risk of PD than nonregular users during the follow-up (Chen, H. et al (2003)). A subsequent study by the same investigators, who followed a group of 186,000 participants for a total of 1,254,165 person-years, showed that regular ibuprofen use was associated with a lower risk of developing PD over the study period (Chen, H. et al (2005)). Although other population-based studies using smaller sample sizes have replicated the above findings, suggesting a protective effect for NSAIDs (Bornebroek, M. et al (2007)), others have not (Wahner, A.D. et al (2007)).

HMG-CoA reductase inhibitors, commonly known as statins, are widely used for cholesterol reduction (see Atherosclerosis) but are known to have a plethora of pleiotropic effects. Population-based studies have provided evidence of their efficacy in preventing various cardiovascular disorders (stroke, angina, heart failure), types of cancer (prostate, breast, melanoma) and disorders ranging from macular degeneration to sexual dysfunction. An analysis of data from the U.S. Veterans Affairs database has provided evidence of a further protective effect for one statin, simvastatin, against dementia and Parkinson’s disease. Among the 4.5 million subjects in the database, the incidence of Parkinson’s disease was shown to be lower in subjects taking simvastatin, even after adjusting for covariates known to be related to PD (Wolozin, B. et al (2007)). Analysis of data from a prospective study including nearly 40,000 subjects from the Health Professional Follow-up Study and the Nurses’ Health Study has provided further evidence of the protective activity of statins. In this study cohort, regular use of cholesterol-lowering statins (at least twice-weekly) was associated with a modest decrease in the risk of incident Parkinson’s disease during the 12-year follow-up period (RR = 0.74) as compared to subjects who did not use statins. This effect was limited to patients who were under at 60 years at baseline (Gao, X. et al (2012)).
TREATMENT

Parkinson’s disease is a progressive and incurable neurological disease, and no effective disease-modifying treatment has been discovered (Savitt, J.M. et al (2006)). Nevertheless, drugs that alleviate the symptoms and slow progression of the disease are available, and in fact the successful development of drugs to treat the symptoms of PD has been called “one of the most notable successes of neurology” (Schapira, A.H. (2007)). With the help of medical management, life expectancy of PD patients is near normal and quality of life can be satisfactory.

The objectives of treatment for Parkinson’s disease are to control both motor and nonmotor symptoms, reduce functional disability and slow or arrest the progression of the disease. Treatment options can be grouped into three categories: drug treatment, nonpharmacological treatment and surgery. Great advances have been made in the field of drug treatment, albeit with greater success in the area of symptom control than on neuroprotection or slowing of disease progression. Nonpharmacological treatments have also been developed, and these include surgical approaches, support, education, rehabilitation strategies that help to maintain function and improve morale, exercise (Nutt, J.G. et al (2005)) and proper nutrition (Barichella, M. et al (2009)). Treatment of comorbidities is an equally important aspect of the management of the PD patient (Aarsland, D. et al (2009); Varanese, S. et al (2011)).

PHARMACOTHERAPY

Covered in full briefing

ENDOGENOUS DOPAMINE-INCREASING AGENTS

Covered in full briefing

DOPAMINE PRECURSORS

Covered in full briefing

DOPA DECARBOXYLASE INHIBITORS

Covered in full briefing

CATECHOL-O-METHYLTRANSFERASE INHIBITORS

Levodopa is metabolized by peripheral decarboxylase; in the presence of a dopa decarboxylase inhibitor, however, it can also be metabolized by catechol-O-methyltransferase (COMT) (Stocchi, F. (2009)).
Inhibition of COMT further increases the absorption and decreases the metabolism of levodopa. Thus COMT inhibitors were designed as a new drug class that would spare levodopa, prolonging its half-life and evening out drug plasma levels during chronic administration, with the goal of reducing dyskinesias and enabling a reduction in levodopa dose requirements (Widnell, K.L. et al (2005); Bonifácio, M.J. et al (2007)). COMT inhibitors may also increase the incidence of dopaminergic side effects of levodopa (Horstink, M. et al (2006)).

**DOPAMINE: CEREBRAL CATABOLISM**

Due to postmarketing findings of potentially fatal, acute fulminant liver failure in patients treated with the first COMT inhibitor to reach the market, Roche's tolcapone (Tasmar), the product was withdrawn from all markets worldwide except the U.S., where use is restricted to patients who cannot be adequately controlled with any other antiparkinsonian drugs.

The newer COMT inhibitor entacapone (Comtess/Comtan) is used in conjunction with levodopa and a dopa decarboxylase inhibitor to improve symptom control and reduce the incidence of dyskinesias. As entacapone must be taken several times day in combination with levodopa and carbidopa, Orion developed Stalevo, a new oral formulation containing the three drugs in a single tablet that was launched in 2003.
<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>ORGANIZATIONS</th>
<th>MECHANISMS</th>
<th>PHASE</th>
<th>STRUCTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opicapone</td>
<td>BIAL</td>
<td>COMT Inhibitors</td>
<td>Phase III</td>
<td></td>
</tr>
<tr>
<td>ODM-103</td>
<td>Orion (Fi)</td>
<td>COMT Inhibitors</td>
<td>Phase I</td>
<td>Structure not yet disclosed - in full product, alerts can update you upon structure disclosure</td>
</tr>
<tr>
<td>ODM-104</td>
<td>Orion (Fi)</td>
<td>COMT Inhibitors</td>
<td>Phase I</td>
<td>Structure not yet disclosed - in full product, alerts can update you upon structure disclosure</td>
</tr>
<tr>
<td>ADD-LD</td>
<td>Aposense</td>
<td>COMT Inhibitors; Dopamine Precursors; Signal Transduction Modulators</td>
<td>Preclinical</td>
<td>Structure not yet disclosed - in full product, alerts can update you upon structure disclosure</td>
</tr>
</tbody>
</table>

**MONOAMINE OXIDASE B INHIBITORS**
Covered in full briefing

**DOPAMINE AGONISTS**
Covered in full briefing

**ANTICHOLINERGIC DRUGS**
Covered in full briefing

**NICOTINIC ACETYLCHOLINE RECEPTOR AGONISTS**
Covered in full briefing

**DISEASE-MODIFYING THERAPY**
Covered in full briefing
DRUGS ACTING ON GLUTAMATE RECEPTORS

Excitotoxicity is thought to play an important role in the pathogenesis of certain neurodegenerative disorders. In the case of Parkinson’s disease, abnormally high glutamatergic activity within the striatum is thought to contribute to peak-dose dyskinesia (Fox, S.H. et al (2008)), leading to the theory that glutamate receptor antagonists could exert neuroprotective effects in Parkinson’s disease. Potential targets for PD within the glutamate receptor family include NMDA receptors, especially NR2B, as well as AMPA and metabotropic glutamate receptors (mGluRs) (Schapira, A.H. et al (2006); Fox, S.H. et al (2008)).
The following table presents information on glutamate receptor-acting drugs in development for the treatment of Parkinson’s disease.

### DRUGS ACTING ON GLUTAMATE RECEPTORS IN DEVELOPMENT FOR PARKINSON’S DISEASE

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>ORGANIZATIONS</th>
<th>MECHANISMS</th>
<th>PHASE</th>
<th>STRUCTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mavoglurant</td>
<td>Novartis</td>
<td>Signal Transduction Modulators; mgluR5 Antagonists</td>
<td>Phase II</td>
<td><img src="structure.png" alt="Structure Image" /></td>
</tr>
<tr>
<td>Neu-120</td>
<td>Neurim Pharmaceuticals</td>
<td>NMDA Modulators; Signal Transduction Modulators</td>
<td>Phase I</td>
<td>Structure not yet disclosed - in full product, alerts can update you upon structure disclosure</td>
</tr>
<tr>
<td>4-Chlorokynurenine</td>
<td>VistaGen</td>
<td>NMDA Glycine B Receptor Antagonists; Signal Transduction Modulators</td>
<td>Preclinical</td>
<td><img src="structure.png" alt="Structure Image" /></td>
</tr>
<tr>
<td>ADX-88178</td>
<td>Merck &amp; Co.; Addex Therapeutics</td>
<td>Signal Transduction Modulators; mgluR4 Modulators</td>
<td>Preclinical</td>
<td><img src="structure.png" alt="Structure Image" /></td>
</tr>
</tbody>
</table>

**ADENOSINE A2A ANTAGONISTS**

*Covered in full briefing*

**NEUROTROPHIC AGENTS AND NEUROTROPHIC FACTORS**

*Covered in full briefing*

**ANTIINFLAMMATORY AGENTS**

*Covered in full briefing*

**CELL THERAPY**

*Covered in full briefing*
Gene therapy is considered by some investigators to represent a promising future approach to the treatment of Parkinson's disease (Rascol, O. et al (2011)). Various justifications for pursuing a viral vector-mediated gene therapeutic approach in the context of PD have been identified: 1) PD pathophysiology underlying motor symptoms is largely confined to the nigrostriatal pathway; hence, a limited area will require treatment. 2) Because of the physically restricted environment of the brain, repeated injections into the nigrostriatum are not desirable. Long-term gene expression following a single treatment is therefore the most attractive option. 3) Viral vectors (adeno-associated virus or AAV and lentivirus) are diffusible and are theoretically capable of efficient transduction of the striatum. 4) Candidate genes have been identified that can either modulate the neuronal phenotype or act as neuroprotective agents (Feng, L.R. et al (2010)).

Candidate genes that may be included in a gene therapy for PD include those that boost dopamine production, e.g., those encoding tyrosine hydroxylase, guanosine triphosphate cyclohydrolase I and aromatic L-amino acid decarboxylase, or alternatively, those promoting the survival of dopaminergic neurons, e.g., glial cell line-derived neurotrophic factor. Other potential gene therapies that have been tested successfully in animal models include the genes encoding vesicular monoamine transporter-2 and glutamic acid decarboxylase (Chen, Q. et al (2005); Gottwald, D.M. et al (2008)). It is important to note the risks associated with a treatment that will continue to act for the rest of the patient's life (Fiandaca, M. et al (2008)).

Intranigral pretreatment with a recombinant adeno-associated virus engineered to secrete glial-derived neurotrophic factor (raav-GDNF) has proven safe and potentially useful in preventing parkinsonism in MPTP-treated primates and 6-hydroxydopamine-lesioned rats. The treatment produced functional improvements in the latter model as seen by the recovery of some behavioral characteristics, including spontaneous use of the paws. Autopsy revealed that previously destroyed dopamine fibers in the treated animals had begun to regenerate (Kirik, D. et al (2000)).

Using two different primate models of Parkinson's disease, researchers from Rush Presbyterian-St. Luke's Medical Center and collaborators from elsewhere in the U.S. and Switzerland have also successfully demonstrated the feasibility of gene transfer of GDNF using a lentiviral vector. Injection of lenti-GDNF directly into the striatum and substantia nigra of young MPTP-lesioned or aged, nonlesioned rhesus monkeys resulted in extensive GDNF gene expression in all animals. In aged primates, dopaminergic function increased in response to lenti-GDNF. In all animals, the gene therapy corrected functional defects associated with aging or MPTP, prevented nigrostriatal degeneration and induced regeneration. Gene expression was long-lasting, with evidence of gene transfer detected fully eight months after administration of lenti-GDNF. These results support the efficacy and feasibility of lentiviral vector delivery of GDNF in the treatment of Parkinson's disease (Kordower, J.H. et al (2000)).

In another study, raav vector expressing GDNF was used to confer protection from 6-OHDA insult without affecting normal DA levels in a marmoset model. Unilateral intrastriatal injection of raav-GDNF into striatum that promotes high levels of GDNF expression led to increased levels of TH protein and its activity as well as produced higher rates of DA turnover. Injection of a vector conferring low levels of GDNF expression affected very slightly DA synthesis, and this effect was present only on the injected side. Most importantly, the low levels of GDNF expression exerted neuroprotective actions rendering about 85% protection of the nigral DA neurons and their projection to the striatum in the 6-OHDA-lesioned hemisphere. The treatment also produced behavioral benefits, such as attenuation of sensorimotor neglect, head position bias and amphetamine-induced rotation (Esilamboli, A. et al (2005)). The advantage of this method over direct administration of GDNF, an approach that has been shown infeasible in clinical trials, is that the body would be forced to produce the GDNF protein naturally. This therapy is aimed at managing the patients at the onset of Parkinson's disease.

The following table presents an overview of gene therapies in active development for the treatment of Parkinson's disease.
<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>ORGANIZATIONS</th>
<th>DESCRIPTION</th>
<th>PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERE-120</td>
<td>Ceregene</td>
<td>Adeno-associated virus type 2 vector encoding a modified human neurturin (NRTN) gene that carries the prepro domain of human nerve growth factor beta (NGF)</td>
<td>Phase II</td>
</tr>
<tr>
<td>rAAV-hAADC</td>
<td>Genzyme</td>
<td>Adeno-associated virus (AAV) vector containing the gene that encodes the enzyme L-amino acid decarboxylase (AADC), under the control of the CMV promoter</td>
<td>Phase II</td>
</tr>
<tr>
<td>Lenti-TH-AADC-CH1</td>
<td>Oxford BioMedica</td>
<td>Tricistonic lentiviral vector derived from the equine infectious anaemia virus (EIAV) encoding human tyrosine hydroxylase, aromatic L-amino acid decarboxylase and GTP cyclohydrolase 1</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>AAV2-GDNF</td>
<td>University of California,</td>
<td>Adeno-associated virus (AAV2) containing human glial cell line-derived neurotrophic factor (GDNF) delivered with the use of a convection enhanced delivery (CED)-compatible reflux-free step-design cannula</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Oakland; Natl. Inst. Neurol.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dis. and Stroke; Georgetown</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>University</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAV2-GDNF</td>
<td>University of California,</td>
<td>Adeno-associated virus type 2 (AAV-2) encoding glial cell-derived neurotrophic factor (GDNF)</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>San Francisco; uniQure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beperminogene</td>
<td>AnGes</td>
<td>DNA (plasmid pVAX1HGF/MGBI)</td>
<td>Preclinical</td>
</tr>
<tr>
<td>perplasmid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ND-602</td>
<td>Neurodyn Life Sciences</td>
<td>Viral vector carrying human growth factor-like progranulin gene (PGRN)</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>
Drug Name | Organizations | Description | Phase
--- | --- | --- | ---
OXB-102 | Oxford BioMedica | Lentiviral vector encoding a fusion protein comprising human tyrosine hydroxylase (TH) fused to human GTP-cyclohydrolase 1 (CH1), via a modified GS15 linker (GS15mod), a poliovirus internal ribosome entry site (PV IRES) element, human aromatic amino acid dopa decarboxylase (AADC) and woodchuck hepatitis virus post-transcriptional regulatory element (WPRE), under the control of cytomegalovirus (CMV) promoter | Preclinical

CURRENT PARKINSON’S DISEASE PIPELINE

Consult the tables below for an overview of all products mentioned in this review, including drugs, biologics and diagnostic agents that have been marketed or are under active development for this indication. Tables may also include drugs not covered in the preceding sections because their mechanism of action is unknown or not well characterized.

REPRESENTATIVE DRUGS MARKETED FOR THE TREATMENT OF PARKINSON’S DISEASE

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Originator/Licensee</th>
<th>Year of First Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trihexyphenidyl hydrochloride (Artane)</td>
<td>Pfizer</td>
<td>1949</td>
</tr>
<tr>
<td>Procyclidine hydrochloride (Kemadrin)</td>
<td>GlaxoSmithKline</td>
<td>1951</td>
</tr>
<tr>
<td>Benztropine mesilate (Cogentin)</td>
<td>Merck &amp; Co.</td>
<td>1954</td>
</tr>
<tr>
<td>Biperiden (Akineton)</td>
<td>AbbVie</td>
<td>1954</td>
</tr>
<tr>
<td>Orphenadrine hydrochloride (Disipal)</td>
<td>3M Pharmaceuticals</td>
<td>1955</td>
</tr>
<tr>
<td>Metixene hydrochloride (Tremaril)</td>
<td>Novartis</td>
<td>1962</td>
</tr>
</tbody>
</table>

Dopamine receptor agonists

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Originator/Licensee</th>
<th>Year of First Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apomorphine hydrochloride (Apofin)</td>
<td>Chiesi</td>
<td>1951</td>
</tr>
<tr>
<td>Amantadine hydrochloride (Symmetrel)</td>
<td>Bristol-Myers Squibb/ Endo</td>
<td>1964</td>
</tr>
<tr>
<td>Piribedil (Trivastan)</td>
<td>Servier</td>
<td>1969</td>
</tr>
<tr>
<td>Bromocriptine mesilate (Parlodol)</td>
<td>Novartis</td>
<td>1975</td>
</tr>
<tr>
<td>DRUG NAME</td>
<td>ORIGINATOR/LICENSEE</td>
<td>YEAR OF FIRST LAUNCH</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Lisuride maleate (Dopergin)</td>
<td>Merck &amp; Co.</td>
<td>1982</td>
</tr>
<tr>
<td>Dihydro-α-ergokryptine mesylate (Daverium)</td>
<td>Poli Industria Chimica/ Pfizer</td>
<td>1989</td>
</tr>
<tr>
<td>Pergolide mesylate (Permax, Parkotil)</td>
<td>Lilly/Valeant</td>
<td>1989 (withdrawn 2007)</td>
</tr>
<tr>
<td>Cabergoline (Cabaser)</td>
<td>Pfizer</td>
<td>1993</td>
</tr>
<tr>
<td>Ropinirole hydrochloride (Requip)</td>
<td>GlaxoSmithKline</td>
<td>1996</td>
</tr>
<tr>
<td>Talipexole dihydrochloride (Domino)</td>
<td>Boehringer Ingelheim</td>
<td>1996</td>
</tr>
<tr>
<td>Pramipexole hydrochloride (Mirapex, Sifrol)</td>
<td>Boehringer Ingelheim</td>
<td>1997</td>
</tr>
<tr>
<td>Rotigotine (Neupro)</td>
<td>UCB Pharma</td>
<td>2006</td>
</tr>
</tbody>
</table>

**Dopamine precursors**
- Levodopa (Larodopa) | Roche/Bristol-Myers Squibb | 1970 |
- Melevodopa hydrochloride (Levomet) | Chiesi | 2000 |

**L-Noradrenaline precursor**
- Droxidopa (DOPS) | Dainippon Sumitomo Pharma | 1989 |

**MAO-B inhibitors**
- Selegiline hydrochloride (Deprenyl) | Chiesi/Merck & Co. | 1981 |
- Rasagiline mesilate (Azilect) | Teva/Lundbeck | 2005 |

**NMDA antagonists**
- Budipine hydrochloride (Parkinsan) | Altana/Lundbeck | 1997 |

**COMT inhibitors**
- Tolcapone (Tasmar)* | Roche | 1997 |
- Entacapone (Comtess, Comtan) | Orion/Novartis/ Bristol-Myers Squibb | 1998 |

**Ion channel modulators**
- Zonisamide (Trerief) | Dainippon Sumitomo Pharma | 2009 |

**Adenosine A2A antagonists**
- Istradefylline (Nouriast) | Kyowa Hakko Kirin | 2013 |

**Combination products**
- Levodopa/carbidopa (Synemet) | Merck & Co./ Bristol-Myers Squibb | 1972 |
- Levodopa/benserazide hydrochloride (Madopar) | Roche | 1974 |
- Levodopa/carbidopa/entacapone (Stalevo) | Orion/Novartis | 2003 |
- Melevodopa hydrochloride/carbidopa (Levomet Complex) | Chiesi | N.A. |

*Withdrawn worldwide except U.S. due to hepatotoxicity.
### Drugs in Development for the Treatment of Parkinson's Disease

<table>
<thead>
<tr>
<th><strong>Drug Name</strong></th>
<th><strong>Organizations</strong></th>
<th><strong>Mechanisms</strong></th>
<th><strong>Phase</strong></th>
<th><strong>Structure</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Safinamide mesilate</td>
<td>Zambon; Newron</td>
<td>Calcium Channel Modulators; Dopamine Reuptake Inhibitors; Glutamate Release Inhibitors; MAO-B Inhibitors; Signal Transduction Modulators; Sodium Channel Blockers</td>
<td>Pre-Registered</td>
<td><img src="image1.png" alt="Structure" /></td>
</tr>
<tr>
<td>Opicapone</td>
<td>BIAL</td>
<td>COMT Inhibitors</td>
<td>Phase III</td>
<td><img src="image2.png" alt="Structure" /></td>
</tr>
<tr>
<td>[123I]-E-IACT</td>
<td>Navidea Biopharmaceuticals</td>
<td>Drugs Acting on Dopaminergic Transmission; Signal Transduction Modulators</td>
<td>Phase III</td>
<td><img src="image3.png" alt="Structure" /></td>
</tr>
<tr>
<td>Florbenazine F18</td>
<td>Lilly</td>
<td>Signal Transduction Modulators; Vesicular Monoamine Transporter 2 (VMAT2) Ligands</td>
<td>Phase II/III</td>
<td><img src="image4.png" alt="Structure" /></td>
</tr>
<tr>
<td>Oxaloacetate</td>
<td>Terra Biological; University of Kansas</td>
<td>Antioxidants; Glutamate Release Inhibitors; Signal Transduction Modulators</td>
<td>Phase II/III</td>
<td><img src="image5.png" alt="Structure" /></td>
</tr>
<tr>
<td>Rasagiline mesilate/pramipexole hydrochloride</td>
<td>Pharma Two B</td>
<td>Dopamine D3 Agonists; MAO-B Inhibitors; Signal Transduction Modulators</td>
<td>Phase II/III</td>
<td>Fixed-dose combination</td>
</tr>
<tr>
<td>Tozadenant</td>
<td>Biotie Therapies</td>
<td>Adenosine A2A Antagonists; Signal Transduction Modulators</td>
<td>Phase II/III</td>
<td><img src="image6.png" alt="Structure" /></td>
</tr>
<tr>
<td>(+)-Phenserine</td>
<td>QR Pharma</td>
<td>beta-Amyloid (Abeta) Production Inhibitors</td>
<td>Phase II</td>
<td><img src="image7.png" alt="Structure" /></td>
</tr>
<tr>
<td>AZD-3241</td>
<td>AstraZeneca</td>
<td>Myeloperoxidase Inhibitors</td>
<td>Phase II</td>
<td>Structure not yet disclosed - in full product, alerts can update you upon structure disclosure</td>
</tr>
<tr>
<td>CERE-120</td>
<td>Ceregene</td>
<td></td>
<td>Phase II</td>
<td>Gene therapy</td>
</tr>
</tbody>
</table>
### DRUGS IN DEVELOPMENT FOR THE TREATMENT OF PARKINSON’S DISEASE, CONTINUED

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>ORGANIZATIONS</th>
<th>MECHANISMS</th>
<th>PHASE</th>
<th>STRUCTURE</th>
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</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>University College London</td>
<td>GLP-1 Receptor Agonists; Insulin Secretagogues;</td>
<td>Phase II</td>
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<td></td>
<td></td>
<td>Signal Transduction Modulators</td>
<td></td>
<td></td>
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<td>GM-602</td>
<td>Genervon</td>
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<td>Phase II</td>
<td></td>
</tr>
<tr>
<td>Ganglioside</td>
<td>Thomas Jefferson University; LZ Therapeutics</td>
<td></td>
<td>Phase II</td>
<td></td>
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<tr>
<td>GM1</td>
<td></td>
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<tr>
<td>Isradipine</td>
<td>Northwestern University</td>
<td>Calcium Channel Blockers</td>
<td>Phase II</td>
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</tr>
<tr>
<td>Mavoglurant</td>
<td>Novartis</td>
<td>Signal Transduction Modulators; mgluR5 Antagonists</td>
<td>Phase II</td>
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</tr>
</tbody>
</table>

Complete table provided in full briefing.
COMPLEMENTARY AND ALTERNATIVE MEDICINE
Covered in full briefing

TREATMENT OF NONMOTOR SYMPTOMS
Covered in full briefing

REHABILITATION STRATEGIES
Covered in full briefing

SURGERY
Covered in full briefing

TARGETS FOR THERAPEUTIC INTERVENTION

For an overview of validated therapeutic targets for this indication, consult the targetscape below. The targetscape shows an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of the condition and their biological actions. An arrow indicates a positive effect; a dash indicates a negative effect. Gray or lighter symbols are targets that are not validated. For in-depth information on a specific target or mechanism of action, see the corresponding section in this report.

PARKINSON’S DISEASE TARGETSCAPE
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