

# Farmakoterapia choroby Parkinsona: przegląd literatury

## *Pharmacotherapy of Parkinson's disease: a literature review*

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### Streszczenie

Choroba Parkinsona jest przewlekłym, postępującym, neurodegeneracyjnym schorzeniem ośrodkowego układu nerwowego (OUN), charakteryzującym się uszkodzeniem komórek dopaminergicznych w istocie czarnej mózgu. Obecnie dostępne terapie farmakologiczne mają jedynie na celu redukcję objawów choroby. W pracy dokonano przeglądu literatury z bazy Medline opublikowanej w latach 2013-2015, dostępnej w języku angielskim i dotyczącej aktualnego postępowania farmakologicznego w chorobie Parkinsona. Na podstawie przeglądu literatury stwierdzono, że najskuteczniejszą metodą farmakologiczną leczenia choroby Parkinsona nadal pozostaje zastosowanie lewodopy w połączeniu z inhibitorami obwodowej dekarboksylazy. Odkrywanie nowych leków jest procesem długim i drogim, jednak ważnym do zrozumienia sposobu leczenia pacjentów z chorobą Parkinsona. (*Farm Współ 2015; 8: 1-6*)

*Słowa kluczowe: choroba Parkinsona, leczenie farmakologiczne, wytyczne*

### Summary

Parkinson's disease (PD) is chronic progressive neurodegenerative disorder characterized by profound loss of dopaminergic neurons in the nigrostriatal pathway. Current available pharmacological therapies for Parkinson's disease are aimed at reducing disease symptoms. A Medline search was performed to identify studies that assess the pharmacological management of Parkinson's disease. References were identified between January 2013 and April 2015 for English-language human studies. Administration of combined preparations of levodopa and peripheral decarboxylase inhibitors (benserazide/carbidopa) is postulated to be the most efficient therapeutic option for Parkinson's disease. Researching and developing new medicines is an expensive and lengthy process, but very important to understanding how to treat patients with PD. (*Farm Współ 2015; 8: 1-6*)

*Keywords: Parkinson's disease, pharmacological treatment,*

### Objective

Parkinson's disease (PD) is a progressively, degenerative and neurological disorder, belongs to a group of conditions called – motor system disorders, which are the result of the loss of dopamine – producing brain cells. When approximately 70-80% of the dopamine -producing cells are damaged, the symptoms of Parkinson's disease appear. Also other neurons are lost in Parkinson's disease, leading to the disorders of cholinergic, noradrenergic and serotonergic systems [1,2].

The symptoms of Parkinson's disease develop slowly and progress gradually in the course of the disease. Different people will experience a different combination of symptoms, but usually signs show up in one or more of four ways: rigidity or stiffness of limbs and trunk; bradykinesia or slowness of movement; tremor in hands, arms, legs and face; postural instability or impaired balance and coordination. Other clinical features include non – motor symptoms for example: autonomic dysfunction,

neurobehavioral abnormalities, sleep disorders and sensory abnormalities [3-7].

Many affected individuals have quiet and monotonous voice and problems with speaking. Additionally, changes in handwriting (micrography) can be observed [3-7].

Treatment for Parkinson's disease is aimed at restoring the levels of dopamine in patient's brain and controlling symptoms of disease. There are six main types of medications available to treat symptoms of Parkinson disease: levodopa, dopamine agonists (DAs), inhibitors of enzymes that inactivate dopamine (MAO-B inhibitors and COMT inhibitors), anticholinergics, and amantadine. Typically, dopamine treatment is started when Parkinson's disease symptoms begin to decrease patient quality of life. This review describes the standard and new pharmacological treatment of PD [8,9].

## Methods

A Medline search was performed to identify studies that assess the pharmacological management of Parkinson's disease. References were identified between January 2013 and April 2015 for English-language human studies. Search terms included: "Parkinson's disease", "Pharmacological management of Parkinson's disease" and "Therapeutic guidelines regarding Parkinson's disease".

## Results

Parkinson's disease is solely a clinical diagnosis and cannot be verified by any test. Current medicines for PD are approved to treat the symptoms of the disease, such as tremors and mobility problems. Therefore, the aim of pharmacotherapy is to alleviate the signs of this condition.

There are evidence-based therapeutic guidelines of PD. The recommendations of the National Institute for Health and Clinical Excellence (NICE) emphasize the individualization of patient-oriented approach, based on the stage of the disease, age, and lifestyle of a given individual. The NICE guidelines stratify the type of therapy according to early or late stage of the disease. In early Parkinson's disease, the dose of levodopa should remain at the lowest possible level sufficient to delay dyskinesia [10].

## Levodopa medicines for Parkinson's disease

Levodopa, the chemical precursor of dopamine, acts by replenishing depleted striatal dopamine. It is given with an extracerebral dopa-decarboxylase inhibitor that reduces the peripheral conversion of levodopa to dopamine, thereby limiting side-effects such as: cardiovascular effects, nausea and vomiting. The extracerebral dopa-decarboxylase inhibitors used with levodopa are benserazide and carbidopa [11-13].

Levodopa helps reduce tremor, stiffness, and slowness and improve muscle control, balance, and walking. It does not affect freezing, dementia or problems with autonomic functions, such as constipation, impotence, urinary problems. Levodopa therapy should be initiated at a low dose and increased in small steps. The final dose should be as low as possible. Intervals between doses should be chosen to suit the needs of the individual patients [11-13].

The side effects of Levodopa can include dyskinesia, low blood pressure, arrhythmia, gastrointestinal problems, nausea, hair loss, sleep disorders, confusion, anxiety and hallucinations. Motor fluctuations develop in about 40% of people treated for 4-6 years [11-13].

## Dopamine agonists for Parkinson's disease

According to the European Federation of Neurological Societies (EFNS) and Movement Disorder Society – European Section (MDS-ES), dopamine agonists should be prescribed to younger patients due to more frequent occurrence of dyskinesia.

The dopaminergic therapy is based on the administration of dopamine agonists, which dose is gradually increased if no improvement is observed. There are two subclasses of dopamine agonists: ergoline and non – ergoline agonists. Both of these subclasses target dopamine D2-type receptors. The ergoline dopamine agonists include bromocriptine, pergolide and cabergoline, whereas ropinirole and pramipexole are non-ergoline agonists.

The dopamine receptor agonists: bromocriptine, cabergoline, pergolide, pramipexole, ropinirole and rotigotine have a direct action on dopamine receptors.

The treatment of new patients is often started with dopamine receptor agonists. They are also used with levodopa in more advanced disease. When used alone, dopamine receptor agonists cause fewer motor complications in long-term treatment compared with

levodopa treatment but the overall motor performance improves slightly less. The dopamine receptor agonists are associated with more neuropsychiatric side – effects than levodopa. Doses of dopamine receptors agonists should be increased slowly according to response and tolerability [14,15].

### **Catechol-O-methyltransferase (COMT inhibitors)**

According to the National Institute for Health and Clinical Excellence (NICE) at advanced stages of the disease, catechol-O-methyltransferase inhibitors (COMT inhibitors) can be added to the therapeutic protocol. Importantly, always the lowest efficacious dose of the agent should be used [16].

Entacapone and tolcapone (COMT inhibitors) prevent the peripheral breakdown of levodopa, by inhibiting catechol-O-methyltransferase, allowing more levodopa to reach the brain. They are licensed for use for patients with Parkinson's disease who experience "and-of-dose" deterioration. COMT inhibitors are only used in conjunction with levodopa [17].

### **Amantadine**

Other groups of agents included in the National Institute for Health and Clinical Excellence guidelines are amantadine hydrochloride (not recommended as first line therapy).

Amantadine hydrochloride is the antiviral drug, which is used in the treatment of influenza A infection and also has some ability to reduce symptoms of tremor and bradykinesia in patients affected by Parkinson's disease. The mechanism of its antiparkinsonic effect is not fully understood, but it appears to be releasing dopamine from the nerve endings of the brain cells, together with stimulation of norepinephrine response. It also has NMDA receptor antagonistic effects. It can be combined with levodopa to reduce the risk of dyskinesia [18].

The adverse reactions reported most frequently at the recommended dose of Amantadine hydrochloride are: nausea, dizziness and insomnia. Less frequently reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, constipation, ataxia, peripheral edema, orthostatic hypotension, headache, somnolence, nervousness, dream abnormality, dry nose, diarrhea and fatigue [18].

### **Monoamine – oxidase – B inhibitors (MAO – B inhibitors)**

According to the European Federation of Neurological Societies (EFNS) and Movement Disorder Society – European Section (MDS-ES), levodopa is the most effective anti-Parkinsonian agent recommended for older patients. Dopamine agonists should be prescribed to younger patients due to more frequent occurrence of dyskinesia. The use of anticholinergic agents is also recommended in this age group, while they are not as well tolerated by older individuals. Monoamine – oxidase – B inhibitors (MAO-B inhibitors) like levodopa are recommended as first line therapy due to good tolerance and easy administration [19-21].

Selegiline is a MAO-B inhibitor used in conjunction with levodopa to reduce "and-of-dose" deterioration in advanced Parkinson's disease. Early treatment with selegiline alone may delay the need for levodopa therapy [20].

Rasagiline – a MAO-B inhibitor is licensed for the management of Parkinson's disease used alone or as an adjunct to levodopa for "and-of-dose" fluctuations. Both selegiline and rasagiline have a neuroprotective potential [20,21].

### **Scottish Intercollegiate Guidelines Network (SIGN) recommendations**

According to the Scottish Intercollegiate Guidelines Network (SIGN) recommendations, patients at the early stages of the disease should receive levodopa as the first line agent in combination with decarboxylase inhibitor. Dopamine agonists and MAO-B constitute another group of agents. SIGN does not recommend using anticholinergic agents and amantadine at early stages of the disease. The drugs which are recommended at late Parkinson's disease by the Scottish Intercollegiate Guidelines Network include MAO-B inhibitors, COMT inhibitors (with entacapone as a preferred agent), and non-ergoline dopamine agonists in combination with levodopa [22].

### **Therapy of Parkinson's disease in Poland**

The following groups of anti-Parkinsonian agents are used in Polish clinical practice in accordance with the international guidelines: levodopa preparations, dopamine receptor agonists, MAO-B inhibitors and COMT inhibitors. In contrast, amantadine and anticholinergic agents are of lesser importance in the therapy of Parkinson's disease.

## New pharmacological treatment of Parkinson's disease

In the last decade new medicines were approved to treat the motor and non-motor symptoms associated with PD. These new medicines are important for disease management and improved quality of life for patients.

Istradefylline is a highly selective antagonist at the A2A receptor is an analog of caffeine. It has been found to be useful in the treatment of Parkinson's disease. Istradefylline reduces dyskinesia resulting from long-term treatment with classical antiparkinson drugs such as levodopa. Overall, istradefylline has been well tolerated in clinical trials. The most commonly reported adverse events have been nausea, vomiting and dizziness [23-25].

Tozadenant is also a selective adenosine A2A receptor antagonist that improves motor function in animal models of Parkinson's disease. Parkinson's therapy tozadenant will enter Phase III in mid-2015 [25,26].

Safinamide is an alpha-aminoamide that inhibits monoamine oxidase-B, sodium channel blockade and modulates release of glutamate with resulting dopaminergic and non-dopaminergic effects. Safinamide has been endorsed for the treatment of adult patients with idiopathic Parkinson's disease as add-on therapy to a stable dose of Levodopa alone or in combination with other PD drugs in patients with mid-to-late-stage fluctuating disease [27-29].

Zonisamide, a benzisoxazole derivative, is an antiepileptic drug. Three nationwide, double-blind, placebo-controlled studies carried out in Japan prompted the approval of zonisamide as an antiparkinsonian agent in early 2009. At that time, the use of zonisamide in PD is still investigational. Further studies are warranted to confirm the preliminary promising findings and to better define effects, indications and tolerability of zonisamide in PD [30].

Dalfampridine is a potassium channel blocker. In clinical trials the drug showed improved walking speeds, demonstrating efficacy in all four types of multiple sclerosis (MS). A Randomized Trial show, that dalfampridine may have potentially favorable effects in certain

aspects of walking in patients with PD. Larger studies are necessary to establish the effects of dalfampridine in patients with PD and gait dysfunction [31].

Opicapone is a novel catechol-O-methyltransferase (COMT) inhibitor, providing potent and sustained COMT inhibition. This action enhances the beneficial effects of levodopa in Parkinson's disease patients with motor fluctuations. In the study (Phase 3, randomized, double-blind, active- and placebo-controlled, group study BIPARK-I), opicapone 50 mg once-daily achieved significant reductions (2.0 hours) in absolute OFF-time ( $p=0.0005$  vs 0.9 hours for placebo). Opicapone was considered overall safe and well tolerated [32].

## Conclusions

At present, there are various therapeutic modalities of Parkinson's disease. Drug therapy does not prevent disease progression, but it improves most patients' quality of life. Early diagnosis and treatment are important to help minimize dopamine loss in the brain and maintain motor function.

Administration of combined preparations of levodopa and peripheral decarboxylase inhibitors (benserazide/carbidopa) is postulated to be the most efficient therapeutic option for Parkinson's disease and for more than 30 years constitutes the gold standard in treatment of this condition.

Researching and developing new medicines is an expensive and lengthy process, but very important to understanding how to treat patients with PD.

## Conflict of interest

None

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