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Review Article

Parkinson's Disorder: Definitions, Contexts, Neural Correlates, Strategies and Clinical Approaches

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Abstract
Starting from the definition analysis of Parkinson's disorder, we proceeded to study the clinical, psychological and socio-environmental context, to better analyze the intrinsic and extrinsic aspects of this chronic progressive neurodegenerative pathology, placing emphasis also on secondary forms. The present contribution focuses in particular on all the most significant elements, also from an etiological and neurobiological point of view, in order to present the best therapies and treatments known today in medical and neuropsychotherapeutic profiles.

Keywords: psychology; neuroscience; substantia nigra; limbic system; Parkinson; Parkinson's disorder; psychotherapy; psychopharmacology; strategic and clinical approaches.

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1. Definition and clinical contexts of Parkinson's disorder

1.1. Historical profile

Parkinson's disease is a neurodegenerative disease with a slow but progressive evolution, which mainly involves some functions such as cognitive abilities, movement control and balance. [1] Not surprisingly, this disease is part of a group of diseases called "neurological movement disorders"; among these it is the most frequent. [2]

The first description would have been found in an Indian medical paper that referred to a period around 7,000 years ago, while another document, this time Chinese, dates back to 2,500 years ago. Several ancient sources, including an Egyptian papyrus, a treatise on Ayurveda medicine, the Bible and the writings of Galen, describe symptoms similar to those of Parkinson's disease. After Galen and until the end of the seventeenth century, there are no other clear references relating to the disease. In the following centuries, several authors have documented the various characteristics of the disease. Among them we remember: Franciscus Sylvius, Hieronymus David Gaubius, John Hunter and Auguste François Chomel. [3] [4] [5] [6]

In 1817, an English doctor named James Parkinson published an essay in which he reported six cases of "shaking paralysis": the author described in detail the characteristic resting tremor, the posture and abnormal gait, and again paralysis, the decrease in muscle strength and the way the condition progresses over time. Forty years later he called this syndrome "Parkinson's disease", inserting it in his treatise "Leçons sur les maladies du système nervoux". [5]

The first neurologists who contributed to the better understanding of the disease, in its entirety, were Armand Trousseau, William Richard Gowers, Samuel Alexander Kinnier Wilson, Wilhelm Heinrich Erb and Jean-Martin Charcot; in particular, the latter's studies, conducted between 1868 and 1881, were a constant and robust reference point for the following decades. [10] Among the various discoveries, Charcot must be credited with having made the distinction between rigidity, weakness and bradykinesia; thanks to these terminological differences, Frederic Lewy arrived in 1912 to distinguish the "Lewy body disease" from Parkinson's disease, while in 1919 Konstantin Tretiakoff discovered that the substantia nigra was the main brain structure affected (confirmed and shared discovery in the scientific community only after the publications by Rolf Hassler, in 1938). [5]

The second half of the twentieth century was characterized by research aimed at understanding the aetiology of the pathology and for a definitive cure. The biochemical changes underlying the brain, linked to dopamine, were identified in the 1950s by Arvid Carlsson, identifying the alterations of this neurotransmitter as the central role of the pathological condition, whereas in 1997 alone, the alpha-synuclein was found to be the main component in the Lewy body disease. The last twenty years instead has focused mainly on surgical, pharmacological and psychotherapeutic therapies, such as excision surgery and deep stimulation. [5] [8] [9] [10] [11]

1.2. The etiopathological profile

The aetiology is still uncertain. Various risk factors have been identified (pesticides, solvent hydrocarbons, head trauma, insecticides, exposure to heavy metals, organic substances such as trichlorethylene, perchlorethylene and carbon tetrachloride) [2] [12 to 20] and other protective (caffeine, nicotine, vitamin C, vitamin D, Omega 3-6-9, estrogenic hormones and non-steroidal anti-inflammatory drugs) [2] [21,22,23,24] however, most people with Parkinson's disease have an idiopathic condition. A small percentage of cases, on the other hand, can be attributed to known genetic and environmental factors. Parkinson's disease has traditionally been considered a non-genetic disease; however, about 15% of individuals with Parkinson's disease

have a first-degree relative with the same condition and present mutations to several specific genes, such as those coding for alpha-synuclein (SNCA), parkin (PRKN), protein dardarin (LRRK2), putative induced PTEN kinase 1 (PINK1), DJ-1 and ATP13A2. Mutations in glucocerebrosidase (GBA), on the other hand, are known to cause Gaucher disease. [25] [26] [27]

1.3. The epidemiological profile

Epidemiologically, Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease. The prevalence of the condition in industrialized countries is around 0.3%. Parkinson's disease is more common in the elderly and the prevalence increases from 1% in those over 60 years of age, up to 4% of the population over 80 years. The average age of onset is around 60 years, although 5-10% of cases, classified as young onset, begin between 20 and 50 years. The disease would be less common in populations of African and Asian origin, although this is disputed. Some studies have proposed that it is more common in men than women, but others have not found particular differences between the sexes. The incidence of Parkinson's disease is between 8 and 18 per 100,000 person-years. [2] [28]

1.4. Il profilo clinico e sintomatologico

Parkinson's disease produces clinical symptoms of motor and neuropsychiatric nature. [1] Four motor characteristics are considered as the symptomatic basis of Parkinson's disease [1] [28] [29] [30] [31] [32] [33] [34] [35] [36]:

a) tremor is the most obvious and most common symptom, although around 30% of individuals with Parkinson's disease do not show it at the onset. The tremor is typically "at rest", with low frequency, disappears during voluntary movements and generally worsens in situations of emotional stress, while it is absent during sleep. It mostly involves the most distal portion of the limb and at onset it typically appears in a single arm or leg, subsequently becoming bilateral. The frequency of parkinsonian tremor is between 4 and 6 hertz (cycles per second).

b) bradykinesia (slowness of movement) is another characteristic of the disease and is associated with difficulties throughout the movement process, from planning to initiation and, finally, execution. Sequential and simultaneous movement is hindered. Bradykinesia is not the same for all movements; in fact, some patients are able to walk with great difficulty, but still manage to ride a bicycle. Generally individuals with bradykinesia show less difficulty if they are provided with aids.

c) stiffness and resistance to movement of the limbs is caused by excessive and continuous contraction of the muscles. In parkinsonism, stiffness can be uniform (a "lead tube") or jerky ("cogwheel") and the combination of tremor and increased muscle tone are considered the origin of cogwheel rigidity. Stiffness may still be associated with joint pain, especially in the early stages of the disease, where stiffness is often asymmetric and tends to affect the muscles of the neck and shoulders, compared to the muscles of the face and limbs.

d) postural instability is typical of the last phases, while it is almost completely absent in the younger subjects. This leads to balance disorders and frequent falls that can cause bone fractures. The walking typically takes place through small steps, streaks, with a very problematic start and often the phenomenon of "festination" is observed, that is the progressive acceleration of the walk until it falls.

In addition, connected with motor disorders there are also: swallowing disorders; the language can become monotonous, not very expressive, slow (bradilalia); facial expression is poor and the expression impassive; writing evolves in the same way (parkinsonian micrograph) with a spelling that tends to become smaller.

Parkinson's disease can also cause neuropsychiatric disorders, which can be mild to severe, and include speech, cognition, mood, behavior and thought disorders. In particular:

a) cognitive disorders may occur in the early stages of the disease and sometimes before diagnosis. The most common cognitive impairment is executive dysfunction, which may include difficulties in planning, cognitive flexibility, abstract thinking, initiating appropriate actions and inhibiting inappropriate operations. Attention fluctuations and slowing cognitive speed are further problems at the cognitive level. Memory is influenced, in particular, in remembering the information learned; however, an improvement appears when the recall of memories is helped by stimuli. A person with Parkinson's disease has a risk of suffering from dementia 2 to 6 times greater than the general population; therefore the welfare aspect plays a central role in the qualitative, operational and functional management of the patient suffering from this pathological syndrome.

b) behavioral and mood changes are more common in Parkinson's disease than in the general population. The most frequent problems are depression, apathy and anxiety. Mania, bipolarity and difficulty in controlling impulses can occur, which can lead to drug abuse, compulsive eating, hypersexuality and pathological gambling.

c) psychotic symptoms, such as hallucinations or delusions, occur in 4% of patients and it is assumed that the main cause is an excess of dopamine secondary to the treatment, they become more common with increasing age and with the intake of levodopa.

Finally, Parkinson's disease can compromise other body functions; the typical forms are: sleep-wake disorders, orthostatic hypotension, seborrheic dermatitis, hyperhidrosis, urinary incontinence and alteration of genital and sexual function. Added to this are: constipation and disorders of gastric motility, visual problems and sensory alterations, up to paresthesia and neuroperipheral pain.

The NICE guidelines (based on the diagnostic criteria of the UK Parkinson's disease Brain Bank) for the diagnosis of Parkinson's disease are [37]:

Phase 1. Diagnosis of parkinsonian syndrome

Bradykinesia associated with at least one of the following signs / symptoms:

- Muscle stiffness;
- Tremor at rest (4-6 Hz);
- Postural instability unrelated to primary visual, cerebellar, vestibular or proprioceptive dysfunction.

Phase 2. Exclusion criteria for Parkinson's disease

Past medical history of:

- Relapsing stroke with gradual deficit progression;
- Repeated brain trauma;
- Antipsychotic or antidopaminergic drugs;
- Defined encephalitis or oculogire crisis not under drug treatment;
- More than an affected relative;
- Permanent remission of deficits;
- Negative response to high doses of levodopa (if malabsorption is excluded);
- Only monolateral symptomatology after 3 years;
- Other neurological conditions: progressive supranuclear palsy, cerebellar signs, early and severe involvement of the autonomic nervous system, pyramidal signs (Babinski), early and severe dementia characterized by speech, memory and praxis disorders;
- Exposure to known neurotoxins;

- Presence of cerebral neoplasia or hydrocephalus communicating to neuroimaging.

Phase 3. Criteria supporting a diagnosis of Parkinson's disease

Make a definitive diagnosis of Parkinson's disease in the presence of at least 3 of the following:
- Unilateral onset of symptoms;
- Excellent response to levodopa;
- Presence of resting tremor;
- Severe Korea-induced levodopa;
- Progressive symptoms;
- Response to levodopa for over 5 years;
- Persistent asymmetry of symptoms, with greater involvement of the onset side;
- Clinical course of over 10 years.

1.5. The differential diagnosis and secondary parkinsonisms

The other forms must be distinguished from the typical form of parkinsonism [38]:

1) secondary parkinsonism is the condition resulting from the block or physiological alteration of dopamine in the basal ganglia. These circumstances imply the onset of typical Parkinson's symptoms. The most frequent causes are:
   - the "use of drugs" that reduce the dopaminergic action, such as antipsychotics, antiemetics and those that decrease dopamine levels (eg reserpine and tetrabenazine);
   - hydrocephalus;
   - brain and / or metastatic oncological diseases;
   - neurovascular and hypoxic diseases;
   - brain injuries and injuries;
   - hypoparathyroidism;
   - viral and / or autoimmune encephalitis;
   - neurotoxins (carbon monoxide, methanol, manganese).

2) atypical parkinsonism is the condition of those suffering from chronic progressive neurodegenerative diseases that have common Parkinson's symptoms, such as:
   - the "progressive supranuclear palsy", which manifests itself first with gait and balance disorders, while in Parkinson's the latter symptom is present in the more advanced phases of the disease;
   - "Lewy body dementia", characterized by video-spatial deficits, even before the typical symptoms of Parkinson's;
   - "Alzheimer's disease", characterized by maraca memory deficit;
   - "fronto-temporal dementia", characterized by language deficits;
   - "corticobasal degeneration", which starts asymmetrically, generally after 60 years. It causes cortical and basal ganglia signs, often with apraxia, dystonia, myoclonus, and alien limb syndrome (movement of a limb that appears to be independent of the patient's conscious control). It causes immobility after about 5 years and death after about 10 years. Responds little to antiparkinsonian drugs;
   - "multisystemic atrophy", which presents high-grade autonomic and cerebellar dysfunctions. It can include severe parkinsonian features, usually with poor response to levodopa. It often causes early falls and balance disorders. Responds little to antiparkinsonian drugs
   - "amyotrophic lateral sclerosis" and "dementia of Guam", which respond little to antiparkinsonian drugs;
   - the "ataxias", which show poor coordination, do not respond to antiparkinsonian drugs.

2. The neural correlates in Parkinson's disorder

The nuclei of the base, a group of brain structures innervated by the dopaminergic system, are the most affected brain areas in Parkinson's disease. [39] The basal ganglia include: the caudate nucleus, the Putamen, the pale globe, the subthalamic nucleus and the Substantia nigra. [1] [43] The main pathological characteristic of the condition is the death of cells in the substantia nigra and, more specifically, in the ventral (anterior) part of the pars compacta, causing the death of cells up to 70% of their total over time. [27].

In the brain, there are 5 main circuits that connect the brain areas to the basal ganglia. These circuits are known as: motor circuit, oculomotor circuit, associative circuit, limbic circuit and orbit-front circuit, with names that indicate the main areas that are served by each circuit. In Parkinson's disease, all the circuits listed may be affected, which explains many of the symptoms. In fact, a variety of functions are controlled by these circuits, including those of movement, attention and learning. [39]

At the cutting of the brainstem [40], macroscopic changes can be noted in which neuronal loss can be deduced from a reduction in the pigmentation of melanin in the substantia nigra and in the locus coeruleus. Histopathology (microscopic anatomy of the substantia nigra and of the different brain regions, shows a neuronal loss and Lewy bodies in many of the remaining nerve cells; neuronal loss is accompanied by death of astrocytes (star-shaped glial cells) and the activation of microglia (another type of glial cell).

Then there are several proposed mechanisms by which brain cells, in the disease, undergo death. [39] One of these predicts that an abnormal accumulation of alpha-synuclein protein, linked to ubiquitin, damages cells. This insoluble protein accumulates within neurons forming inclusions, called Lewy bodies. According to the Braak staging, a classification of the disease based on the pathological picture, the Lewy bodies first appear in the olfactory bulb, in the medulla oblongata and in the pontine tegmentum, with the patients that are asymptomatic. As the disease progresses, Lewy bodies develop in the substantia nigra, in the midbrain and prosencephalobasal areas and, in the last phase, in the neocortex. These areas of the brain are the main areas of neuronal degeneration in Parkinson's disease. However, Lewy bodies cannot be the direct cause of cell death. In patients with dementia a generalized presence of Lewy bodies is common in cortical areas. Neurofibrillary clusters and senile plaques, characteristically found in Alzheimer's disease, are not common unless the patient has a form of dementia. Other mechanisms leading to cell death include dysfunction of lysosomal and proteosomal systems and reduced mitochondrial activity. The accumulation of iron in the substantia nigra is typically observed in combination with protein inclusions. This may be related to oxidative stress, protein aggregation and neuronal death, but the mechanisms that regulate this phenomenon are not fully understood. [41] [42]

3. Clinical strategies for the management of the pathological conditions

The NICE guidelines (based on the diagnostic criteria of UK Parkinson's disease Brain Bank) for the treatment of Parkinson's disease are [37]:

1. Pharmacological treatment of motor symptoms

Involve the patient, family members and caregivers (if appropriate) in all decisions. Consider clinical conditions, needs and life circumstances of patients, as well as therapeutic goals and preferences about the potential benefits and side effects of different classes of drugs. Oral levodopa remains the first line drug for patients with clinically relevant motor symptoms. At the start of treatment, information on adverse drug events should be provided.

As for dopaminergic therapy, adverse events may include impulse control disorder (particularly for dopamine agonists), excessive sleepiness, hallucinations and delirium (which are associated with all

Parkinson's disease treatments, particularly for dopamine-agonists). Table 1 reports the benefits and adverse effects of first-line drugs.

Prescribe levodopa to patients with initial Parkinson's disease whose motor symptoms affect quality of life. Consider the choice of dopamine agonists, levodopa or monoamine oxidase B (MAO-B) inhibitors for patients with initial Parkinson's disease whose motor symptoms do not affect quality of life. When a patient with Parkinson's disease develops dyskinesia or fluctuations in motor response (including wearing-off episodes, when the effects of the drugs begin to decrease between the various administrations), adjuvant treatment may be added on the advice of the specialist Parkinson's disease specialist. Prescribe one of several dopamine agonists, monoamine oxidase B inhibitors or catechol-O-methyl transferase inhibitors in addition to levodopa for patients with Parkinson's disease who developed dyskinesias or fluctuations in motor response despite optimal therapy with levodopa. If it is not possible to adequately control dyskinesias by modifying therapy, consider amantadine.

The inability to resist impulses (ICD) instead consists in the impossibility of resisting the temptation to perform acts harmful for oneself or for others, such as compulsive gambling, hypersexuality, binge eating and obsessive shopping. These symptoms are due to known adverse effects of dopamine replacement therapies and occur in 14-24% of Parkinson's disease patients taking these drugs. ICD behaviors can cause stress to patients and caregivers, financial difficulties and even legal issues such as criminal convictions. They can be difficult to recognize, particularly if patients hide their behavior from family members and caregivers. If a patient with Parkinson's disease has developed an ICD behavior, discuss the following points with the patient, family members and caregivers (if appropriate): how the impulse control disorder is affecting their life; illustrate the therapeutic possibilities, such as reducing or stopping dopaminergic therapy; what are the advantages and disadvantages of reducing or interrupting dopaminergic therapy. In the presence of ICD behaviors modify dopaminergic therapy by gradually reducing any dopamine agonist. Monitor for improvements and any symptoms due to dopamine agonist withdrawal. Prescribe a cognitive-behavioral therapy targeted to ICD if the changes to dopaminergic therapy are not effective.

2. Non-pharmacological treatment of motor symptoms

Consider a specialist consultation of physiatrists and physiotherapists, occupational therapists, speech therapists and dieticians in the early stages of the disease. In particular:

- prescribe specific physiotherapy for Parkinson's disease to patients who experience problems with balance or motility;
- prescribe a specific occupational therapy for patients who have difficulties in daily activities;
- prescribe a speech therapy therapy for patients with Parkinson's disease who have problems with verbal communication, swallowing or salivation.

3. Pharmacological treatment of non-motor symptoms

After excluding the modifiable causes and non-pharmacological treatments:

a) "Excessive daytime sleepiness": consider modafinil.
b) "REM sleep disorder": consider clonazepam or melatonin.
c) "Nighttime Akinesia": consider levodopa or dopamine-agonists orally. If ineffective, consider rotigotine.
d) "Orthostatic hypotension": consider midodrine (taking into account contraindications and monitoring criteria). If midodrine is contraindicated, not tolerated or ineffective, consider fludrocortisone (taking into account its safety profile and potential interactions with others drugs).
e) "Depression": identify and treat according to the recommendations of the LG NICE on depression in adults with a chronic physical health problem.
f) "Hallucinations and delusions": do not treat if well tolerated. Use quetiapine in patients without cognitive deficits. If standard treatment is not effective, prescribe clozapine to patients without cognitive deficits (patient registration to a monitoring service is required). Compared to other indications, lower doses of quetiapine and clozapine are required in patients with Parkinson's disease. Do not prescribe olanzapine.
g) "Dementia": prescribe a cholinesterase inhibitor for mild or moderate dementia (rivastigmine, donepezil or galantamine capsules or rivastigmine patches). Consider a cholinesterase inhibitor for severe dementia. Consider memantine if cholinesterase inhibitors are not tolerated or are contraindicated.
h) "Sialorrhea": Consider glycopyrronium bromide. If glycopyrronium bromide is not effective, not tolerated or contraindicated, consider a specialist consultation for treatment with botulinum toxin A. Consider anticholinergic drugs other than glycopyrronium bromide only if it is believed that the patient has a minimal risk of developing symptoms unwanted cognitive impairments.

4. Treatment of advanced disease

In patients with advanced Parkinson's disease, consider deep brain neurostimulation only when the symptoms are not controlled with the best possible pharmacological treatment (which may include subcutaneous apomorphine administered intermittently or by continuous infusion). Evidence shows that the levodopa-carbidopa intestinal gel is not cost-effective in patients with advanced Parkinson's disease.
Consider a consultation with a palliative care team for patients at any stage of Parkinson's disease, to give them, family members and caregivers (if appropriate) an opportunity to discuss palliative care and end-of-life care.

However, the NICE guidelines [37] analyzed so far are not updated to the current year and do not systematically and functionally consider the non-pharmacological treatment of Parkinson's disease due to psychic symptoms. In fact, if even today there is no definitive cure, other treatments can greatly alleviate the suffered symptomatology, according to an excellent multidisciplinary pathological condition:

a) surgical therapy. [44] [45] [46] [47] [48]
Until the seventies and eighties of the last century, surgical intervention was the practice, partially replaced with the administration of levodopa. In recent years, however, many surgical techniques have been perfected, necessary for the management of severe or drug-resistant forms: stereotactic surgery that allows the treatment of points in depth in the brain parenchyma with millimeter precision, thanks to the aid of radiological devices. The surgical treatment under examination can be divided into 2 main groups: deep brain stimulation (Deep Brain Stimulation, DBS) and lesion surgery. The sectors of intervention are the thalamus, the pale globe or the subthalamic nucleus. Deep brain stimulation (DBS) is the most commonly used surgical treatment and allows good clinical remission and a significant reduction in levodopa dependence. It involves the implantation of a medical device, called a brain pacemaker, which sends electrical impulses to specific areas of the brain. DBS is recommended for patients with Parkinson's who suffer from severe tremor that is not adequately controlled by drugs or those who are intolerant to drug treatment. A study published in the Journal of the American Medical Association and carried out on a sample of 225 patients, showed, in 71% of the cases, decisive improvements in the movements and in the decrease of the tremors following the DBS, compared to the 32% that took only drugs. Other, but less common, surgical therapies involve the creation of lesions in specific subcortical areas (a technique known

as pallidotomy, in the event that the lesion is produced in the pale globe).

b) rehabilitation and psychological therapy. [49][50]
Although the studies in this regard are scarce and do not take into account a sufficiently representative sample, the experience provides some evidence that language and mobility problems are able to improve thanks to rehabilitation, as well as motor, cognitive and emotional disorders in general.

c) food therapy. [51]
The muscles and nerves that control digestion can be affected by the disease, resulting in constipation and gastroparesis (food remains in the stomach for a longer period of time than normal). A balanced diet, based on periodic nutritional evaluations, is recommended and must be aimed at avoiding weight loss or gain and minimizing the consequences of gastrointestinal dysfunction. With the progression of the disease, dysphagia, or difficulty in swallowing, may appear. In these cases it may be useful to use thickeners for fluid intake and assume an upright posture when eating, as both measures reduce the risk of suffocation. In more serious cases, gastrostomy can be used to bring food directly into the stomach. The levodopa drug and proteins use, in competition, the same transport system in the intestine and in the blood-brain barrier. This means that, if taken together, the effectiveness of the drug appears reduced. Therefore, when using levodopa, excessive protein consumption is not recommended and a balanced Mediterranean diet is recommended. In advanced stages, supplementary intake of hypoproteinic products, such as bread or pasta, is recommended for similar reasons. To minimize the interaction with proteins, levodopa should be taken 30 minutes before meals.

c) other functional treatments.
Transcranial magnetic stimulation has been shown to temporarily improve levodopa-induced dyskinesia, [52] although other studies are contradictory on this point. [53] [54] Several nutrients have instead been proposed as possible treatments, but there is no evidence that vitamins or food additives are able to improve symptoms [55]; just as there is no definitive evidence to support that acupuncture and the practice of Qigong or T'ai chi have beneficial effects on the course of the disease or symptoms. [56] [57] [58] Mucuna pruriens and vicia faba are natural sources of levodopa and are taken by many people with the disease: although some clinical studies have shown some efficacy, [59] their ingestion could generate even lethal consequences, such as neuroleptic malignant syndrome. [60] [61].

4. Conclusions

To date there is no cure that resolves the disease and Parkinson's disease always progresses with time, according to the scale proposed by Hoehn and Yahr, in 5 stages. [62]

Considering that the life expectancy of Parkinson's patients appears to be reduced and mortality rates are about twice those of unaffected people, the need to intervene quickly is urgent. Cognitive decline and dementia, onset in old age, a more advanced state of illness and the presence of problems in swallowing are all factors that increase the risk of mortality. On the other hand, a disease characterized mainly by tremor with respect to stiffness, provides for a longer survival. Death from pneumonia ab ingestis is twice as frequent in subjects with Parkinson's disease compared to the healthy population. [63]

Future research is directed precisely in this direction: identifying the causes, blocking the symptoms and finding a cure that resolves the pathology. However, it appears very unlikely that new revolutionary treatments for Parkinson's disease will be introduced in a short period of time, despite:
a) the flourishing of new studies with combined techniques; [64]
b) the strengthening of targeted gene therapies;
c) stem cell transplantation;
d) the use of neuroprotective agents and biomarkers. [65] [66] [67]

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