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RESEARCH ARTICLE

Parkinson's Disease, Therapy with Drugs and Nanotechnology

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ABSTRACT

Parkinson's disease (PD) is a disorder that destroys neurons in the extrapyramidal dopaminergic pathway in the brain. In the world, the number of patients with PD is 10 million now and PD is a disease whose incidence increases with age. In particular, genetic and environmental factors are believed to cause PD. Rigidity in striated muscles, characteristic tremors and posture disorder are specified as main clinical symptoms of PD. Although radical treatment of PD is not possible today, some drugs that slow the progression of it and effective on its symptoms are used successfully in the clinic. Among them, the essential drug is levodopa. However, an important disadvantage in the drug treatment of PD is that the beneficial effects of the drugs decrease over time in long-term use. Moreover, the use of them is associated with serious side effects. Therefore, it is important to develop new treatment strategies in the treatment of PD. When a great effort continues to discover new drugs having different action mechanisms, it is expected that developed nanotechnology-based drugs for PD therapy become important, additionally.

Contents

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1. Introduction

With Parkinson's disease (PD) is the second most common neurodegenerative disease in the world [1], and destroys neurons in the extrapyramidal dopaminergic pathway in the nigrostriatal region of the basal ganglia in the brain [2]. It was first described clinically by James Parkinson, and the most important symptoms seen in patients with PD are tremor and stiffness in muscles, bradykinesia and loss of balance[3] . PD is characterized by the presence of Lewy bodies in the midbrain and the loss of activity of dopaminergic neurons, especially in the substantia nigra[2] .

It may take many years for the identified neuromotor symptoms of PD to appear so the onset of PD may indicate a long prodromal period. In patients with prodromal period of PD, the most common symptoms are constipation, loss or decrease in sense of smell, and REM (Rapid eye movement) sleep disorder, which are not related to motor movements[4] . However, it has been reported that patients with PD also show non-motor symptoms which is the most important one is pain. And the underlying mechanism of pain is not understood. Some studies have shown evidence that it is related to motor symptoms [5, 6].

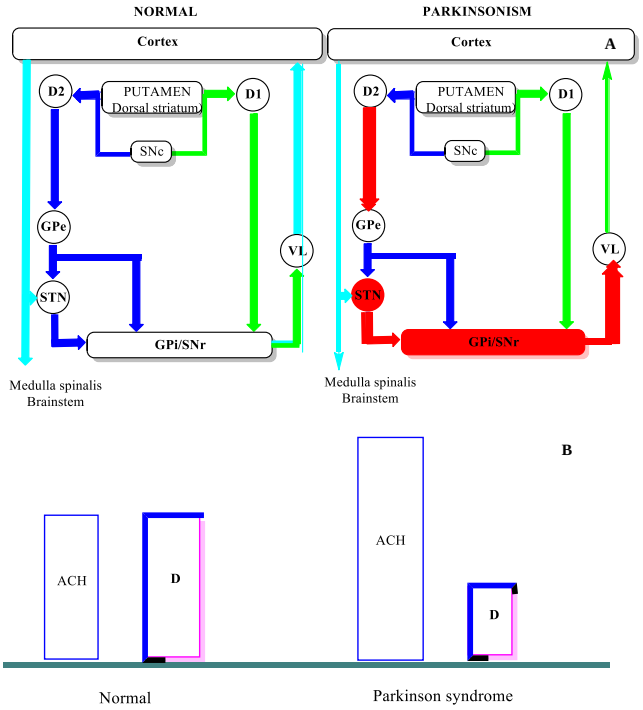
PD is generally known as a progressive neurodegenerative disorder that is seen 2 to 3% of the global population aged >65 years and older and much less frequently in young people. PD prevalence is estimated to rise double in 2030[2] . The incidence of PD varies between 40 and 1900 cases per 100000 and the possibility of its incidence increases with age. Even though the onset of PD symptoms is between 60 and 70 years, the incidence peak of the disease is in the 70-79 age range. Men are more affected by PD than women [7]. However, limited data are available on patients with advanced PD prevalence. According to some epidemiological studies, it has been determined that approximately 10% of all PD patients have an advanced PD prevalence [8] . PD creates a huge burden on the population and economy all over the world and this situation is expected to worsen in the future. Today, there is estimated seven to ten million PD patients around the world [1]. The number of patients with PD in Turkey is approximately 150000 [2].

2. Causes of PD

PD are believed to be related to exposure to environmental toxins and the normal aging process. Familial history is an important risk factor. However, the exposure environment may be a more determining factor than genetic predisposition [9] .

The most important pathological distinguishing features of PD in the brain are the specific loss of dopaminergic (DA) neurons in the substantia nigra pars compacta and the identification of intracellular inclusions called Lewy bodies in surviving DA neurons [10]. Damage or any loss of DA neurons causes motor symptoms such as tremor, rigidity, postural instability, joint, and muscle stiffness and bradykinesia [11].

One of the symptoms of PD, tremors occur in the fingers, hands, and arms in about 60% of patients at rest and sometimes when standing, and 30% of patients have slowed movements and limb movements. A dull expression may sometimes occur on a patient's face. Especially in young patients, the first symptom of PD is dystonia, an involuntary contraction of an inward-facing foot or a downward curvature of the toes. In almost all patients, symptoms occur in one half of the body, and over time, it indicates itself in the opposite body half, becoming lighter. PD usually begins insidiously and its symptoms progress extremely slowly but gradually over the years, so PD patients often cannot pinpoint the date of onset of the disease. What should be emphasized here is that PD is the only disease that responds well to medications and surgical treatments among the diseases that develop as a result of cell loss process in the brain [1].



ACH: Acetylcholine
D: Dopamine

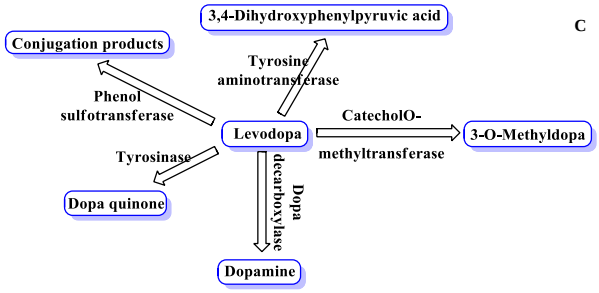


Figure 1 Activity status of basal ganglia-thalamus-cortex connections in normal condition and in PD (A). Comparison of acetylcholine and dopamine levels in individuals with normal and PD syndrome (B). The metabolic pathways of levodopa (C).

The majority of affected individuals have idiopathic PD, possibly caused by the interaction of environmental and genetic susceptibility factors. However, a direct genetic predisposition can be determined in 5-10% of patients. According to the findings obtained from genome studies, it was determined that there are 26 gene loci associated with

the possibility of PD [12]. Mutations in genes (SNCA, LRRK2, EIF4G1, VPS35, PRKN, DJ1, PINK1, and ATP13A2) in 8 of these loci have been shown to cause familial PD [13]. In addition to these genes, variations in SNCA (α-Synuclein), MAPT (Microtubule Associated Protein Tau) and LRRK2 (Leucine-Rich Repeat Kinase 2) genes have also been found to create a risk for PD. Normally, when the activity in the direct and indirect pathways is in balance, as a result of degeneration in the nigrostriatal pathways (the pathways from SNc to putaman), the activity in the direct pathway decreases and the indirect pathway increases. As shown in Figure 1, the clear effect of this change is the increase in suppressive signals from the basal ganglia to the thalamus [14].

The genetics of PD have been extensively studied in the last 20 years[2]. A recent genome-wide association study (GWAS) identified 90 independent risk variants that account for less than 50% of the inheritance of PD. In addition, this study suggest that other, unknown, common and rare genetic variants affect PD risk. A novel p.Y314S variant encoding the ubiquinol-cytochrome c reductase core protein (UQCRC1) in UQCRC1 was recently identified in 5 Taiwanese family members with Parkinsonism by complete exome sequencing [15]. UQCRC1 is part of a mitochondrial protein and respiratory chain III complex that may play a role in mitochondrial respiration [15–17].

There are several toxins associated with PD risk. Among these toxins, heavy metals, especially pesticides, and compounds that have a stimulating effect on the central nervous system (CNS) can be counted. Toxic metal ions such as mercury and manganese, organophosphates, organochlorines, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), Rotenone, Agent Orange (2,4,5-trichlorophenoxyacetic acid) cause PD [18]. MPP^+ (1-methyl-4-phenylpyridinium), the MPTP metabolite formed by the effect of monoamine oxidase B enzyme (MAO B), kills dopaminergic nerve cells and causes nigrostriatal degeneration and PD [19]. This reaction is shown in Figure 2. Additionally, there are data that acetic acid also cause PD [18].

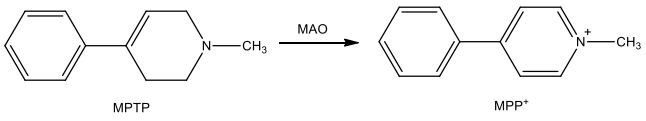


Figure 2 Conversion of MPTP to toxic metabolite MPP^+ *via* MAO B enzyme.

The corpus striatum where acetylcholine and dopamine that play the role in impulse transcension at synapses are stored controls the normal tone and contraction of the striated muscles. As shown in Figure 1.A and Figure 1.B, thes e neuromediators have opposite effects on neurons in the striatum and dopamine provides inhibition of striatal neurons, while acetylcholine provides excitation. Investigations revealed that the amount of dopamine in the corpus striatum is severely reduced, so the balance between cholinergic and dopaminergic systems is disrupted in favor of the cholinergic system in PD patients. The dopamine level in the striatum must decrease by more than 80% for the symptoms of the disease to appear. Two mechanisms are effective in the pre-clinical phase of PD: the first is a presynaptic mechanism and occurs as a result of a 30% decrease in dopamine level so dopamine metabolisation and homovanilic acid / dopamine ratio increases in dopaminergic nerve endings. The second mechanism is effective when the dopamine level decreases over 80% in this way, there is an increase in the frequency of postsynaptic dopamine receptors in the striatum. Eventually, sensitivity to dopamine develops in the postsynaptic membrane [20].

3. Symptoms of PD

Loss of dopamine neurotransmission primarily causes the loss of fine motor control, especially when the muscles are at rest. The main symptoms of PD are:

- Rigidity in striated muscles,
- Characteristic tremors that occur at rest,
- Posture disorder.

The external view of the individual with PD are shown in Figure 3. Muscle stiffness slows down movement as the disease progresses (bradykinesia) and can lead to balance and coordination difficulties. Additionally, perception and mood disorders may also occur [20].

Figure 3 External appearance of a patient with PD.

4. Therapy

Radical therapy for PD is not possible, today. Current PD therapy focuses on relieving the severe motor symptoms of the disease, and no approved therapy can slow the progression of the disease. Another important point in the treatment of PD is to start the treatment as early as possible [8] .

Dopamine receptors found in the human body are G-protein linked receptors. D1 and D2 receptors are expressed in different regions of the brain. D1 receptors are expressed in the striatum, nucleus, olfactory tubercle, cerebral cortex, amygdala, and subthalamic nucleus, while D2 receptors are mainly expressed in the striatum, nucleus accumbens,

olfactory tubercle and additionally in the substantia nigra pars compacta and ventral tegmental area. These receptors likely act as autoreceptors. On the other hand, D3 receptors are localized in the forebrain limbic areas and their expressions are low in the striatum [9, 21].

Most pharmacotherapies focus on dopamine D1 (D1R) and D2 (D2R) type receptors in the striatum. The stimuli on the dopamine D3 receptor (D3R) play an important role during the origin and development of PD [22, 23]. The effectiveness of dopamine agonist drugs used in treatment of PD depends on the activation of postsynaptic D2R receptors. The simultaneously activation of postsynaptic D1R receptors enhances the activity through D2R receptors. D3R, on the other hand, can both provide a biomarker for early stage pathological changes and set a target for the development of new therapeutics [23].

Until the late 1970s, dopamine receptors were considered to belong to two pharmacological families [24]. It has been determined that there are five different genes encoding dopamine receptors (D1-D5) involved in mammalian metabolism, each with a different expression pattern. Dopamine D1 and D5 receptors which are linked to the stimulation of adenylate cyclase and having high affinity for the SCH23390 gene are often referred to as "D1-like" receptors. On the other hand, the D2, D3 and D4 receptors are referred to as "D2-like" receptors and show preference for butyrophenone (e.g. spiperone) and benzamide (e.g. sulpyrid) ligands. These are associated with many different signaling systems including inhibition of adenylate cyclase, opening of K^+ ion channels, and effects on Na^+ ion currents [25–27].

5. Drugs Used for PD

Drugs used to treat PD can be classified as follows:

- Dopamine replacement therapy
- MAO inhibitors
- Catechol-O-methyl transferase (COMT) inhibitors
- Dopamine receptor agonists
- Adenosine A2A receptor ($A_{2A}R$) antagonists
- Antimuscarinic and antihistaminic adjunctive therapy [9] .

6. Dopamine Replacement Therapy

As shown in Figure 4, dopamine is a neuromediator that is endogenously synthesized in the body from tyrosine. It is not possible to treat PD with dopamine directly, because dopamine cannot cross the blood brain barrier. Therefore, PD treatment is required by using dopamine precursor that can cross the blood brain barrier. The dopamine precursor used to increase the insufficient dopamine level in the treatment of PD is levodopa that can cross the blood brain barrier.

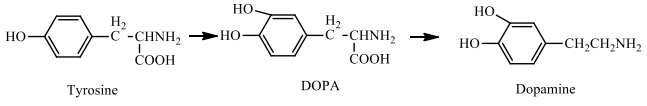


Figure 4 Formation of dopamine from tyrosine in the body.

The metabolic pathways of levodopa are given in Figure 1.C. With the rapid onset of levodopa therapy, an increase in survival has been shown as well as relief of symptoms [28]. Optimal treatment requires constant dopamine levels equivalent to the physiological one [29]. However, progression of PD requires gradual increases in levodopa dosage for adequate motor control, leading to the development of motor complications such as motor fluctuations and dyskinesia [1]. As shown in Figure 5, levodopa is converted to dopamine by dopa decarboxylase enzyme.

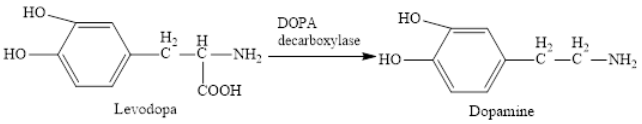


Figure 5 Conversion of levodopa to dopamine by decarboxylation in the CNS.

Approximately 90% of orally taken levodopa is converted into dopamine with 9% of the serum and peripheral dopamine able to pass into the CNS. With combined use of the dopa decarboxylase inhibitors, carbidopa or benserazide as shown in Figure 6, the passing of levodopa to the CNS can be increased up to 10%. Levodopa, as an amino acid, crosses the blood-brain barrier by active transport. It is well absorbed after oral administration and its bioavailability is between 70-75% in rapid release formulations then, is excreted in the urine as homovalinic acid and dihydroxyphenyl acetic acid 8 hours later [28].

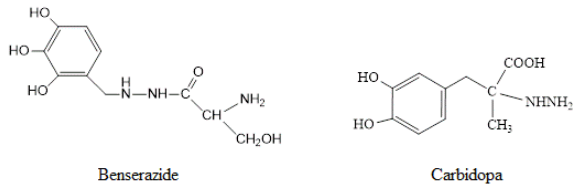


Figure 6 The chemical structures of dopa decarboxylase inhibitors used in PD.

7. MAO Inhibitors

MAO is an external mitochondrial membrane enzyme that catalyzes the oxidative deamination of neurotransmitters. There are two isoforms of this enzyme in the human brain, MAO A and MAO B. Of these, MAO A deaminates serotonin and norepinephrine, while MAO B deaminates phenylethylamine and benzylamine [30, 31], so MAO B is an isoform involved in dopamine metabolism. Selegiline and rasagiline are the selective MAO B inhibitors used in PD therapy and their chemical structures are shown in Figure 7. Nonselective MAO inhibitors (Phenelzine, tranylcypromine) are not used in PD treatment, as they can cause hypertensive crisis when administered with levodopa. Selegiline and rasagiline contain a N-propargylamine group that is the structural component for inhibiting MAO B enzyme. This functional group binds to the structure of MAO B covalently, causing irreversible inhibition of the enzyme. For PD treatment, acidic salts of selegiline and rasagiline can be administered orally are used. Selegiline is also formulated as a 24-hour transdermal patch in free base form. Some side effects may occur with the use of these drugs such as hypertension, some reactions in application site (selegiline

transdermal patch) and suicidal ideation (selegiline) in young adults [9, 32].

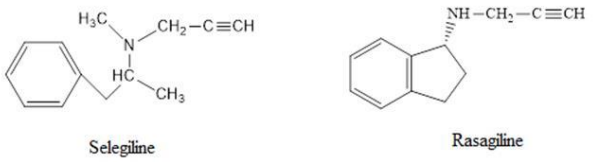


Figure 7 The chemical formulas of selective MAO B inhibitors used in PD.

8. COMT Inhibitors

In mammals, the COMT gene exists in two different forms, membrane-bound and soluble, generally situated in the brain and other organs. The COMT gene polymorphism found in humans has been showed to occur through methylation of the amino acid residue rs4680 (Val180Met in soluble COMT form). A break occurs in this section, and the isoform formed as a result of the polymorphism is less stable. It was determined that Val/Val homozygotes in the COMT enzyme structure had 38% higher activity than Met/Met homozygotes [33–36]. Furthermore, a COMT homologue named TOMT or COMT2 has been identified and purified in human and rodent species. This enzyme found in the inner ear of mice has been determined to methylate noradrenaline [37]. Dopamine is metabolized by methylation mediated by the COMT enzyme in the prefrontal cortex of the brain. Val108Met polymorphism has been evaluated as an important risk factor causing psychiatric disorders, especially schizophrenia, and many studies have been conducted on it. Although no definitive evidence can be obtained as a result of these studies, it has been determined that it is effective on some behaviors, including estrogen [38]. Another important function of COMT is related to the pain process in the nervous system. Additionally, COMT has been determined to play a major role in the regulation of natriuresis in kidney tissue [39, 40].

COMT enzyme has been found in higher levels in all tissues, human liver, brain, kidneys, adrenals and lungs. After COMT enzyme has been purifying and characterizing from different sources, several classes of COMT inhibitors have been identified and many of them contain catechol or some related bioisosteric structures such as gallic acid, caffeic acid, 2-hydroxyestrogens U-0521, quercetin and rutin. Additionally, various other non-catecholic compounds such as ascorbic acid, tropolons, 8-hydroxyquinoline derivatives, and 3-hydroxylated pyrons and pyridones have been identified as COMT inhibitors [36, 40, 41].

Potent and selective COMT inhibitors was discovered in the late 1980s. These compounds obtained by the addition of the nitro group in catechol structure are called as second generation inhibitors. The most used scaffold is 3,5-dinitrocatechol. Although it showed potent COMT inhibitory activity *in vitro*, its use as a drug was limited due to toxicity concerns *in vivo*. Studies have shown that by modifying this structure, compounds with low toxicity can be obtained [42–45]. This class of inhibitors are characterized as reversible tight-binding inhibitors of COMT [9, 46] and tolcapone, entacapone, opicapone are in this group. Their chemical formulas are shown in Figure 8.

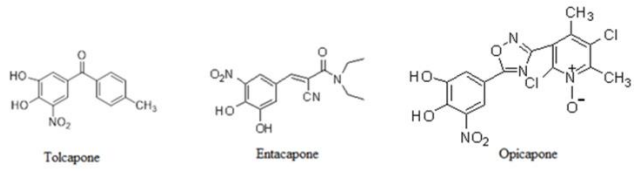


Figure 8 COMT inhibitors used in PD treatment.

Today, entacapone and tolcapone in combination with levodopa and a dopa decarboxylase inhibitor are widely used in the treatment of PD disease [40, 45, 47, 48]. Since tolcapone can cross the blood brain barrier, it inhibits the COMT enzyme both in the CNS and in the periphery, while entacapone is especially effective in the periphery. The catechol core carried by these drugs allows the inhibitor to recognize the enzyme, and the adjacent nitro group is required for inhibition. Different side chains of COMT inhibitors affect the enzyme affinity. These drugs can cause side effects such as diarrhea, postural hypotension, nausea, anorexia, dyskinesia, hallucinations, and sleep disturbances. Furthermore, tolcapone has hepatotoxicity so the liver enzyme levels should be monitored during the treatment [49–51].

Opicapone, the newest third-generation COMT inhibitor, acts reversibly in the periphery. In June 2016, it was first approved by the European Commission for use in the treatment of PD as a potent COMT inhibitor, and then by the U. S. Food and Drug Administration (FDA) in 2020. Opicapone has a long duration of action exceeding 24 hours, so it can be used once-daily. Furthermore, it shows the lowest cytotoxicity risk than the other COMT inhibitors. However, constipation, dry mouth, difficulty falling asleep or staying asleep, dizziness, weight loss, unusual or uncontrolled body movements can be occurred in therapy with opicapone. Moreover, it can cause serious side effects such as hallucinations, delusions, aggressive behavior and fainting.

9. Dopamine Receptor Agonists

These drugs were developed in 1970 to reduce the occurrence, frequency and severity of complications in motor behavior due to long-term PD treatment with levodopa. Bromocriptine is the first dopamine receptor agonist used against complications in motor behaviors of PD clinically [52]. Another dopamine receptor agonist, pergolide has been used in the treatment of advanced PD. Dopamine receptor agonists were recommended as monotherapy in the first-line treatment of PD patients, not only in advanced treatment stages, in later PD treatment. After the studies with newer dopamine receptor agonists such as ropinirole, pramipexole and rotigotine had shown better results in the treatment of PD patients in clinical trials, these drugs were widely used as monotherapy. The theoretical data indicated that the use of dopamine receptor agonists could be used instead of levodopa in the early stages of PD. Moreover, these drugs act directly on dopamine receptors without the need for a carrier and do not generate free radicals or other toxic metabolites in metabolism. And

also, they produce dopamine receptor stimulation with a longer half-life than levodopa [53, 54].

Dopamine receptor agonists commonly used are divided into two main groups:

(a) Ergolines, which are derivatives of ergot alkaloids and include bromocriptine, pergolide, lisuride, alphadihydroergocriptine and cabergoline.

(b) Non-ergolines such as apomorphine, piribedil, ropinirole, pramipexole and rotigotine.

Ergolines are referred to as first generation dopamine receptor agonists. Almost all non-ergolines except apomorphine have been developed recently. Although they have different chemical structures and physical properties, their activity is probably due to their molecular structure similar to dopamine and these drugs can directly stimulate dopamine receptors. Older agents for example bromocriptine, lisuride, pergolide bind with high affinity to dopamine D2 receptors. New agents, on the contrary, are more specific agonists for D2 and D3 receptors and have high affinity [55].

The dopamine agonists used in PD therapy target D2 receptors and need a cationic amine group for interaction. For best compatibility with target receptors, these drugs should have an extended *trans* conformation between the aromatic residue and the cationic amine nitrogen in their structures. They bind to functional receptors in the substantia nigra (black body), replacing endogenous dopamine, which can no longer be produced in disrupted nerve endings [56].

As shown in Figure 9, bromocriptine, partial D2 agonist, is a semi-synthetic ergot alkaloid containing lysergic acid derivative and increases the effect of dopamine released from nerve endings or activates D2 receptors. The bromine atom in its structure makes it possible to show strong affinity for D2 receptors. It is used alone as an alternative to levodopa in cases where it is inconvenient to use it or in patients who do not respond to this drug [57]. Thus, bromocriptine provides motor control of dopaminergic neurons in the extrapyramidal system and regulation of tuber infundibular pituitary prolactin secretion. Increased secretion of prolactin hormone causes disorders and some of the endocrinological effects of bromocriptine cause the suppression of somatotropin hormone secretion, while it increases in healthy individuals, temporarily. Other side effects occurred in treatment with bromocriptine are hypotension, vomiting, nausea, hallucinations and heart rhythm disturbance [58, 59].

Apomorphine, which is a non-ergot dopamine agonist, activates both D1 and D2 receptors. It is used to treat “off” episodes in advanced PD and the chemical formula of apomorphine is shown in Figure 9 [9, 60].

Pramipexole, a non-ergot derivative dopamine receptor agonist, has greater affinity for D3 receptors, which are more concentrated in the mesolimbic area than D2 receptors and its formula is shown in Figure 9. It can be used both as a single drug and in combination with levodopa in PD treatment and is available in tablet and extended release tablet forms. It is metabolized by N-dealkylation, C7 hydroxylation, deamination/oxidation to carboxylic acid, glucuronidation. Studies show that pramipexole is an effective and safe drug in PD treatment in terms of improving motor functions and daily life activities. Treatment with pramipexole may result in some psychotic and hypomanic cases [9, 60, 61]. It is also used in the treatment of depression that occurs in PD, and in the treatment of resistant depression [62, 63].

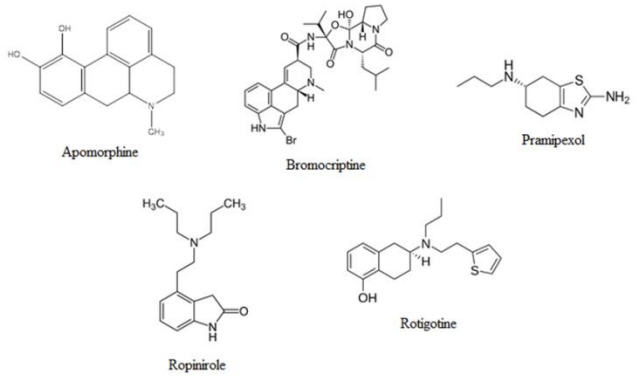


Figure 9 The chemical structures of dopamine receptor agonists.

As shown in Figure 9, ropinirole has high affinity for D2-like receptors (D2, D3, D4), while it has no affinity for benzodiazepine or Gamma-aminobutyric acid (GABA) receptors at D1-like receptors. The high affinity of ropinirole on D3 receptors results in some neuropsychiatric effects. Moreover, the cardiovascular effects caused by ropinirole are explained by the affinity of this drug on α2 adrenoceptors and these effects are blocked *via* domperidone. Although ropinirole has also been found to bind to lactotrophs in the anterior pituitary, its significance in the treatment of PD is minimal [9, 64–66].

Rotigotine, as shown in Figure 9, preferentially binds to D3 receptors [21] however, animal experiments and cell culture studies have shown that it can bind to all dopamine receptors. (D1-D5). This drug is metabolized through N-dealkylation of propyl and conjugation of phenol group by glucuronide and sulfate. Rotigotine is used as a transdermal patch and may cause reactions in the application area [9, 67].

9.1. $A_{2A}R$ Antagonists

$A_{2A}R$ antagonists act through a non-dopaminergic mechanism. In preclinical studies, it has been shown that $A_{2A}R$ antagonists prevent PD-induced neuronal loss. $A_{2A}R$ antagonists in the striatum increase GABA innervation to compensate for dopamine-mediated loss of GABA release. They are used in the treatment of PD in combination with levodopa or dopamine agonist drugs so that motor symptoms are affected and can reverse them. It has been determined that $A_{2A}R$ antagonists improve motor function and even prevent the onset of involuntary movements without causing involuntary movements that can be occurred during PD therapy. This group includes amantadine, originally an antiviral drug and its chemical formula is shown in Figure 10 [68, 69]. In immune reactions involved in mitogen-induced T cell activation, it has been determined that a cytokine interleukin-2 (IL-2) is higher than those treated with amantadine [70, 71]. Long-term treatments with amantadine affect the immunological system in two ways: first lymphocytes and antigen presenting cells and second ensuring long-term protection of the elderly from viral infections. It has been claimed that amantadine has an

inhibitory effect on antigen-presenting cells, and inhibits polyclonal T cell and B cell activation *in vitro*. Some studies showed that amantadine improves the immune system by protecting PD patients against viral infections. Amantadine is available as tablet, capsule, and syrup that can be taken orally. Although treatment with amantadine may cause anticholinergic effects such as blurred vision and arrhythmia, these side effects are rarely seen at recommended doses [72].

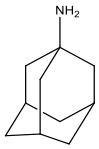


Figure 10 Chemical formula of $A_{2A}R$ antagonist amantadine.

9.2. Antimuscarinic and antihistaminic adjunctive therapy

These drugs increase the effect of levodopa with a synergistic effect in idiopathic PD so they can be used in combination with levodopa. Initially, PD patients with tremor can be treated with antimuscarinic and antihistaminic adjunctive therapy which correct the central cholinergic excess. These drugs contain tertiary or secondary amine whose central effects are stronger than their peripheral effects. With long-term use, tolerance develops to their actions. Due to few side effects, they are the first-line drugs used in initial mild cases. However, anticholinergic side effects such as sedation, blurred vision, urinary retention, constipation, and cardiac arrhythmia limit the therapeutic efficacy of them. According to their chemical structures, these drugs can be classified into two groups: tertiary alcohol, derivatives, as shown in Figure 11, and benzhydryl ethers as shown in Figure 12 [73, 74].

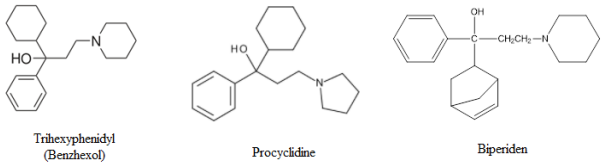


Figure 11 Chemical structures of tertiary alcohol derivatives.

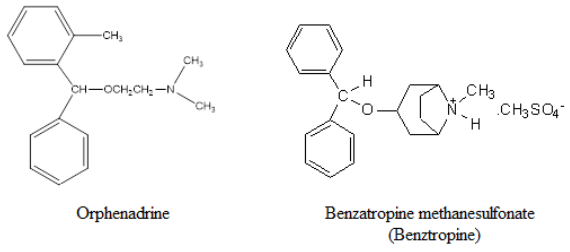


Figure 12 Chemical formulas of benzhydryl ether derivatives.

9.3. Tertiary alcohol derivatives

Trihexyphenidyl (Benzhexol), which competitively inhibits cholinergic transmission at muscarinic receptors, is the most preferred centrally acting anticholinergic drug due to few undesirable effects [73]. It inhibits intrastriatal cholinergic activity, thus improves brain functions and symptoms of PD. This drug may cause some negative mental effects [73, 75, 76].

Procyclidine, a non-selective and competitive inhibitor of cholinergic muscarinic receptors, is the first synthetic centrally acting antimuscarinic drug used in the treatment of PD. Furthermore, it has also N-methyl-D-aspartic acid (NMDA) receptor antagonist properties and can be administered orally, intramuscularly and intravenously. The most important side effect in the use of NMDA antagonists in the treatment of PD patients is the induction of psychomimetic reactions. *In vivo* studies on rats have been found to cause behavioral disorders and pathological damage to cerebrocortical neurons [77, 78]. However, it has been proven that some agents prevent the negative effects caused by NMDA antagonists so they may be used as antidotes [79].

Biperiden has been found to be four times more effective than other drugs known such as atropine or trihexyphenidyl to have antinicotinic effect. It has positive effects on the motor functions in PD patients. Constipation and mydriasis caused by biperiden as side effects were found to be equivalent to those caused by trihexyphenidyl. Moreover, it has also been reported to have side effects related to vision [80, 81].

9.4. Benzhydryl ether derivatives

Orphenadrine, having antihistamine effect also, inhibits dopamine reuptake from the nerve ending, so it is used to ameliorate tremors caused by PD [82].

Benzatropine methanesulfonate (Benztropine) is a drug that competitively inhibits cholinergic excess at muscarinic receptors and the reuptake of dopamine from nerve ending [74].

10. Nanotechnology and Nanomedicine

With the production and characterization of nano-sized atoms, compounds and molecules, it has found wide application in different sciences such as physics, chemistry, biology, computer, electrical - electronics, medicine and pharmacy. In particular, their transforming of bulk form to nano form increased their superior strength, resistance and changed their electrical-optical properties. In addition, their ability to react at nanoscale has increased their usage [83]. Studies have shown that nano-based ones are most effective in drug delivery and release systems. In studies using nano-systems in PD disease, it is aimed that drugs could pass the blood-brain barrier and that could release into the brain depending on time [84–87].

Another factor that promotes the progression of PD is thought to be the SNCA protein that accumulates in the brain cells. Knowing the effective reaction mechanism between nanoparticles (NPs) and SNCA protein will make it possible to fight irregular Lewy bodies (clusters). In some studies, it has been reported that NPs have the ability to inhibit SNCA protein. Another advantage of drug delivery systems with NPs is to reduce toxicity by regulating continuous drug release [88, 89].

We can classify nanoparticle-based drug delivery systems as NPs, nanocapsules and nanospheres. These structures have large surface areas and sizes range from 10 to 1000 nm, so they have a high drug loading capacity. Nano-based polymeric systems and capsules prevent the degradation of drug during transport and thus, ensure the drug to reach its target without any problems. They are stable in nature and can be modified to escape from macrophages [89, 90].

Nanospheres are polymeric structures in which the drug is dispersed and synthesized to contain a core in which the drug is entrapped there. Nanocapsules, on the other hand, contain the drug molecule encapsulated within the lipid surrounded by a polymeric layer. Nanogels are cross-linked polymer networks that usually combine ionic and nonionic polymeric chains and are prepared using an emulsification solvent evaporation approach [91]. Nanogels are capable of swelling in water and can retain deoxyribonucleic acid (DNA), protein, small interfering ribonucleic acid (siRNA) and drugs inside and their drug retaining capacity are between 40% and 60%. Some studies have shown that nanogel systems that allow the drug to cross the blood-brain barrier and reach the brain successfully perform the task of transporting the cross-linked drug. The most important advantages of synthesized nanogels are high drug loading capacity, ease of synthesis, success in penetrating the CNS and applicability to many different drugs [91–95].

Magnetic Fe_3O_4 NPs and Au NPs are the most used nano metals *in vitro* and *in vivo* due to their superior physical and chemical properties. In particular, nanomaterials loaded with drugs are used to improve the damage caused due to their orientation properties. In addition, the most used NPs in PD treatment are 47-50. In a study carried out the 6-hydroxydopamine (6-OHDA) rat model, the neuroprotective ability of magnetic Fe_3O_4 NPs was investigated and it was determined that mitochondrial function and lesion volume increased in control groups compared to the PD group [96, 97].

It was found that Au NPs inhibit SNCA accumulation and fibrillation, additionally increase cell survival in PD lesion cell model [98]. It has been determined that Au nanoclusters defend dopaminergic neurons and decrease the mental problems of model mice with PD. The findings have created a new option to develop anti-PD drugs and show that Au nanoclusters lead a different path in medical applications [99, 100].

Quantum dots (QDs) are zero-dimensional nanostructures that have received considerable attention in the delivery of drugs because of their outstanding electrical and optical properties. New evidence has shown that PD pathogenesis is highly associated with the transmission and accumulation of SNCA protein in the midbrain. So far, no clinical antiaggregation strategy for the treatment of PD has been known [101, 102]. However, more recently, it was shown that graphene at QDs (GQDs) could inhibit SNCA fertilization and GQDs directly interfere with mature fibrils to enable their dispersal. Furthermore, it was determined that GQDs penetrate the blood-brain barrier and protect against the loss of dopamine neurons caused by fibrils, behavioral deficiencies, and Lewy neuritis pathology produced by SNCA *in vivo* [101, 103].

Due to the unique property of cerium oxide (CeO_2) NPs in the field of biology and medicine, it has received great attention in recent years [104]. The specific effects of CeO_2 NPs have recently been indicated in some neurodegenerative syndromes. It was shown that CeO_2 NPs reduce the dose-dependent toxic effects of SNCA and overcome SNCA-induced mitochondrial dysfunction and minimize yeast cell growth of reactive oxygen species (ROS) because SNCA was adsorbed on the surface of CeO_2 NPs. Thus, NPs can be evaluated as a potent SNCA toxicity inhibitor (or as a radical scavenger through a direct SNCA interaction) [105, 106].

11. Conclusion

In conclusion, PD is a progressive neurological condition and causes some problems in patients' brain and their daily life. Although, there is currently no effective neuroprotective therapy that will stop the progression of PD and cure it completely, different pharmacotherapeutic approaches are available for the management of the disease. Early diagnosis and onset of the treatment have important also. Progressive physical and mental difficulties of PD create the most challenging pharmacological treatment process, especially in the later stages. Nanotechnology-based drug delivery systems, which are developing day by day, are promising developments for PD therapy by ensuring that drugs reach the CNS and release them in a controlled and long-term manner.

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Abbreviations

PD : Parkinson's disease
REM : Rapid eye movement
DA : Dopaminergic
SNCA : α-Synuclein
MAPT : Microtubule Associated Protein Tau
LRRK2 : Leucine-Rich Repeat Kinase 2
ACH : Acetylcholine
D : Dopamine
GWAS : Genome-wide association study
UQCRC1 : Ubiquinol-cytochrome c reductase core protein
CNS : Central nervous system
MPTP : 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPP^+ : 1-methyl-4-phenylpyridinium
MAO : Monoamine oxidase enzyme
D1R : Dopamine D1 receptor
D2R : Dopamin D2 receptor
D3R : Dopamin D3 receptor
COMT : Catechol-O-methyl transferase

$A_{2A}R$: Adenosine A2A receptor
FDA : U. S. Food and Drug Administration
GABA : Gamma-aminobutyric acid
NMDA : N-methyl-D-aspartic acid
NP : Nanoparticle
DNA : Deoxyribonucleic acid
siRNA : Small interfering ribonucleic acid
6-OHDA : 6-hydroxydopamine
QDs : Quantum dots
GQDs : Graphene at QDs
ROS : Reactive oxygen species

Declaration of Conflict of Interest

Authors declare that they have no conflict of interest with any person, institution, or company.

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