Parkinson's disease: neurological bases for psychiatrists

Enrique Chávez-León,[1] Martha Patricia Ontiveros-Uribe,[2] José Damián Carrillo-Ruiz[3]

Thematic updates

SUMMARY

Parkinson's disease is a degenerative and progressive disease caused by the loss of dopaminergic neurons of the substantia nigra in the midbrain. Its manifestations are: tremors at rest, stiffness and slowness of the movements, alterations in posture and gait. The early appearance of memory problems or hallucinations, not caused by the treatment, indicates the presence of dementia with Lewy bodies. The scales used for evaluating the stage and gravity of Parkinson's disease are: the Hoehn and Yahr scale and the Unified Parkinson's Disease Rating Scale (UPDRS). Although there is no drug that can stop the evolution of Parkinson's disease yet, the current treatment of Parkinson's disease consists of improving the symptoms by means of: a) dopamine replacement through the use of its precursor, levodopa (L-Dopa), b) administration of substances that increase dopaminergic activity by stimulating its receptors (ropinirole, pramipexole, bromocriptine), and c) inhibition of the enzymes that destroy dopamine like cathecol-O-methyl transferase (COMT) with entacapone, and monoamine oxidase type B (MAO_B) with selegiline and rasagiline. There is a surgical treatment of Parkinson's disease which consists of ablative procedures and deep brain stimulation. In this revision the basic elements of the disease, its clinical picture and complications are described. In a second part the medical treatment is addressed, along with its indications, administration and side effects, and at the end the surgical treatment will be described.

Key words: Parkinson's disease, antiparkinsonians, clinical picture, treatment, dopamine agonists, MAO inhibitors.

RESUMEN

La enfermedad de Parkinson es una enfermedad degenerativa y progresiva debida a la pérdida de las neuronas dopaminérgicas de la sustancia nigra del mesencéfalo. Sus manifestaciones son: temblor en reposo, rigidez y enlentecimiento de los movimientos, alteraciones en la postura y en la marcha. La aparición temprana de problemas en la memoria o alucinaciones, no debidas al tratamiento, indica la presencia de demencia con cuerpos de Lewy. Las escalas utilizadas para evaluar el estadio y la gravedad de la enfermedad de Parkinson son: la Escala de los Estadios de Hoehn y Yahr y la Escala Unificada de Calificación de la Enfermedad de Parkinson (UPDRS). Aunque todavía no existe un medicamento que detenga la evolución de la enfermedad de Parkinson, el tratamiento actual consiste en mejorar los síntomas mediante: a) la reposición de la dopamina por medio del uso de su precursor (levodopa, L-Dopa), b) la administración de sustancias que aumentan la actividad dopaminérgica al estimular a sus receptores (ropinirol, pramipexol, bromocriptina) y c) la inhibición de las enzimas que destruyen la dopamina como la catecol- O- metiltransferasa (COMT) con la entacapona, y a la monoamino oxidasa tipo B (MAO_B) con la selegilina y la rasagilina. Existe además el tratamiento quirúrgico de la enfermedad de Parkinson que consiste en procedimientos ablativos y la estimulación cerebral profunda. En esta revisión se describen los elementos básicos de la enfermedad, su cuadro clínico y sus complicaciones. En una segunda parte se aborda el tratamiento médico con sus indicaciones, administración y efectos secundarios, y para terminar se describirá el tratamiento quirúrgico.

Palabras clave: Enfermedad de Parkinson, antiparkinsónicos, cuadro clínico, tratamiento, agonistas dopaminérgicos, inhibidores de la MAO.

INTRODUCTION

In psychiatry, neurology knowledge is necessary to perform an integral and ethic practice. Usually, the typical clinical activity of the psychiatrist consists of handling the mental alterations which accompany neurological problems, such as Parkinson's and Alzheimer's disease, dementia with Levy bodies, Huntington's chorea, the effects of traumatic brain injuries, multiple sclerosis and epilepsy, and of ailments characterized by neurological symptoms that do not properly correspond to the pathology of Neurology such as the conversion, somatization and dissociative disorders. Due to all of the above it is necessary to count with the knowledge provided by Neurology.[1] Thus, the objective of the present

work are: describing the signs and symptoms associated with Parkinson's disease, emphasizing the importance of appropriate diagnosis for the handling of this ailment and describing the pharmacological agents that are generally used for its different stages. In a second work the mental and behavioral alterations that frequently accompany Parkinson's disease will be examined. Parkinson's disease is an abiotrophia, that is, a neurological degenerative and progressive disease caused by the loss of dopaminergic neurons of the substantia nigra in the midbrain, whose etiology is unknown (idiopathic). The characteristic manifestations of this disease consist of the motor triad of tremors at rest, stiffness and slowness of the movements (bradykinesia) or incapability to start them (akinesia), as well as alterations in posture and gait, which are frequently presented in late stages, although some patients can start with problems in walking. The diagnosis of the disease is made with the presence of these two symptoms and the response to the administration of L-dopa or to a dopamine agonist. Although a curative treatment has not been discovered yet, there are therapeutics which improve the most important motor symptomatology.[2]

HISTORY

The first to describe the disease that bears his name was James Parkinson in 1817. Parkinson thought that the cause of the disease was an alteration in the functioning of the spinal cord that could extend to the medulla oblongata, pointing out that there was no "modification of or senses".[3] In 1880 Jean-Martin Charcot named the shaking palsy as "Parkinson's disease", and used scopolamine for the treatment of the tremors.[4] Substantia nigra in the midbrain had been discovered by Félix Vicq d'Azyr. Over a century later, Paul Blocq and Georges Marinesco established their part in Parkinson's disease with the discovery, in a tuberculosis patient which suffered from tremor in the contralateral hemibody by an abscess in the substantia nigra. Two years later, in 1895, Edouard Brissaud suggested a vascular etiology of Parkinson's disease. In 1913, the German pathologist Friederich Lewy described Lewy bodies and suggested them to be a sign of the disease. Between 1918 and 1920 the global epidemic (pandemic) of Spanish flu, described by Von Economo, caused that approximately five million people developed parkinsonian symptoms after suffering from it. In 1919 Constantin Tretiakoff validated the hypothesis suggested by Brissaud by describing the loss of neurons in that area of the midbrain in both idiopathic and postencephalitic Parkinsonism. By the 1940's, the original treatment of Parkinson's disease was surgical based on the original works of Spiegel and Wycis in the basal ganglia, concretely the damage in the thalamus, the Fields of Forel and the subthalamic region, for being later modified by Cooper by tying the posterior choroidal artery, and using the globus pallidus as target as well. Fenelon and Guiot in 1955, by dam-

aging the *globus pallidus*, had success in 73% of their patients. However, in 1966 Arvid Carlsson discovered the alteration in dopamine concentration and maintained that parkinsonian symptomatology was caused by the diminishment of this neurotransmitter; consequently he received, the year 2000, the Nobel Prize in Physiology. In 1960, Hornikyewicz and Birkmayer injected Dopa to patients with Parkinson's disease, and observed spectacular results. In 1967, George Constantin Cotzias, from the Brookhaven National Laboratories in New York, administered L-Dopa orally, thus creating an effective therapeutic method. The use of surgery declined until the 1980's, where it was pointed out that the sole use of medication could not cure the disease, on top of the presence of other side effects.

With a better understanding of the pathogeny, the efforts were led to surgically address other parts of the basal ganglia by tissue implant, deep stimulation in previously known nuclei, besides the subthalamic nucleus, as well as the use of radiosurgery.[5-8]

EPIDEMIOLOGY

Parkinsonian symptoms, mainly the tremors and bradykinesia, caused by Parkinson's disease, progressive supranuclear palsy, corticobasal degeneration, frontotemporal dementia and Lewy bodies dementia, can be observed in 15% of elderly people and almost 50% in people older than 80 years; Parkinson's disease is the most frequent cause of parkinsonian symptoms. On industrialized countries, Parkinson's disease is the second most frequent neurodegenerative disease after Alzheimer's disease, which affects 1% of the population older than 55 years and 3% of the ones older than 70 years. The average age of onset beginning is 60 years of age and 80% of the cases the patients develop this disease between 40 and 70 years of age; only 5% have symptoms before 40 years of age. The people who develop the disease between 21 and 40 years are diagnosed with hereditary early-onset Parkinson's disease; the beginning at different ages can limit its diagnosis.[9] The World Health Organization considers that nearly 40 million people suffer from this disease and that an additional 30% has not been diagnosed.[10] In Mexico, according to the Secretariat of Health, it affects half a million Mexicans older than 60 years.

ETIOLOGY

Although it is known that the pathological alteration underneath Parkinson's disease is the loss of dopaminergic neurons in the ventral area of the *pars compacta* of the substantia nigra, the cause of Parkinson's disease is still unknown; in most cases, it is due to the interaction of environmental and genetic factors.

The mechanisms suggested as a cause of this disease include:[7]

Oxidative stress, result of the effect of "reactive oxygen species" (free radicals and peroxides) produced from normal metabolic reactions, like the energy generation of the mitochondria, of the activity of the hepatic cythochrome p450 enzyme system, by the exposure to tobacco smoke or to the gases emitted from automobiles and industries (manganese, carbon monoxide, organophosphates), asbestos and ionizing radiations, to the excessive consumption of alcohol and to viral infections (for example influenza). Excitotoxicity caused by a sustained and excessive activation of the excitatory amino acid receptors, such as glutamic acid, with the consequent increase of intracellular calcium concentration, brain damage and neural death.

Other suggested mechanisms are: mitochondrial dysfunction, alterations of the neuronal cytoskeleton and of the axonal transport and programmed cell death.

Diabetes increases the risk of suffering from Parkinson's disease except on young women;[11] on the other hand, coffee consumption and smoking diminishes the risk of suffering from Parkinson's disease.

GENETICS

Family and twin studies have allowed the identification of causal genes and genetic variants that increase the risk of suffering from Parkinson's disease. For example, the so-called PARK8, located on chromosome 12, the SNCA gene mutated from alfa-synuclein, component of Lewy bodies, located on chromosome 4, first identified mutation in Parkinson's disease with autosomal dominant transmission. Mutations in the genes of chromosome 6 which decode Parkin protein (PRKN) are the hereditary defects most frequently observed and are especially associated with the early onset autosomal recessive juvenile form of Parkinson's disease.

The loss of dopaminergic neurons generally occurs during old age; however, it is less serious and affects other cell types of the pars compacta of the substantia nigra on the midbrain. The loss of dopaminergic neurons in the frontal cortico-striatal-thalamic circuits is related to the motor symptoms of Parkinson's disease.[9] Since the 1980's there is a standard outline of the disease mediated by the dopaminergic receptors D1-D5, D2 to D4 by the direct and indirect paths from the substantia nigra towards the neostriatum. Its unbalance produces the disease.[12] (Figure 1)

RATING SCALES

The scales used for evaluating the stage and the gravity of Parkinson's disease are the following:

1. Hoehn and Yahr scale.[13]
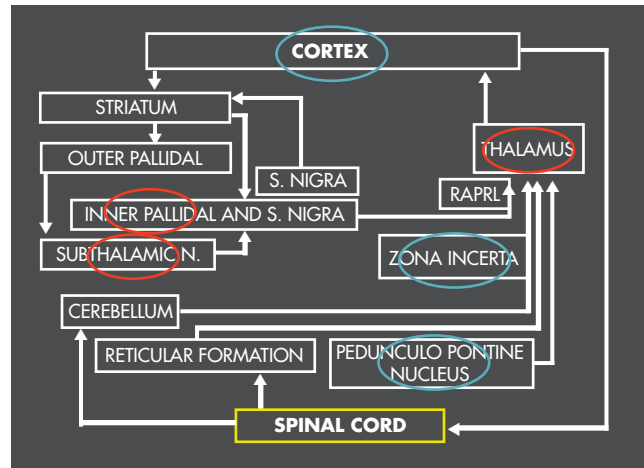
Figure 1. Circuits involved in the disease, with presence at the sites of stimulation and basal ganglia injury. Traditional ones are shown in bold type and emergent in regular type.

2. Unified Parkinson's Disease Rating Scale (UPDRS).

Both are accessible on the Internet in English.[14]

Hoehn and Yahr Scale

One of the forms of assessment frequently referred in scientific literature about Parkinson's disease which can also be easily applied in daily clinics is the Hoehn and Yahr Scale.[13] Its scoring goes from zero (no signs of disease), one (symptoms on one side only (unilateral)), 1.5 (symptoms unilateral and also involving the neck and spine), two (symptoms on both sides (bilateral) but no impairment of balance), 2.5 (mild bilateral symptoms with recovery when the 'pull' test is given), three (balance impairment. Mild to moderate disease. Physically independent), four (severe disability, but still able to walk or stand unassisted), to five (needing a wheelchair or bedridden unless assisted)[13] This scale is also contained on the Unified Parkinson's Disease Rating Scale (UPDRS).

Unified Parkinson's Disease Rating Scale (UPDRS)

The Unified Parkinson's Disease Rating Scale (UPDRS) has various parts, which are mostly rated from zero to four: zero being no alterations and four, a symptom with much deterioration. Part I evaluates the mentation, behavior and mood. Part II includes the activities of daily living. In part III discusses the motor examination. Part IV contains the complications of therapy. The last two parts contain two scales: part V covers the Modified Hoehn and Yahr Staging Scale, and part VI includes the Schwab and England Activities of Daily Living Scale. This scale is accessible in the Internet.[14] Recently, the Movement Disorder Society submitted it for revision.[15]

CLINICAL PICTURE

Parkinson's disease, a chronic and progressive condition, belongs to the group of movement disorders. The key symptoms of Parkinson's disease are: a) tremors in hands, arms, legs or lower jaw, b) stiffness of limbs and trunk, c) movement slowness, d) postural instability or balance disorders, e) gait disorders. Besides the motor symptoms, patients also display: cognitive, mental and behavioral alterations,[2] as well as vegetative disorders such as sialorrhea, constipation and seborrhea.

Nearly 20% of the patients with Parkinson's disease present an initial symptomatology that is not of the motor type; the symptoms consist of fatigue, musculoskeletal pain and depression. Many patients live with these symptoms between four and eight years, before motor symptoms appear.

Motor symptoms

Motor manifestations begin focally, usually in one of the limbs, when dopamine concentration drops below 60% to 70% in the motor region of the contralateral striatum (posterior putamen). At first they appear only on one side of the body, and they gradually move on to the opposite side. The motor symptoms consist of akinesia (hypokinesia and bradykinesia), augmentation of muscular tone (stiffness) and tremors. These symptoms will be more widely described below.

A. *Tremors*. It is the most frequent symptom at the beginning of the disease. The tremor at rest is of 4-6 Hz and of a distal predominance. The fingers are most affected, where the "pill-rolling" sign can be seen; tremors on the lower limbs can also exist. The jaw and tongue muscles can be affected, but the trunk and neck muscles rarely are. The tremors increase when other parts of the body are being moved, when arithmetic operations are being made and with stress, and they disappear during sleep.

B. *Muscle tone alterations*. Both the flexor and extensor muscles of the patient are affected with Parkinson's disease, thence the following muscle tone alterations can be observed: muscle tone augmentation during rest, distension decrease during passive mobilization, increase in the resistance to extension and greater facilitation to flexion. The increase in the resistance is much clearer when the affected limb is slowly extended. During physical examination it can be identified by the sign of the cogwheel. The "poker face" (inexpressive) can be developed by the patients, and as the disease progresses speech disorders (tachyphemia or cluttering) and dysphagia due to musculoskeletal alterations.

C. *Akinesia*. Akinesia is defined as the lack of movement and has various manifestations: 1. Hypokinesia consists on the diminishment of frequency and amplitude of spontaneous movements. Typical manifestations are decreased blinking and facial expressions, reduction or

absence of arm swing, and absence of movements related to daily activities, when getting up, moving and walking. Micrographia or diminishment in amplitude of the stroke and slowness at writing are manifestations of hypokinesia. 2. Parkinsonian gait is characterized by a tendency towards flexion, diminishment in the stride's amplitude and the elevation of the foot when walking. The difficulties for starting the gait make the patient take a lot of time to start it and even stay "frozen". A characteristic part of the disease is what is known as the festinant gait, with a great difficulty giving the first step. 3. Bradykinesia is characterized by diminishment in the movement's speed with a gradual diminishment of its amplitude until the disappearance of movement; for the patient with Parkinson it is difficult to accomplish sequential or simultaneous movements. The most affected movements are the ones started by the individual. See figure 2.

The diagnosis of Parkinson's diseases is done clinically. Most experts point out that the presence of two out three cardinal symptoms (akinesia, stiffness and tremors) and a good response to L-Dopa allows for the establishment of the diagnosis. At the beginning of the disease it can be difficult to establish the diagnosis, because the symptoms are subtle and even the patient himself cannot note them; on the other hand some of the symptoms appear due to normal aging.

Besides the previously mentioned symptomatology, it has been said that patients with Parkinson's disease can also display other symptoms such as: sialorrhea, dysarthria, sweating, visual disturbances and genitourinary pain, sleep disorders, seborrhea, edema, constipation, paresthesias and diminished sense of smell.[9] Urinary dysfunction is frequent in patients with Parkinson's disease, even since its early stages. Urodynamics testing in patients without treatment show abnormalities in the storage phase with hyperactivity of the bladder's detrusor muscle and an increase in urinary urgency. During the voiding phase abnormalities consist of hypoactivity of said detrusor and alteration in the urethral relaxation due to the sphincter's bad functioning. They do not seem to keep relation to the gravity of Parkinson's disease.[17] Sleep disorders become clearer as the disease progresses. For example, the patient may have difficulty falling asleep due to the tremors, stiffness and cold he is experiencing. He can wake up early as well due to the dyskinesias provoked by medicines and insomnia related to sleep apnea and the restless legs syndrome.

Gastrointestinal alterations include constipation due to slowing down peristalsis, dysphagia and gastroesophageal reflux.[2]

DIFFERENTIAL DIAGNOSIS

Parkinson's disease progresses much more slowly than other parkinsonian disorders and responds to L-Dopa. Some oth-

er disorders such as progressive supranuclear palsy or multisystem atrophy involve rapid progression with postural instability and falls from early stages, low response to L-Dopa, orthostatic hypotension and other symptoms of autonomic dysfunction, dysphagia and upward eye-movement paralysis. Early onset of amnesia and hallucinations, unrelated to treatment, signals the presence of dementia with Lewy bodies or Alzheimer's disease, even when the disease develops cognitive problems in as much as 20% of the patients. Presence of myclonias (involuntary, brief, jerky movement similar to a sudden muscle contraction), pyramidal signs —such as Babisnki's sign— and cerebellum signs point out to the diagnosis of other causes of parkinsonian symptoms and not to Parkinson's disease. Confusion may also arise with other extrapyramidal diseases such as Wilson's disease, dystonia and even with posterior spasticity and brain infarct.

TREATMENT

Until now there is no drug that prevents the evolution of Parkinson's disease. However, since the motor manifestations of the ailment are due to dopamine depletion of nigrostrial system, the main treatment consists in administering substances or performing maneuvers which augment concentration.

Current treatment of Parkinson's consists in the replacement of dopamine through the use of its precursor, L-dopa, or of substances increasing the activity of this neurotransmitter at stimulating dopaminergic receptors (ropinirole, pramipexole, bromocriptine). Other drugs work by inhibiting enzymes which destroy dopamine such as catechol-O-methyltranspherase (COMT) (entacapone) and type B monoamine oxidase (MAO_B) (selegiline and rasagiline).

Figure 2. Patient in Hoehn & Yahr stage 4, with great shaking, rigidity and bradykinesia. Apart from alterations in marching and posture, which if it were not with the help of the relative, the patient would fall down.

Dopaminergic agonists, pramipexole and ropirinole, are effective, though they may provoke secondary effects (sedation, sleepiness attacks, behavior alterations and hallucinations) more frequently than L-Dopa.[18] These drugs reduce the risk of dyskinesia and motor fluctuations during the early stages of Parkinson's disease and in those patients whose manifestations started before 40 years of age.

No drug has shown to have a neuroprotective effect for Parkinson's disease, though studies by means of brain imaging show that dopaminergic agonists such as ropinirole and pramipexole diminish the loss of dopaminergic neurons,[19,20] and that the use of rasagiline from the beginning of the treatment slows down the progression of the ailment.[21]

Dopaminergic Agonists

Levodopa (L-Dopa)

Carbidopa/Levodopa. The use of the combination carbidopa/levodopa (C/L) almost 40 years ago, significantly increased the survival of patients with Parkinson's disease. This drug continues to be the most effective treatment; however, more recent treatments can be used from the start. Carbidopa/levodopa is beneficial during the early stages of treatment and has a persistent effect in the long term. Recovery of mobility and continuous physical activity have a positive influence on the integrity of the Central Nervous System and neuroplasticity.[22] However, as time goes by, and due to the evolution of the ailment, it becomes less useful and frequently carries symptoms of dyskinesia.

The commercial presentation of combined carbidopa/levodopa shows two figures. The first one shows the concentration of carbidopa: carbidopa/levodopa (25/259) =25 mg carbidopa and 250 mg L-dopa. Carbidopa prevents nausea, thus it is preferable to use this combination. Approximately 70 to 100 mg per day of carbidopa are necessary to saturate the enzyme dopadescarboxilase and to prevent the transformation of L-dopa into dopamine in the periphery, which is the cause of nausea and vomit.

Prolonged release presentation has a lower bioavailability than the immediate release presentation, its effect is more varied and a lot slower, it is more expensive and food interferes with its liberation.

L-dopa is an amino acid that crosses the blood-brain barrier through a molecular transporter which binds this and other amino acids, thus saturating easily. Other products of the digestion of proteins which are simultaneously present in the diet compete with L-dopa, diminishing its efficiency. It is recommended to take the drug one hour before food intake or two hours later. If the patient feels nausea at taking it on an empty stomach it can be taken with some bread, crackers, a banana or some other food with no protein. Even when it is preferable to use the minimum effective dose, it is important to attempt that the patient be in the best possible functioning level. Treatment

must be distributed in three doses, one hour before each meal.

Carbidopa/levodopa (25/250) (Sinemet®, Cloisone®). For the combination carbidopa/levodopa (25/250) the loading dose is half a tablet one or two times a day to add half a tablet more to complete three daily doses. After a week there can be a gradual increase of half a tablet until the desired improvement is achieved or up to a limit of three tablets daily. This presentation of the drug has as a disadvantage a low concentration of carbidopa, insufficient to prevent nausea. In elderly patients, the tablet may be fractioned to prevent dyskinesia or to diminish the *ON-OFF* effect.

Benserazide/levodopa (25/100) (Madopar®). The combination Benserazide/levodopa, 25 and 100 mg, respectively, is similar to carbidopa/levodopa (25/100) and its administration can be determined by the guidelines mentioned above. Benserazide just as carbidopa, inhibits peripheral decarboxylase. Conversion of L-dopa into dopamine in the bloodstream may provoke nausea. Though circulating dopamine does not cross the blood-brain barrier, it can stimulate the chemoreceptive areas in the brainstem. Nausea is managed with ondansetron (antagonist of serotonin type 3, $5HT_3$ receptors) and with domperidone (an antagonist of peripheral dopaminergic receptors which does not cross the blood-brain barrier though it increases the levels of prolactin). Dopaminergic antagonist drugs with an effect on the Central Nervous System such as metoclopramide or thiethylperazine should not be used.

Patients with Parkinson's disease may present autonomic instability and arterial hypotension; it is thence recommended to measure the arterial pressure before the beginning of the treatment with carbidopa/levodopa and only prescribe it when the systolic blood pressure is 90 mm Hg or higher. Later, blood pressure must be assessed, especially when it is necessary to increase the dose of dopaminergic precursor L-dopa. The objective of the treatment is to attain the greatest response to L-dopa, that is, the dose that allows the patient to lead an active life which includes doing exercise.

If it were necessary to withdraw the drug, the diminishment must be made gradually following the same weekly rate, due to the risk of neuroleptic malignant syndrome if suspended abruptly.

During the first years of treatment patients respond in a steady way and they stay well all day long. However, after several years, the effect lasts a much shorter time; it fluctuates and is observed at the moment of taking the medication. For example, the effect of the drug could last from one to six hours. Morning intake allows the patient to start walking one hour after waking up, and some hours later they have difficulty mobilizing again. Increasing the dose at such time does not produce any important benefit; instead, the doses may be redistributed and the intakes made closer. At the same time that the action time of the drug is shortened, patients may show dyskinesia (involuntary movements of choreic kind in the trunk, limbs, neck and head because of the drug). Dyskinesia is a manifestation of an excessive dose of L-dopa, so it is convenient to diminish the individual dose provoking abnormal effects. Unfortunately the reduction of L-dopa conditions the reappearance of parkinsonism. In this case it is convenient to add amantadine to the treatment.

Amantadine (Kinestrel® y PK-Merz®). If the adjustment of L-Dopa cannot improve the symptoms of dyskinesia without inducing parkinsonism, it is necessary to administer 100 mg amantadine two times a day in the beginning and later three or four times a day according to the response.

Dopaminergic Agonists

The American Academy of Neurology has established that dopaminergic agonists (ropinirole and pramipexole) can be used as an alternative in the initial treatment or as additional treatment to L-Dopa to diminish long term motor complications.[24]

This treatment is especially convenient for younger patients with mild disease in whom it is intended to delay as much as possible the use, ultimately inevitable, of L-Dopa.[25]

Dopaminergic agonists act in a direct fashion on dopaminergic receptors of the postsynaptic neuron of the striated body, without need to be stored by those neurons in the nigrostriatal via. All dopaminergic agonists used for the control of motor symptomatology of the patient with Parkinson's disease act on type 2 (D_2) dopamine receptors, with a high concentration on the striated body, though of varied affinity.

Dopaminergic agonists might be or not derived byproducts of ergot. Thus, dopaminergic agonists derived from ergot are: pergolide, apomorphine and bromocriptine. And from those which are not derived from ergot (non ergolines), the ones most widely used at present are: ropirinole and pramipexole.[26]

Though symptoms are better controlled with L-Dopa, dopaminergic agonists diminish the risk of developing dyskinesia, dystonia and fluctuations in motor activity. However, they are associated to a series of secondary effects such as edema, somnolence, constipation, dizziness, hallucinations and nausea, which provoke that the treatment be abandoned more frequently.[25]

Ropinirole

Ropinirole is a powerful dopamine agonist which acts on type 2 and 3 (D_2 and D_3) dopamine receptors. Apart from being indicated in treatment of Parkinson's disease, it also proves to be useful for restless legs syndrome. Due to its dopaminergic activity at hypothalamic level, it inhibits the secretion of prolactin. Ropinirole is metabolized in the liver by is enzyme CYP1A2, which provokes that, when ciprofloxacin, enoxacine, fluvoxamine or estrogens are administered there might be an increase in seric levels. On the other hand, tobacco addiction is related to a diminishment of the concentration of ropirinole.

Administration of ropirinole in patients with Parkinson's must begin with 0.25 mg three times a day, the second week 0.5 mg must be administered three times a day, the third week 0.75 mg must be administered three times a day and the fourth week 1 mg must be administered three times a day. Therapeutic range is wide, from three to nine milligrams daily. Though it can be administered with food, its presence diminished absorption speed. When ropinirole has been added to L-dopa treatment, it is possible to diminish its dose up to 20%. One must always be aware that treatment must not be suspended abruptly since that may provoke a neuroleptic malignant syndrome.[27,28]

Ropinirole (*Requip IR*®) comes in 0.25 and 1 mg tablets.

Pramipexole

Pramipexole is a dopamine agonist with an affinity to D2 and D3 receptors. As this drug is eliminated mainly via the kidneys, cimetidine and other substances inhibiting renal tubular excretion may diminish its elimination. There is no interaction with selegiline; with L-Dopa it may be necessary to diminish its dose; with amantadine, also of renal elimination, there might be some interaction. Its administration must begin with 0.125 mg three times a day, with later increments to 0.250 mg three times a day on the second week and to 0.50 three times a day on the third week. Therapeutic effect is observed with this 1.5 mg daily posology. If the maximum therapeutic effect is wanted, later increments must be done adding 0.750 mg per week, not faster, assessing the presence of secondary effects and not surpassing 4.5 mg daily, which is the maximum dose.[28]

Pramipexole (*Sifrol*®) comes in 0.125, 0.25, 0.50, 1.0 and 1.5mg tablets.

Bromocriptine

Even if bromocriptine tends to produce less collateral effects on the motor level, many patients abandon treatment due to these effects or to the lack of response to treatment. When bromocriptine has been used combined with L-Dopa it does not seem to prevent or delay motor complications.[28,29]

Bromocriptine (*Parlodel*®) comes in 2.5 and 5mg tablets.

Rotigotine (Nubrenza)

Dopaminergic agonist not derived from ergot that is transdermally administered through patches. Its indications are the treatment of Parkinson's disease and Restless legs syndrome. From the year 2008 it has not been available in the United States but it is available in Mexico (Table 1).

Dopamine methabolism inhibitors

MAO B Inhibitors

Degeneration of dopaminergic neurons from the nigrostriatal system provokes akinesia/bradykinesia, rigidity and tremor. Inhibitors of type B monoamine oxidase (MAO$_B$), such as selegiline, rasagiline and safinamide, are used to increase the concentration of dopamine at the synapse at preventing monoamine oxidase (MAO) from acting. The function of MAO is to destroy dopamine and other neurotransmitters once they have been recaptured in the presynaptic neuron.[30] Selegiline and rasagiline may be used from the beginning of the treat-

Table 1. Dopaminergic agonists used in treatment of Parkinson's disease

Drugs (Commercial name)	Daily dose	Administration
Dopaminergic agonists (First generation)		
Carbidopa/Levodopa 25/250mg (Sinemet, Cloisone)	75/750mg/day	3 times a day
Benserazide/Levodopa 25/100mg (Madopar)	75/300mg/day	3 times a day
Amantadine 100mg (Kinestrel, PK-Merz)	200mg/day	2 times a day
Bromocriptine 2.5mg y 5mg (Parlodel)	5 a 10mg/day	2 times a day
Dopaminergic agonists (Second generation)		
Ropinirole 0.25mg y 1mg (Requip-IR)	0.25 mg/day /week 0.50 mg/day /week 0.75 mg/day /week 1 mg/day /week	Start 3 times a day and increase every week Maximum dose 3 to 9mg/day
Pramipexol 0.125mg, 0.250mg, 0.50mg, 1mg y 1.5mg (Sifrol)	0.725 mg/day/week 1.250 mg/day/week 1.500 mg/day/week	Start 3 times a day and increase every week Maximum dose 1.5 to 4.5mg/day
Rotigotine 2mg, 4mg, 6mg y 8mg (Nubrenza)	2 o 4 mg/day/week 6 u 8mg/day/week	Use of patches everyday with weekly upsurge

ment of Parkinson's disease though they are recommended for later stages and in those cases in which treatment with L-Dopa causes important fluctuations. Probably they also carry neuroprotective actions as proved by studies performed in animals. When selegiline has been used as load treatment on patients with Parkinson's disease, it has been necessary to add L-Dopa after three or four years.[29] Selegiline selectively inhibits type B monoamine oxidase (MAO$_B$), diminishing catabolism of dopamine at the presynaptic neuron and increasing concentration and activity of this neurotransmitter.[30] Selegiline inhibits MAO, selectively and reversibly, and it only inhibits MAO$_B$, which permits the metabolism of chemical substances which may affect the right functioning of Central Nervous System, thence it is not indispensable to avoid those foods containing tyramine, such as cheese, wine, beer, cold cuts, pickled foods, yoghurt, soy and beans. However, the presence of hypertension must be continuously assessed and the use of opioids and antidepressants must be avoided. These recommendations and restrictions must be maintained up to one week after the suspension of selegiline administration. The administration of selegiline must be started with 2.5 mg in the morning and, if no important secondary effects are observed (vertigo, nausea, vomiting, headache, hypotension, anxiety, palpitations, hallucinations or confusion), it may be increased to 5 mg daily, divided into two doses, assessing secondary effects and the interaction with other medication and foods. The regular dose is 10 mg daily, 5 mg two times a day.[28] Selegiline (*Niar*®) comes in 5 mg. At present, its use has decreased with the use of other drugs.

Rasagiline is another selective inhibitor of MAO-B which, at a 1 mg dose, provokes improvement of motor symptoms.[31] Rasagiline (*Azilect*®) comes in 1mg tablets (Table 2).

COMT Inhibitors

Entacapone

The combination carbidopa/levodopa with entacapone, inhibitor of the enzyme catechol-O-methyltranspherase (COMT), in charge of the metabolism of catecholamines at the synaptic cleft, has been used as an initial treatment; however, its effect may not be greater than that of carbidopa/levodopa by itself.[32] This combination is indicated when motor fluctuations are present due to the *ON/OFF* effect of L-Dopa. Nevertheless, the benefit on them and on dyskinesia may not be enough and, there may instead appear greater secondary effects, including nausea and diarreah.[28,29] There is some evidence that the use of this COMT inhibitor may increase the risk of cardiovascular problems and prostate cancer.[29]

Stalevo® contains 200 mg entacapone with variable L-Dopa (50, 100, 150 and 200mg) and carbidopa (12.5, 25, 37.5 y 50mg) concentrations (Table 2).

Anticholinergics

Anticholinergics may be of some use, but they provoke serious secondary effects such as confusion, memory alterations, restlessness and hallucinations. Their use is contraindicated in senile patients, especially those suffering from dementia.[29]

Trihexyphenidyl (*Artane*® and *Hipokinon*®) and biperiden (*Akineron*® and *Kinex*®) are two anticholinergics which are available. They respectively come in 5mg, and 2 and 4mg. Anticholinergics may be the initial treatment in patients whose only manifestation is tremor or incipient rigidity and they may also be combined with the previously described drugs (Table 2).

Table 2. Other drugs used for the treatment of Parkinson's disease

Drugs (Commercial name)	Daily dose	Administration
MAO Inhibitors		
Selegiline 2.5mg (Niar)	5 to 10mg/day	2 to 3 times a day
Rasagiline 1mg (Azilect)	2 to 3mg/day	2 to 3 times a day
COMT inhibitors		
Entacapone 200mg+Levodopa 50mg+Carbidopa 12.5mg	200mg	1 or 2 times a day
Entacapone 200mg+Levodopa 100mg+Carbidopa 25mg	200mg	1 or 2 times a day
Entacapone 200mg+Levodopa 150mg+Carbidopa 37.5mg (Stalevo)	200mg	1 or 2 times a day
Entacapone 200mg, administrate with Levodopa/Carbidopa (Comtan)	200mg	1 or 2 times a day
Anticholinergics		
Trihexyphenidyl 5mg (Artane, Hipokinon)	15mg/day	2 or 3 times a day
Biperiden 2mg and 4mg (Akineton y Kinex)	8 to 12mg/day	2 or 3 times a day

Surgical Treatment of Parkinson's Disease

In general, there are two kinds of surgical procedures for patients suffering from Parkinson's disease:[28] lesion procedures and deep brain stimulation.

Lesion procedures. Lesion surgery consists on inserting an electrode which burns the nucleus or those fibers which are targets for the improvement of symptoms. Among these surgical procedures are: thalamotomy (destruction of VOa, VOp or Vim thalamic nuclei), pallidotomy (lesion of the inner globus pallidus); RAPRL leucotomy (prelemniscal radiations) and subthalamotomy (fulguration of the subthalamic nucleus).[33] Transplant of dopamine-producing cells, either fetal or from the adrenal medulla are also two surgical maneuvers used in the treatment of Parkinson's disease.[34]

Deep brain stimulation. Deep brain stimulation is an effective treatment for patients with motor symptoms refractory to drugs, It is based on the same principle as cardiac pacemakers and it consists of the implant of electrodes in the same targets used for the lesion, such as the thalamus, mainly for the treatment of tremor, or on the globus pallidus, to treat rigidity and in a lesser extent, tremor; they allow for electric stimulation through a device similar to a cardiac pacesetter controlled by the patients themselves.[35]

At present, the golden rule to treat most of the symptoms of the disease is deep brain stimulation of the subthalamic nucleus, which improves motor function, including gait and balance, of the patient suffering Parkinson's disease.[36]

In ten-year follow up studies, significant improvement has been observed in motor activity, in tremor, both at rest and during activity, as well as in bradykinesia. On the other hand, it also reduces the presence of dyskinesia and of motor fluctuations and it makes it possible to use lower doses of drugs.[37] Other sites are suggesting RAPRL, motor cortex, pedunculo-pontine nucleus and zona incerta as possible targets for brain stimulation.[38]

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