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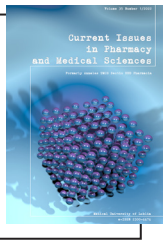

# The recent guidelines for pharmacotherapy of Parkinson's Disease

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**ABSTRACT**

Parkinson's Disease (PD) is one of the most frequent disorders of the central nervous system (CNS). PD is an age-related disease in that morbidity increases with age. The main symptoms of it are motor symptoms like bradykinesia, rigidity and resting tremor. These symptoms diminish the comfort of the patient's life and may lead to immobility. Hence, rapid diagnosis and start of treatment are very important.

The pharmacotherapy of PD is difficult. PD involves an imbalance between the dopaminergic and cholinergic systems. Therefore, the mechanisms of action of currently available drugs are highly connected with the pathology of PD, and follow dopaminergic or anticholinergic control strategies. However, long-term use of many PD medications comes with serious side effects. Therefore, the search for new, more effective drugs involving different strategies to that current and having different targets is still on-going.

## THE UNDERLYING CAUSE OF PARKINSON'S DISEASE (PD)

Parkinson's disease (PD) is nowadays the second most common chronic neurodegenerative disorder of the central nervous system (CNS) after Alzheimer's Disease (AD). Although PD mainly affects elderly people, younger individuals also suffer from this disease. Morbidity of PD increases with the age – 3% of population under the age of 65 have PD and that statistic grows to 5% in people over the age of 85 [1]. If the first symptoms occur before the age of 40, PD is deemed Early-onset PD (EOPD). If onset of features is before the age of 21, it is Young-onset PD (YOPD). EOPD and YOPD account for 3-5% of all PD cases [2]. In PD, gender also matters.

The risk of PD is about 1,5 times higher in men than in women, because female sex hormones have protective effects [1,2]. Additionally, PD may be caused by mutations of some genes, such as SNCA (alfa-synuclein) – which encodes α-synuclein (α-syn) or LRRK2 (Leucine rich repeat kinase 2) – which affects mitochondrial function. The strongest risk factors identified to date are GBA (glucocerebrosidase gene) mutations, which may involve misfolded proteins or lysosomal dysfunction [1]. About 5-10% of PD cases are is the result of mutations of these genes [2]. In addition, some environmental factors can increase the chance of being afflicted with PD. It is well-documented that exposure to pesticides, including rotenone, increases the risk for PD. Other risk factors are the consumption of dairy products or traumatic brain injury. In contrast, there are also some protective factors. The ways to decrease the risk of PD are consuming caffeine, being active physically and having high serum urate concentrations [1].

All neurodegenerative disorders result from progressive damage to cells and nervous system connections that are essential for mobility, coordination, strength, sensation and cognition. In the context of PD, the cause of this disease is connected with a common histopathological hallmark: synucleinopathy, which is similar to dementia with lewy body (DLB) and multiple system atrophy (MSA). In the course of PD, the presence of proteinaceous deposits is notable. Amyloid fibrils of α-synuclein form the main component of these. In PD, this protein is stored mainly in the dopaminergic neurons, and form Lewy Bodies (LBs) in substantia nigra pars compacta and the result of this is a progressive neuron death and a reduction of the amount of dopamine (DA) [3]. LBs also involve other cells that are responsible for producing acetylcholine (ACh), noradrenaline (NA), serotonin (5-HT), histamine (H) and glutamate (Glu). The result of changed amount of these neurotransmitters is a wide spectrum of clinical symptoms [1].

The most important in the context of symptoms of PD are changes in the DA and ACh levels in the brain. DA is a catecholamine that plays an important role in the body,

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in the CNS and peripheral nervous systems (PNS). DA is used to communicate between neurons, and is involved in the regulation of muscle tension, blood pressure, the work of glands and in emotional expression, it is also a part of the reward system. The lack of DA is the reason for PD's characteristic motor symptoms such as bradykinesia, resting tremor and rigidity. Usually these features are asymmetric at the beginning of disease. As the disease progresses, spontaneous movements decrease, facial expressions diminish, speech becomes a monotone, and writing often becomes small. In patients with PD, gait also changes. Moreover, asymmetric reduction in arm swing is notable, as are changes in stride length and decreases in walking speed. In addition, posture becomes unstable [1].

In PD, motor symptoms are accompanied by non-motor symptoms, such as sleep disorders (for example, insomnia), mood disorders, depression, cognitive decline, hyposmia and disturbance in autonomic function (e.g. orthostatic hypotension, constipation, urogenital dysfunction, urinary incontinence and the most common – chronic pain) [1,2]. Some of these non-motor features may appear several years, even a decade, before the main motor symptoms do [2].

ACh level is also related to levels of DA. Decline of DA causes a rise of ACh concentration and breakdown of balance between DA and ACh. The effects are certain non-motor symptoms. If about 60-70% of neurons of *substantia nigra* are lost and levels of DA decrease, the symptoms will be notable [2].

## CURRENT PHARMACOTHERAPY OF PD

This review intends to bring about an understanding of PD, its symptoms and methods of treatment, especially pharmacotherapy. The goal is a presentation of recent guidelines for the pharmacotherapy of PD and some possible future agents. Additionally, the authors want to inform readers of drug performances, their mechanisms of action and the side effects of their administration. For this purpose, various databases, websites, like Pubmed, Drugbank, ClinicaTrials.gov were searched. The pharmacotherapy of PD is difficult. Therefore, the search for new, more effective drugs with new strategies and targets is still on-going. The mechanism of action of current available pharmacotherapy is strictly connected with the pathology of this disease. Current agents take into account two strategies of PD treatment: dopaminergic and anticholinergic therapies.

## DOPAMINERGIC THERAPY – DOPAMINERGIC AGENTS

The dopaminergic strategy is based on mitigating the loss of DA or dopaminergic dysfunction in PD patients. According to current understanding, deficits in dopaminergic neurotransmission lead to many severe clinical symptoms of PD, like motor dysfunction, including resting tremor, bradykinesia, rigidity and postural instability. Hence, it is important to restore the functions of the dopaminergic system and DA levels to the physiological level. There are several ways to increase DA concentration in a pharmacological manner. These include: administration of the metabolic precursor of DA – Levodopa (L-DOPA), and administration of inhibitors of enzymes: monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT), which metabolize DA to inactive forms. A third approach is administration of dopaminergic receptors agonists.

Today, dopaminergic agents still represent the major therapeutic approaches for alleviating the motor symptoms of PD. Therefore, the dopaminergic strategy is the basic and most important one in the current therapy of PD.

### L-DOPA

L-DOPA has been the gold standard in treatment of PD for more than 50 years. It is a metabolic precursor of DA. L-DOPA, as opposed to DA, is able to cross the blood-brain barrier (BBB). When L-DOPA crosses this barrier, it is metabolized in a reaction of decarboxylation to DA [4]. Unfortunately, L-DOPA can also be metabolized before crossing BBB by certain peripheral enzymes – the aromatic amino acid decarboxylase (AADC), MAO-B and/or COMT. These metabolic processes are responsible for L-DOPA's poor efficacy and pose a risk of peripheral side effects, such as nausea and hypotension. Therefore, in order to increase the effectiveness of L-DOPA therapy, it is used in combination with inhibitors of AADC, such as carbidopa or benserazide. These drugs pass through the BBB only to a small extent, so they inhibit for the most part, just the peripheral decarboxylation of L-DOPA. Moreover, it has been proposed to combine L-DOPA with inhibitors of MAO-B or COMT to reduce the metabolism of L-DOPA and increase its level in the CNS [4]. Predominantly, L-DOPA is administrated orally. PD L-DOPA may also be applied by intestinal infusion by portable infusion pump. L-DOPA-carbidopa intestinal gel (LCIG) is used in this method. LCIG can also be delivered continuously by a percutaneous endoscopic gastrojejunostomy tube (PEG-J) [2].

Chronic use of L-DOPA leads to certain non-motor symptoms, like L-DOPA-induced-dyskinesia (LID), motor fluctuations, including early-morning off (lack of the efficiency of drug after wake up), wearing-off (reduction of duration of action), delayed-on (delay of drug action), no-on (dose-failure, lack of effect after drug dosage), and on-off phenomena (ON-time, in which the symptoms are under control and the patient can move without difficulty versus the sudden appearance of OFF- time, when the patient is immobile). The mechanism for this is still unclear [2-6].

### MAO-B INHIBITORS

In humans and animals, two isoforms of MAO are found: type A and type B. These enzymes are responsible for the metabolism of monoamines, including DA, 5-HT, NA, adrenaline (A) and tyramine. In the treatment of PD, selective inhibitors of MAO-B, like selegiline, rasagiline and safinamide, are employed. Those agents are able to inhibit the metabolism of DA [5].

Selegiline and rasagiline irreversibly bind with the active site of MAO-B, hence, regeneration of the enzymes is not

possible and *de novo* synthesis is required. Thus, after the end of treatment with selegiline or rasagiline, several days or weeks must pass before a therapeutic effect is obtained. Conversely, safinamide is a reversible inhibitor of MAO-B and recovery of this enzyme is rapid. Additionally, safinamide binds to voltage-sensitive sodium channels (VSSC) and voltage-sensitive calcium channels (VSCC). As a result, these channels are inhibited [5].

Inhibition of DA metabolism leads to decreased motor symptoms if the employed drugs are used in monotherapy, e.g. selegiline and rasagiline. However, safinamide can be combined with L-DOPA. Safinamide, a third-generation MAO-B inhibitor with reversibility and high selectivity, was approved in 2017 as an adjunctive therapy to L-DOPA for PD patients, especially those demonstrating "wearing-off" episodes. L-DOPA administration can cause many complications, particularly motor fluctuations and dyskinesia (such as LID), after chronic or long-term use. The drug combination of L-DOPA and safinamide allows for reduced daily doses of L-DOPA and minimizes the time spent in the off phase in patients with motor fluctuations [5].

Adverse effects of MAO-B inhibitors are the result of enhancement of dopaminergic transmission in CNS and PNS. Among the three described MOA-B inhibitors, selegiline is the least safe. The safety profile of selegiline is influenced by the fact that selegiline metabolites are compounds based on the structure typical of amphetamine. For this reason, side effects of selegiline include psychiatric effects (delirium, hallucinations, agitation), neurological effects and cardiovascular effects (orthostatic hypotension, hypertension, atrial fibrillation and various types of arrhythmias). Rasagiline has fewer adverse effects, including asthenia, nausea, arthralgia, back pain and headache. Safinamide, due to its high selectivity, is the safest agent among MAO-B inhibitors. The safety profile of this drug is very good. Indeed, frequency of side effects is similar to placebo, however, gastro-intestinal effects, fever and hypotension may occur while using safinamide [5].

### COMT INHIBITORS

COMT is another compound that metabolizes DA. This enzyme also takes part in the metabolism of L-DOPA to 3-O-methyldopa in the liver. Hence, COMT inhibitors are used as adjuvant therapy in combination with L-DOPA. The result is similar to the use of MAO-B inhibitors – reduced daily dose and greater bioavailability of L-DOPA. In addition, they can prolong ON-time. Currently, three COMT Inhibitors are used in the treatment of PD: tolcapone, entacapone and opicapone [6].

### THE SAFETY PROFILE OF INDIVIDUAL DRUGS IN THIS GROUP IS AS FOLLOWS

Tolcapone is the most effective in this group, but has the worst safety profile. Use of this drug leads to damage of the liver. Therefore, it is employed predominantly if the remaining agents have no effect or the patient can not tolerate entacapone or opicapone. The risk of hepatotoxicity is not associated with the use of entacapone. However, entacapone may cause dyskinesia. Moreover, entacapone requires multiple dosing because of low bioavailability and short time of action. Opicapone is the newest agent and is long-active. It is a selective peripherally COMT inhibitor. This medication is the safest among the group. However, similarly to etacapone, the main adverse effect of opicapone is dyskinesia [6].

## DA receptor agonists

DA receptor agonists have no influence on DA concentration, but they directly stimulate brain DA receptors in the postsynaptic membrane and thus they enable the afflicted to better endure the motor complications caused by L-DOPA. Therefore, these drugs are used in combined therapy with L-DOPA, but they are also employed in the monotherapy of PD [7].

There are five types of DA receptors in the brain: D1-D5, which are divided into two groups: D1-like receptors (D1, D5) and D2-like receptors (D2, D3, D4) [8]. DA receptor agonists are divided into ergot and non-ergot derivatives. Ergot derivatives include pergolide and bromocriptine. The non-ergot derivatives include ropinirole, piribedil, rotigotine, pramipexole, apomorphine and sumanirole [7].

Some of these drugs also have affinity to other receptors, such as the adrenergic (α) receptors. These include pergolide, bromocriptine and the serotonergic (5-HT) receptors, e.g. apomorphine, rotigotine and especially pramipexole – which has affinity to the $5\text{-HT}_{1A}$ receptor and has an antidepressant effect [9,10].

Unfortunately, these medications have many adverse effects, predominantly pergolide, ropinirole, piribedil and bromocriptine. The side effects include somnolence, hallucination, dyskinesia, nausea, dizziness and constipation. Moreover, the great affinity for D2 and D3 dopaminergic receptors of some these drugs may cause impulse control disorders. Additionally, piribedil has anticholinergic properties, thereby it can cause the typical anticholinergic side effects that are discussed in a further part of the article [7].

When it comes to use in treating PD, among the DA receptor agonists, apomorphine has the greatest significance. This is due to its efficiency being similar to L-DOPA. Apomorphine has affinity to the dopaminergic D2 receptor and in contrast to other DA receptor agonist, it also has affinity to the D1 receptor. Hence, the mechanism of action is more like that of DA or L-DOPA. Despite apomorphine being derived from morphine, it has no affinity for the opioid receptors [9]. The bioavailability of apomorphine is very low – below 4%. This is because of this agent's first-pass hepatic metabolism. Hence, apomorphine is administrated by subcutaneous injections or infusions, for example, by continuous subcutaneous apomorphine infusion (CSAI) [9]. The side effects of Apomorphine administration include somnolence, hypotension and vomiting, therefore, at the beginning of apomorphine treatment, it may be combined with a novel antiemetic that prevents nausea and vomiting in humans. Apomorphine also has sedative effects and is used in patients with various psychiatric conditions, like mania, hysteria and dementia [9].

## CONTINUOUS DOPAMINERGIC STIMULATION (CDS)

Continuous dopaminergic stimulation (CDS) is a concept that is based on constant drug delivery and continuous stimulation of the striatal DA receptor. In CDS therapy, the positive effects of the drug intake are almost immediate. Additionally, CDS has the potential to prevent or reduce drug-induced dyskinesias, like LID [2].

LCIG, CSAI and rotigotine are supplied to the afflicted via the transdermal route in the form of a patch and an extended-release patch. This form of dosage provides slow and constant administration of the medicine within a 24 hour period [10].

A non-pharmacological form of CDS therapy is deep-brain stimulation (DBS). DBS is a surgical treatment that is performed when motor fluctuations and dyskinesias are too troublesome for the patient. DBS involves the surgical implantation of electrodes that stimulate subcortical structures. DBS is effective in treating various types of PD associated pain symptoms. It is effective against dystonic pain, peripheral and central neuropathic pain and musculoskeletal pain. DBS therapy has demonstrated improvement of the quality of the patient's life. Additionally, DBS reduces the dosage amount of pharmacotherapy, e.g. L-DOPA – by about 60%. The main side effects include intracranial bleeding, cognitive and neuropsychiatric adverse effects, speech dysfunction and device-related complications, like infections. The mortality of this surgery is low – less than 0,5% [1,2,9,11].

## ANTICHOLINERGICTHERAPY–ANTICHOLINERGIC AGENTS

The second form of disturbed transmission in PD is cholinergic transmission. In such cases, the level of ACh in patients with PD is too high and it induces many side effects, e.g. non-motor symptoms like tremor. Anticholinergic agents, as the name suggests, reduce excessive activity of the cholinergic system and restore the physiological level of ACh in the CNS [12].

The mechanism of action of anticholinergic drugs is mainly through the blocking of cholinergic muscarinic receptors (M), because such drugs are competitive antagonists of M receptors. Antagonism of the cholinergic system brings about a restoration of balance between levels of ACh and DA, and automatically reduces the effects of cholinergic neurotransmission in the CNS and PNS. However, blockade of the cholinergic system is unfortunately burdened with a large number of side effects. Central side effects may include headache, impaired memory, reduced cognitive function, behavioural disturbances, anxiety and insomnia at low dosages. At high dosage, observed side effects include signs of agitation, confusion, delirium and seizures [12]. Peripheral side effects result from excessive blockade of peripheral receptors, which are located in various organs. These effects include hyperthermia, anhidrosis (inhibition of sweating), tachycardia, flushing, arrhythmias, urinary retention, reduction of salvia and tear production, sicca symptoms, reduced peristalsis, constipation, vomiting, diminished muscle contraction, blurred vision, mydriasis and narrow-angle glaucoma [7,12]. Therefore, the use of anticholinergic drugs requires caution, especially with regard to elderly patients. The geriatric population is more exposed to the ill-effects of these drugs because of increased permeability of the BBB and diminished transmission of ACh within the CNS [12].

Currently, there are several anticholinergic drugs used in the treatment of PD: benztropine, biperiden, trihexyphenidyl and procyclidyne. All of the mentioned are used in treatment of PD and extrapyramidal symptoms, which include drug-induced Parkinsonism.

Trihexyphenidyl is a non-selective anticholinergic agent. It binds with higher affinity to the central M receptors, and has a wide therapeutic window, so has low risk of overdosing. However, this drug is rarely used. Biperiden is a weak peripheral anticholinergic drug. In addition, it has nicotinolytic activity. Parenteral forms of biperiden are used in treatment of acute episodes of extrapyramidal disturbances. Procyclidyne has the lowest $LD_{50}$ (lethal dose) among those four drugs and binds to protein (albumin) at 100%, therefore, it has high risk of overdosing. Benztropine also has also antihistaminic effects and has very large sedative effects. Its main mechanism of action is through selective inhibition of DA transporters [10].

## AMANATADINE

Originally, amantadine was approved as an agent against influenza A. Amantadine interferes with the release of infectious viral nucleic acid into the host cell through interaction with the transmembrane domain of the M2 protein of the virus. Currently, it is also used to treat PD. In the context of treatment of PD, the mechanism of action of amantadine is connected with both the dopaminergic and non-dopaminergic systems. Amantadine administration increases presynaptically DA release and inhibits DA reuptake. This antiviral drug also has affinity to the glutaminergic receptors and is an antagonist of the N-methyl-D-aspartate (NMDA) receptor. At therapeutic concentrations, amantadine inhibits the release of ACh via the NMDA receptors and thus exhibits anticholinergic activity. Due this mechanism of action, amantadine alleviates bradykinesia, dyskinesia, rigidity and tremor in patients with PD. Potential mild side effects of amantadine include agranulocytosis, seizures and myocarditis. Common neurological side effects of amantadine are connected with its influence on the CNS and may include drowsiness, light headedness, dizziness and confusion. For this reason, amantadine should not be combined with other central stimulus or anticholinergic drugs [13].

## ADENOSINE $A_{2A}$ ANTAGONISTS

Isstradefylline is a drug that does not belong to any of the previously mentioned treatment strategies. It is first-in-class and is actually the only agent in this group. The mechanism of action is through inhibiting adenosine receptors type $A_{2A}$. These receptors are located in the basal ganglia – a region of brain that is highly involved in motor control [8,10].

Istradefylline is used in an adjunctive therapy to L-DOPA and carbidopa [10]. Nowadays, clinical trials of new antagonist of adenosine $A_{2A}$ receptors are ongoing. Three new drugs have been studied: preladenant (SCH420814), tozadenant (SYN115) and vipadenant (BIIB-014) [10,14]. Current pharmacotherapy of PD is presented in Table 1.

***Table 1.*** Current PD pharmacotherapy

| Mechanism/drug type | | Current pharmacotherapy |
|---|---|---|
| Dopaminergic Treatment | Metabolic precursor of DA | L-DOPA |
| | AADC Inhibitors | Carbidopa<br>Benserazide |
| | MAO-B Inhibitors | Selegiline<br>Rasagiline<br>Safinamide |
| | COMT Inhibitors | Tolcapone<br>Entacapone<br>Opicapone |
| | DA receptors agonists | ergot:<br>Pergolide<br>Bromocriptine<br><br>non-ergot:<br>Ropinirole<br>Piribedil<br>Rotigotine<br>Pramipexole<br>Apomorphine<br>Sumanirole |
| Anticholinergic Treatment | Anticholinergic medicines | Benztropine<br>Biperiden<br>Trihexyphenidyl<br>Procyclidyne |
| Other strategies | Antiviral medicines with influence on DA concentration | Amantadine |
| | Adenosine A2A antagonists | Istradefylline |

## FUTURE TREATMENT OF PD

The goal of every treatment is to cure the disease and guarantee a high standard of life. Hence, new drugs are being searched for, created and studied continuously. However, only some medications pass the clinical trials. Nowadays, various new strategies are being advanced. One is α-syn aggregation manipulation. A drug that meets this criterion is prasinezumab (PRX002) [11,14]. This agent is presently in phase II of clinical trials (NCT04777331, NCT03100149 – ClinicalTrials.gov Identifier) [14]. Prasinezumab is a humanised monoclonal antibody targeting the C terminus of the aggregated α-syn, therefore it reduces the level of α-syn in the serum [11]. If clinical trials are successful, prasinezumab will be used in treatment of early PD [14].

Another approach to new PD pharmacotherapy is repurposing already existing drugs [11]. Some medications used in treatment of diabetes mellitus demonstrate potential use in treating PD, for example, analogues of the glucagon-like peptide-1 (GLP-1). These agents are agonists and activators of the GLP-1 receptor. The first of these drugs to have been evaluated is exenatide. It conveys neuroprotective effects in cell and animal models of nigral degeneration. Currently, exenatide is still under research (NCT04305002) [11]. Other analogues of GLP-1 have been subject to study as well, e.g. semaglutide (NCT03659682), lixisenatide (NCT03439943) and liraglutide (NCT02953665) [14].

In recent years, a relationship between impairment of insulin signalling and higher risk of AD and PD has been noted. Insulin is a peptide hormone that is synthesized and secreted by the pancreas. It may also be synthesized in the brain. Insulin crosses the BBB and binds to the insulin receptor (IR), therefore it activates insulin receptor substrate-1 (IRS-1). In CNS, insulin is involved in learning and memory processes. Insulin treatment has positive effects on the development and growth of the nervous system, and it can normalize the production and functionality of DA. In an animal model (rats), insulin treatment has been found to alleviate motor impairment [15]. Hence, the efficiency of intranasal insulin in the treatment of PD is under evaluation (NCT04687878, NCT04251585) [14].

A further pharmacological approach to treating PD is to tweak currently existing strategies, e.g. dopaminergic strategy, specifically, agonists of the DA receptor. The majority of the presently available drugs activate only the D2-like receptors. In the human brain, there are two types of dopaminergic pathways: direct and indirect. D1-like receptors activate the direct pathway and D2-like receptors activate the indirect pathway. In PD, the result of decreased amounts of DA neurons is reduced activity of the direct pathway and overactivity of the indirect pathway, which leads to motor symptoms [5]. Because of this, the D1 receptor has become the target of PD treatment. Therefore, new D1 agonists are being created, e.g. D1/D2 agonist (Lu AE04621 NCT02649608, phase I), D1 partial modulators (PF-06669571 NCT02565628, phase I), D1/D5 agonist (Tavapadon (PF-06649751), NCT04760769, phase III), D1/D5 partial agonist (PF-06412562 NCT03665454 phase I), D1 PAM (positive allosteric modulators) (LY3154207 NCT03305809, phase II).

D2-like receptor agonists are also the subjects of pharmacotherapy research and trials in the treatment of PD, for example, the D2 agonist (KDT-3594, NCT04867551, phase II), D2 specific agonist (CLR4001, NCT01684475, phase II), D3 agonist (Mesdopetam (IRL790) NCT03368170, phase II) and D2 partial agonist, like Sarizotan, which also has affinity to the $5\text{-HT}_{1A}$ receptors (NCT00105508, phase III) [8,10,14].

Moreover, certain MAO-B inhibitors are being re-investigated for PD pharmacotherapy. Zonisamide (NCT04182399) is an anticonvulsant drug that is used in the treatment of partial seizures, and its mechanism of action is similar to safinamide. Like safinamide, zonisamide inhibits VSSC, VSCC and MAO-B. Indeed, it is a multi-active MAO-B inhibitor [5,10,14].

Other interesting clinical trials involve research into potential use of *Ganoderma lingzhi*, known as Reishi mushroom (NCT03594656) or Onabotulinumtoxin A (Botox) which may be used in treatment of rest tremor (NCT03301272) [14].

The described agents are only a few of the possible new drugs being investigated for application in the pharmacotherapy of PD. Such intensive work gives huge hope that the amount of agents for PD treatment will increase in the future and treatment will be easier.

Agents for possible future pharmacotherapy of PD are presented in Table 2.

***Table 2.*** Potential PD pharmacotherapy

| Mechanism/drug type | | Potential pharmacotherapy |
|---|---|---|
| Development of existing strategies | Multi-active MAO-B Inhibitor | Zonisamide |
| | Adenosine A2A antagonists | Preladenant<br>Tozadenant<br>Vipadenant |
| | DA receptors agonists | Lu AE04621<br>PF-06669571<br>Tavapadon<br>LY3154207<br>KDT-3594<br>CLR4001<br>Mesdopetam<br>Sarizotan |
| New strategies | Manipulation of α-syn aggregation | Prasinezumab |
| | Analogues of GLP-1 | Exenatide<br>Semaglutide<br>Lixisenatide<br>Liraglutide |
| | Insulin treatment | Intranasal insulin |
| Other | | Ganoderma lingzhi<br>Onabotulinumtoxin A |

## CONCLUSION

The treatment of PD is difficult, and the drugs used currently in its pharmacotherapy can generate tolerance and various ill side effects. The aim of PD therapy is to reduce symptoms (mainly motor symptoms) with the simultaneous maintenance or restoration of patient's comfort of life. The most important drug applied in treating PD is still L-DOPA, and this is the gold standard. However, long-term use of L-DOPA leads to LID, fluctuations and lowered efficiency. Since 1817, when PD was described for first time, the amount of applicable agents and therapies applied in treating PD has risen and new strategies like CDS have appeared. Still, better treatments and agents need to be found. Fortunately, new trials are on-going and offer hope to the afflicted.

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