A comprehensive review on management of Parkinson’s disease, inclusive of drug discovery and pharmacological approaches

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ABSTRACT
Parkinson’s disease (PD) is the second most prevailing neurodegenerative disorder and is indicated by the degeneration of dopaminergic neurons within the substantia nigra; various categories of drugs aim to ensure the controlling of motor symptoms; nonetheless, the same will contribute to multiple side effects. This review dispatches a synopsis about physiopathology, clinical features, and etiology of PD and demonstrates the most common drug classes currently used in the management of PD as well as future treatment strategies. This review highlights the miscellaneous aims, targets, and drugs concerted during the years, for the management of PD. This assessment targets predominantly most of the drugs and chemical agents that have been used in treating PD and understanding their synthesis, uses (alone or in combination), and their imperfections. In this review, we have identified the current therapies used in treating PD patients along with the promising therapies for treatment of PD.

INTRODUCTION
Definition and historical background
Back in 1817, James Parkinson had mentioned the syndrome of shaking palsy, later named after him as Parkinson’s disease (PD) (Spillantini et al., 1997). Charcot also elucidated that slowness of movement should be differentiated from lessened muscular power, a term that is associated with PD (de Lau and Breteler, 2006). PD is a neuropathological disease that slowly progresses with age, and it is globally the second most common chronic degenerative disease (Ebersbach et al., 2006). PD dominates mainly in elderly people; therefore, it strikes around 1% of the entire population above the age of 50 and around 2.5% of the population over the age of 70 (Firestone et al., 2005).

Pathophysiology and etiology
The disease is asymptomatic at early stages until the attenuation of the percentage of nerve cells in the substantia nigra of the brain, which is a pathological hallmark of PD. These nerve cells are responsible for the release of a neurotransmitter, dopamine. Reduction of dopamine has many ill-fated consequences on PD patients, ranging from movement disability to depression. Lewy body is another pathological hallmark of PD, mainly consisting of aggregated α-synuclein protein encoded by SNCA (Gilks et al., 2005). It is a product of the first ever-identified gene related to PD. SNCA is a gene on chromosome (4q21) that encodes α-synuclein (Goetz et al., 2007). Aggregated α-synuclein has a negative impact on the synaptic function by intervening with the mechanisms of the microtubule-based subcellular transport, causing disruptions to neuronal homeostasis. The main attribution for the cause of PD (Fig. 1) is idiopathic also known as sporadic disease (Goldwurm et al., 2007). Some environmental and genetic factors contribute to the development of the disease as well.

Genetic risk factors participate largely in the likelihood of development of the disease; although there are confirmed 28 well-defined chromosomal regions that are linked to PD (Jankovic, 2008), only six of these regions have been identified to include genes that
are responsible for causing monogenic forms, namely α-synuclein, LRRK2, PINK1, PARK7 (DJ-1), ATPase type 13A2, and PARK2 (Kempster et al., 2007; Klein et al., 2012). Usually, patients with a family history of PD have higher incidents around 5%–7% in mutations of LRRK2, which is a typical cause for late onset of PD (Lai et al., 2002). Therefore, the LRRK2 gene (PARK8) was confirmed to be the most common cause of sporadic PD (Langston et al., 1983). On the other hand, many studies have shown that exposure to certain environmental toxins can cause PD. For instance, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has caused irreversible PD through its neurotoxic metabolite 1-methyl-4-phenylpyridinium (Langston and Ballard, 1983; Marsh, 2000). Additionally, there might be a correlation between PD and the use of pesticides (Meissner et al., 2011; Oguh and Videnovic, 2012; Parkinson, 2002). Living in rural areas and engaging in agriculture work have been suggested as one of the risk factors of PD (Polymeropoulos et al., 1997).

**Clinical features**

PD is distinguished from many other diseases by four typical features that can be grouped under the acronym TRAP (tremors, rigidity, akinesia, and postural instability) (Priyadarshi et al., 2000). Thus, PD is a movement disorder that influences normal activities. In addition, PD has the potential to cause nonmotor symptoms, such as neuropsychiatric or neurobehavioral complications (Ramaker et al., 2002; Singleton et al., 2013). Thus, many rating scales are used as assessment tools for the evaluation of motor impairment and affliction. It had been agreed that the stages of the progress of PD range from stage 0 (no signs of disease) to stage 5 (wheelchair bound) (Jackson-Lewis et al., 2007; Olanow et al., 2009; Zorzon et al., 2002). These stages were made to provide a comprehensive understanding of the manifestations of the disease.

There is no definitive treatment that is able to cure PD. Many medications and procedures can slowdown the progression of the disease and prevent exacerbation of the conditions. These medications are given depending on the patient’s needs and the complications in patient’s condition. The drugs are categorized as dopaminergic (DA) agonists, monoamine oxidase (MAO) inhibitors, catechol-O-methyltransferase (COMT), decarboxylase inhibitors, and anticholinergics, as well as levodopa (L-dopa) and dopamine releasers.

**Biosynthesis and metabolism of catecholamines**

Figure 2 shows the pathways that naturally occur in the human body; when amino acid L-tyrosine (3) enters the brain, it undergoes hydroxylation by tyrosine hydroxylase (TH) providing L-dopa (4). It is then catabolized by two common pathways, in one of which L-dopa will be metabolized by COMT into 3-methoxy-4-hydroxyphenylalanine (5). COMT is selective for methylation on meta position only. In the other pathway, L-dopa will be metabolized by decarboxylase into dopamine (DA) (1). DA is the mediator that acts on the DA receptor. It also stimulates DA receptors to produce more DA. DA will undergo further metabolism.
by either MAO or COMT, and both metabolites are inactive due to the biotransformation of the most important groups required to bind DA receptor as in structures (8–11) (Davis et al., 1979).

Oxidative metabolism of neurotoxic components

Some neurotoxic metabolites are formed through the normal oxidation of DA. MAO enzyme is responsible for the oxidation of DA, norepinephrine (NE), and serotonin. Through the oxidation step, hydrogen peroxide is generated (Equation 1 and Fig. 3), which can undergo a redox reaction with superoxide producing a neurotoxic hydroxyl radical (Equation 2 and Fig. 3).

The formed hydroxyl radical is very toxic and can make a covalent bond with essential macromolecules, such as DA. Once the covalent bond is formed, it will stop activity, synthesis, and production of DA (Nandipati and Litvan, 2016).

Environmental neurotoxic components such as MPTP

There have been multiple pieces of evidence suggesting that environmental neurotoxins play an important role in the etiology of PD, such that people who are exposed to pesticides in agricultural regions will be at higher risk to develop PD (Ovallath et al., 2017). Miscellaneous types of DA neurotoxins will cause significant damage to DA neuron leading to the depletion of DA release. MPTP, a major metabolite produced during the synthesis of meperidine (12, opioid analgesic drug), is nontoxic. MPTP, when metabolized to its active form 1-methyl-4-phenylpyridinium (MPP⁺; 13), is a neurotoxin that causes degeneration of DA neurons in patients with PD. It can also kill cell bodies and fibers in the pars compacta and striatum (Goetz et al., 2007).

Meperidine, 12 MPP⁺, 13

MPTP is nontoxic in nature and hydrophobic and is able to pass through the blood brain barrier (BBB). Once it crosses the BBB, MPTP is further metabolized by MAO-B into MPP⁺, 13. A very toxic metabolite (cationic) mainly attacks the DA neurons present in the pars compacta of the substantia nigra. This will damage neurons responsible for DA release and cause apoptosis. MPP⁺ also interferes with complex I of the electron transport chain, a component of mitochondrial metabolism, leading to death of the cells and forming free radicals. These radicals are very reactive and are able to destroy the neighboring cells. MPTP, however, is nontoxic, but its metabolites are toxic. Thus, inhibition of their formation, by inhibiting MAO-B, will lead to less production of the toxic intermediate MPP⁺. Selegiline inhibits the formation of MPP⁺, therefore minimizing the side effects and neural damage for those patients using this type of drugs. Historically, neurotoxicity of MPTP metabolites was realized in 1976 as shown in Figure 5 (Casimir et al., 1971).
Management therapy available for treatment of PD

There is no cure for PD and neurologists are focusing on controlling the symptoms and delaying the progression of the disease.

IN-PROGRESS TREATMENTS

Levodopa (L-dopa)

Discovery and characterization of L-dopa

L-dopa naturally occurs in seeds of Vicia faba reported in 1913 and is chemically synthetized. L-dopa has a pharmacological profile similar to catecholamines (DA, noradrenaline, and adrenaline) (Birkmayer and Hornykiewicz, 1961). PD is caused by the depletion of DA. In 1961, Hornykiewicz and Birkmayer performed a clinical trial in group of people with PD by injecting L-dopa intravenously and the results showed significant improvements in relief from tremors, akinesia, and other symptoms related to PD (Bruno and Bruno, 1966). L-Dopa, as shown in Figure 6 (L-3,4-dihydroxyphenylalanine; 4), is a DA, (1) replacement therapy for PD. DA alone cannot be taken orally since it will be subjected to intensive metabolism upon entering the body and therefore will not reach the CNS which is the main target of action of DA. It is metabolized mainly by oxidative deamination and conjugation. Upon injection, DA can act peripherally on monoamine receptors resulting in adverse effects, such as hypertension. Effective delivery of DA with minimized peripheral side effects is achieved by administrating the precursor L-dopa (4) that can pass the BBB easily through amino acid transporter, and once entering the brain it will be converted by aromatic amino acid decarboxylase, amino acid decarboxylase (AADC to DA) (Knowles, 2002; Li and Li, 2014).

Industrial processes for production of L-dopa

Four synthetic procedures for large-scale production of L-dopa are mainly utilized by pharmaceutical and/or chemical companies. Those procedures depend on many factors, such as readily available starting material, lower number of steps involved in the synthesis to improve overall yield, general safety of reactions, and avoidance of carcinogenic material or intermediates as well as reagents, reaction time to get final product, and efficiency of the synthesis.

Hoffmann La-Roche synthesis of L-dopa

It was developed in 1960 as a linear synthesis (Fig. 7). The reaction involves Erlenmeyer–Plöchl condensation of vanillin (14) with benzoyl glycine (15), followed by several steps and separation of the S-enantiomer by the use of (+)-dehydroabietylamine (19). The final step involves the deprotection by hydrogen bromide to have two -OH free groups and a free primary amine group.

Even though the overall synthesis is good and the number of steps involved and the starting material used are readily available, there is a main drawback in Hoffmann La-Roche method, that is, the overall yield is dropped due to the resolution step (Milic et al., 2008).

The monsanto synthesis

Monsanto synthesis (Fig. 8) is considered as a commercial process that uses asymmetric synthesis with transition metal complexes. In between the intermediates, enamide (21) is asymmetrically hydrogenated to produce the S-enantiomer and then deprotected to offer the final L-dopa (Pletscher and DaPrada, 1993; Trost, 1991).
**The ajinomoto process**

This process (Fig. 9) is a biosynthetic, three-component method in a one-step reaction under the biocatalysis reagent that helps to produce L-dopa. Tyrosine phenol-lyase (TPL) is an enzyme that uses the nonphysiological substrate catechol. TPL will install a side chain consisting of an amino group by forming a carbon–carbon bond and a carbon–nitrogen bond at the same time by combining three given substrates. Since it is a reversible reaction, L-dopa crystallization induced by seeding shifts the equilibrium to the product side (Milic et al., 2008).

**The sankyo synthesis**

This synthetic method was developed in 1990. It was then introduced commercially for large-scale production in 2008. It is composed of seven reaction steps starting from vanillin (Fig. 10), the OH group of which is protected by methylation, and the aromatic aldehyde (23), resulting in the condensation with hydantoin (24). The intermediate benzylidene-hydantoin (25) is then hydrogenated, producing a racemic mixture. After further steps, the enantiomer of interest is selectively deacylated via enzymatic reaction, followed by the final deprotection step with HBr to deliver L-dopa.

In drug development, any synthetic route that is used for scaling up must be well assessed. Important factors, such as overall efficiency of the process, and the disposition of waste products as well as other factors must be considered. However, atom economy is a technique developed in 1991 by B. M. Trost; the main goal of atom economy is to achieve the synthetic efficiency of transforming available starting materials to the final product (Cedarbaum, 1987; Pletscher and DaPrada, 1993; Trost, 1991).

**Bioavailability and biotransformation of exogenous L-dopa**

L-dopa has a very short half-life in plasma and undergoes extensive first-pass effect due to the presence of AADC enzyme. Peripherally, AADC converts L-dopa to DA and DA will not be able to cross the BBB due to its polarity as a good substrate for MAO enzyme. W. Birkmayer was the first scientist who found that the combination of AADC inhibitor with L-dopa provides a high

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**Figure 7.** Hoffmann La-Roche synthesis.

**Figure 8.** The Monsanto synthesis.

**Figure 9.** The Ajinomoto synthetic route.
improvement in therapeutic profile, including prolonged duration of action accompanied by the increase in L-dopa present in the CNS by 10-folds (Mannisto and Kaakkola, 1989; Nutt and Fellman, 1984). Decarboxylase inhibitors (e.g., carbidopa and benserazide) will prevent metabolism of L-dopa to DA peripherally, and, at the same time, the decarboxylase inhibitors are more hydrophilic, which means they cannot pass the BBB and will not inhibit the AADC in the brain. AADC in the brain is important for conversion of L-dopa to DA to produce its action. The coadministration of L-dopa/carbidopa allowed the reduction in the dose and reduced many of the peripheral adverse events. However, only 5%-10% of an oral dose of L-dopa/carbidopa crosses the BBB (Rascol et al., 2000). In case of coadministration of L-dopa/carbidopa that leads to inhibition of AADC pathway, the metabolism of L-dopa will shift to COMT, producing an inactive metabolite (Sletzinger et al., 1963).

Therefore, this problem has been solved by the coadministration of levodopa/decarboxylase inhibitors and COMT inhibitors (such as entacapone and tolcapone). By inhibiting both COMT and AADC peripherally, it will delay the metabolism of L-dopa, resulting in increased effectiveness due to its increased amount going to the brain. The major disadvantage of long-term use of L-dopa is that the patient may develop motor fluctuations and dyskinesia because of the disease progression and L-dopa pharmacokinetics (Rinne, 1987). Despite the development of several new medications (such as DA agonists, DA releasers, and MOA-B inhibitors) for controlling PD symptoms, L-dopa remains the gold standard treatment of PD.

Drug classes for management of PD

Decarboxylase inhibitors

Decarboxylase inhibitors (like carbidopa and benserazide) prevent the metabolism of L-dopa peripherally; so, a large amount of the orally administrated L-dopa will enter the brain to produce their action. Several studies show that the coadministration of L-dopa/carbidopa will allow the decreasing of dose dependency by fourfold or fivefold and increase the L-dopa efficacy (Karady et al., 1971).

Synthesis of L-carbidopa

The synthesis starts by using hydrazine and potassium cyanide on aryl acetone (13) to give (14) and then is hydrolyzed with cold HCl to give carboxamide (15), as shown in Figure 12. Hydrolysis with 48% of hydrogen bromide leads to demethylation and hydrolysis of the amide bond to produce carbidopa (16) (Brooks, 2000; Jankovic, 2000).

Dopamine agonists

Appropriate knowledge about the receptor and the main interactions important for pharmacodynamics of DA (Fig. 13) allowed scientists to search for molecules that can be natural, semisynthesized, or synthesized, with similar binding groups to mimic the activity of the natural neurotransmitter.

Currently, available DA agonists are used throughout the world, including bromocriptine, pergolide, pramipexole, ropinirole, and rotigotine. Due to the possibility that levodopa is
neurotoxic and its long-term use induces motor fluctuations and dyskinesia, many experts and neurologists recommend delaying the introduction of L-dopa in the therapy until the disease symptoms clearly begin to interfere with patients functioning and normal lifestyle; DA agonists can be used as monotherapy in the early stage of disease and it may delay the introduction of L-dopa by several months or years. A human body has five types of DA receptors: D1, D2, D3, D4, and D5; DA agonists produce their pharmacologic action by directly activating the DA receptors. Clinical studies have shown that activation of the D2 receptors is important to produce anti-Parkinson effects of DA agonists, but also both D1 and D2 stimulations are required to maximize the physiological and behavioral effects (Lieberman and Goldstein, 1985; Tintner et al., 2005).

DA agonists are divided into two categories: ergot (bromocriptine and pergolide) and nonergot (pramipexole, ropinirole, and rotigotine) DA agonists; several pieces of evidence show that ergot DA agonists are associated with a high risk of developing heart failure, while nonergot DA agonists are associated with a lower risk of complications, such as peptic ulcer disease, vasoconstrictive effects, and heart failure, which is why ergot DA agonists have been essentially discontinued from medical practice (Van Hilten et al., 2007).

**Bromocriptine**

It is an ergot DA agonist that activates the D2 receptor localized in the striatum region; bromocriptine, unlike other DA agonists, is used in the treatment of PD; it has mixed “agonist–antagonist” effect on the D2 receptor and also bromocriptine does not induce a conformational change in the D2 receptor. A group of individuals performed clinical trials (involved 850 participants) and found that bromocriptine may be helpful in delaying such fluctuations of movement problems in patients with PD (Aellig and Nuesch, 1977; Goetz and Diederich, 1992).

Bromocriptine (18), as shown in Figure 14, is a semisynthesized product by bromination of ergocryptine (17) (a derivative of lysergic acid), using N-bromosuccinimide (McClure et al., 2010; Schiff Jr, 2006).

**Pergolide**

It is another ergot alkaloid which stimulates D1, D2, and 5HT receptors. Pergolide is considered as a very potent DA agonist. It has higher affinity to D1 receptor. Due to the possibility of causing heart failure and valvular heart disease, pergolide was withdrawn from the US market in 2007 (Eden et al., 1991; Fuller and Clemens, 1991).

**Synthesis of pergolide**

Methyl dihydrolysergate (19) is treated with cyanogen bromide to produce 6-cyano-8-beta-methoxycarbonylergoline (20), which is then treated with zinc and acetic acid to produce 8-beta-methoxycarbonylergoline (21). Alkylation of (21) with propyl bromide gives (22) which is reduced with NaBH₄ to produce (23). The reaction of (23) with mesyl chloride (methanesulfonyl chloride) provides (24). Sodium methanethiolate in the presence of methane sulfonic acid gives pergolide (Fig. 15) (Cabri et al., 2006).

**Pramipexole**

Pramipexole produces its action by directly stimulating the D2 receptor. Previous studies have shown that pramipexole is effective as monotherapy in early PD and as an adjunctive with levodopa in advanced stages. Pramipexole in general is safe to use and well tolerated; however, compared with L-dopa, pramipexole is associated with a higher risk of development of DA adverse effects, such as confusion and memory problems.

**Synthesis of pramipexole**

There are five steps involved in the reaction to produce pramipexole. The first step, bromination of compound (26) (Fig. 16), followed by reaction with thiourea and then deprotection by using hydrogen bromide, will give free amine (29), which is then modified to pramipexole (30).

**Ropinirole**

Ropinirole (31) is an agonist used in early and advanced stages of PD (Fig. 17) and it produces its action by directly
stimulating D2, D3, and D4 but has higher affinity to D2 receptor. In addition, it can be used alone as monotherapy or adjunctive therapy with L-dopa (Johnston, 1968).

Rotigotine

It is a nonergoline DA agonist, available as transdermal patch, which provides a constant supply of the drug for over 24 hours (Bortolato et al., 2008).

Synthesis of rotigotine

The rotigotine synthetic approach (Fig. 18) starts by selective protection of a phenolic group of (32), followed by converting the alcohol group into ketone (34) that undergoes several steps to afford rotigotine as a hydrochloride salt (39).

Monoamine oxidase inhibitors

MAOs are types of proteins that accelerate the breakdown of monoamine neurotransmitters, including DA,
serotonin, epinephrine, and NE in the CNS, and catalyze the oxidative deamination of dietary amine (Kaligutkar et al., 2001).

**Monoamine oxidase catalyzes the oxidative deamination of monoamines**

MAO degrades monoamines to their correspondent aldehydes (R-CHO). The mechanism is named oxidative deamination in which ammonia (NH$_3$) is also produced. Aldehydes are then oxidized by aldehyde dehydrogenase (ALDH) into carboxylic acids. NADH is a critical cofactor for this latter reaction (Fig. 19) (Saura et al., 1997).

MAOs are present in two isoforms: A and B (Kaligutkar et al., 2001). MAO-A has greater activity toward deamination of serotonin and NE, while MAO-B shows greater activity toward benzylamine and phenylethylamine. Both are equally active toward DA and tyramine. In addition, type A is predominantly an intestinal MAO, while type B is predominantly a brain MAO (Clarke et al., 2003b; Saura et al., 1997).

**Classification of MAO inhibitors**

MAO inhibitors can be classified into three categories, as follows:

Irreversible nonselective agents such as phenelzine (40) and tranylcypromine (41).

Irreversible, selective drugs MAO-B inhibitors (selegiline, Fig. 23) and (rasagiline, Fig. 25).

Reversible, selective MAO-A inhibitors (meclobemide).

Selective MAO-A inhibitors are known to potentiate the crisis known as cheese effect (Knoll and Magyar, 1972; Riederer and Laux, 2011; Saura et al., 1990). MAO-A is responsible for the deamination of tyramine. When MAO-A inhibitors are given, tyramine is not deaminated; after being absorbed, NE nerve terminals pick up tyramine, and it acts as a false neurotransmitter. Tyramine displaces the stored NE; once NE releases, it potentiates a hypertensive crisis by activating the alpha-1 adrenergic receptors that cause blood vessels to constrict (Fig. 20) (Finberg, 2014; Kaakkola et al., 1987; Youdim et al., 2004). That is why there is a dietary restriction upon consuming food containing tyramine (like aged cheese).

MAO-B, on the other hand, does not act on tyramine in the gut; the standard doses of MAO-B inhibitors are highly selective for MAO-B only; therefore, they eliminate the need for dietary restriction (Aboukarr, 2018).

The logic behind using MAO-B was based on the idea that DA is mainly metabolized by MAO-B. Therefore, using selective MAO-B inhibitors will prevent the breakdown of DA and prolong its activity which can be used as monotherapy in early stages of PD or as an add-on therapy with L-dopa and DA agonist in the later stages of PD (Kim and Bortan, 2010). The two selective, irreversible MAO-B inhibitors are selegiline and rasagiline. Both provide symptomatic relief in early PD and they are associated with fewer side effects and are highly tolerated (Caccia et al., 2006).

MAO-B inhibitors were also known to prevent the oxidation of MPTP to MPP$^+$ which are toxic to DA neurons and

![Figure 17. The structure of ropinirole.](image1)

![Figure 18. Synthesis of rotigotine.](image2)
increase the risks of having Parkinson’s symptoms in human and animals (Reynolds et al., 1978; Tetrad and Langston, 1989).

**Selegiline**

Selegiline (42) was the first MAO-B inhibitors to be approved by the FDA and it was first synthesized by Joseph Knoll. It is a very similar derivative of 1-methamphetamine (43) (Gill et al., 1967). Selegiline inhibits the deamination of DA and phenethylamine resulting in increased concentration of both monoamines. The active form of selegiline is the L-(-)-form, while the D-(+)-form is 25 times less active.

In the therapeutic dose, selegiline possesses higher affinity with type B than the type A active sites; therefore, it will act selectively for MAO-B only. In contrast doses higher than the recommended dose will begin to dissipate, resulting in higher inhibition of MAO-A.

Selegiline is metabolized to amphetamine (45) and methamphetamine (Cavanaugh et al., 1970). Amphetamine is further metabolized to the false neurotransmitter p-hydroxyephedrine, meaning that it has a diminished effect on postsynaptic receptors when released into the synaptic cleft (Martin et al., 1971; Rangno et al., 1973). This also consumes nerve terminals of NE. As a result, continuous exposure to amphetamine results in a supine pressor response and postural hypotension (Woolverton et al., 1989). Furthermore, chronic exposure to selegiline may result in neuronal toxicity (cardiac and psychiatric) due to amphetamine metabolite (Abu-Raya et al., 2002; Churchyard et al., 1997).

**Synthesis of selegiline**

Amphetamine reacts with ethyl formate, then the product reacts with lithium aluminum hydride to yield methamphetamine, and it will further undergo reaction with bromopropyne in the presence of potassium carbonate, water, and acetonitrile to give the end-product selegiline (Speiser et al., 1998).

**Rasagiline**

It is a propargylamine-based, selective, irreversible MAO-B inhibitor. Metabolism of rasagiline (48) is not as toxic as selegiline; it is metabolized into 1-R-aminoindan (49) (Finberg.
It can be used as monotherapy in early stages of PD or as an adjunct therapy with L-dopa. It also enhances striatal levels of DA with or without L-dopa. Rasagiline has an advantage of a once-daily fixed-dose formulation. Exceptional efficacy of rasagiline was noted in the reduction in “off” time of L-dopa-treated patients and improved motor activity compared to selegiline. Rasagiline is well tolerated at doses up to 20 mg/day and no cases of overdose have been reported (Guldberg and Marsden, 1975; Zheng and Bruice, 1997).

**Synthesis of rasagiline**

The precursor 1-indanone reacts with benzylamine in the presence of acetic acid to form an intermediate. This intermediate will undergo reduction by sodium borohydride forming N-benzyl-1-indanamine, which will further resolve with tartaric acid to yield (R)-(+)-N-benzyl-1-indanamine. The final step of this reaction is to react it with 1-chloropropyne in the presence of potassium carbonate in water to give the final medicinal product of rasagiline (Brenna et al., 2017).

**Catechol-O-methyltransferase inhibitors**

COMT enzyme is responsible for deactivating catechol neurotransmitter (55), such as DA and the drug L-dopa, as shown in Figure 26 (Mannisto and Kaakkola, 1999; Tsao et al., 2011). COMT deactivates DA by catalyzing the methylation reaction leading to the formation of methoxylated product (56, 57) in the presence of mg2+ and S-adenosyl-L-methionine (SAM) (Axelrod, 1966). The inhibition of COMT enzyme has an important action in reducing the elimination of L-dopa and DA, therefore achieving prolonged availability of L-dopa and DA in the brain (Axelrod, 1958; Kaakkola, 2000).

The unfortunate consequence of toxicity in first-generation drugs was related to their pharmacological action (Borgulya et al., 1989). Later in the 1980s, a second generation of COMT inhibitors was discovered; they were more potent and selective (Ma et al., 2014; Mannisto and Kaakkola, 1989). The compounds acted through shutting out the breakdown of L-dopa, therefore enhancing the time available in the brain. The two most common drugs in this class are entacapone and tolcapone (Leegwater-Kim and Waters, 2006). They can act peripherally and centrally; cerebral COMT enzymes accelerate the metabolism of L-dopa to 3-O-methyldopa (3-OMD) (63); however, DA is biotransformed to homovanillic acid (HVA) (64) (Learmonth et al., 2002).

![Figure 22. Metabolism of selegiline to the toxic metabolite amphetamine.](image)

![Figure 23. Chemical synthesis of Selegiline.](image)
The inhibition of COMT enzymes peripherally results in decreased metabolism of L-dopa to 3-OMD, therefore enhancing its therapeutic action. Moreover, inhibiting COMT centrally decreases the metabolism of L-dopa and DA, therefore prolonging the effectiveness.

**Structure activity relationship (SAR) of second-generation COMT inhibitors**

Substitution with the electron-withdrawing group at the aromatic ring, with regard to the catechol group, contributed to enhanced potency (Learmonth et al., 2002; Leegwater-Kim and Waters, 2006). The reason behind increased potency was the nitro group. The electron-withdrawing property of this group leads to the development of a new class of nitrocatecholic COMT inhibitors. Nebicapone is under investigation in clinical trial NCT03097211 (Effect of BIA 6-512 at steady-state on the L-dopa pharmacokinetics with a single dose of levodopa/benserazide 200/50 mg or with a single dose of levodopa/benserazide 200/50 mg plus a single dose of nebicapone 150 mg). Nitecapone [3-(3,4-dihydroxy-5-nitrophenyl) methylene-2,4-pentanedione] (OR-462) is a COMT inhibitor with gastroprotective properties (Fig. 29).

**Tolcapone**

It is a potent selective reversible COMT inhibitor which was launched in EU in 1997 and in the US in 1998 (Mannisto et al., 1992). Oral administration showed higher potency and a longer duration of action than entacapone (Truong, 2009). Tolcapone also has the ability to cross the BBB. Tolcapone is able to inhibit COMT both peripherally and centrally, in addition to the decrease in the levels of HVA and 3-methoxytyramine (3-MT) in the striatum due to tolcapone administration. It has higher penetrability to BBB than entacapone, thus showing higher efficacy in inhibiting brain COMT (Nissinen et al., 1988a). Long-term use of tolcapone has been associated with increased risk of dyskinesia, which can be prevented by decreasing the dose of L-dopa. Dyskinesia mainly occurs due to the accumulation of the methyl donor SAM in the striatum that subsequently induces Parkinson’s symptoms (Nissinen et al., 1992).

**Synthesis of tolcapone**

Benzaldehyde derivative (70) reacts with p-tolyl magnesium bromide (71) to produce (72), which is then converted to the ketone (73) that undergoes further steps which finally lead to the production of tolcapone (Fig. 30) (Harrison et al., 2015).

**Entacapone**

Entacapone peripherally inhibits COMT. Even though there are no observable changes in the striatal level of HVA, it

![Figure 24. Metabolites of rasagiline and selegiline.](image1)

![Figure 25. Chemical synthesis of rasagiline.](image2)

![Figure 26. O-Methylation mechanism of COMT enzyme to catechol neurotransmitters like dopamine.](image3)
has a certain degree of inhibiting the central COMT (Brannan et al., 1997; Chase, 1998; Linden et al., 1988). The inhibition of peripheral COMT protects L-dopa from being methylated in the periphery; therefore, it increases the amount of L-dopa reaching the brain (Nissinen et al., 1988b; Pagano et al., 2015).

Moreover, tolcapone and entacapone both increased the bioavailability of levodopa in PD patients. They maintain levodopa level with fewer fluctuations, resulting in better therapeutic outcomes and lower risk of developing dyskinesia.

**Synthesis of entacapone**

Starting with the reaction of 5-nitrovanillin (4-hydroxy-3-methoxy-5-nitrobenzaldehyde) with hydrobromic acid in the presence of acetic acid, then 3,4-dihydroxy-5-nitrobenzaldehyde reacts with 2-cyano-N,N-diethylacetamide in the presence of piperidine acetate and ethanol, resulting in entacapone as a final product (Fig. 31) (Harrison et al., 2015).

**Anticholinergics**

Acetylcholine acts on the nicotinic (Nn; Nm) and muscarinic (M1, M2, and M3) receptors. The actions on nicotinic receptor produce skeletal muscle contractions and are involved in cognitive function.

**Structure activity relationship of cholinergic drugs**

There are important points on the interaction of acetylcholine with the receptors mentioned as follows: (a) the optimum activity with nitrogen is to be quaternary, and substituting it by phosphorous (P) or sulfur (S) results in the decrease of cholinergic activity. Moreover, the substitution of one of the three methyl groups with higher alkyl groups, like ethyl or propyl, makes the molecules less active than acetylcholine. However, substitution of all the three methyl groups with higher alkyl groups, like ethyl or propyl, provides anticholinergic drugs.

(b) The second segment is the ethylene (CH₂CH₂) group, where an introduction of methyl substituent at alpha position (carbon adjacent to the quaternary nitrogen) results in products of higher selectivity toward nicotinic than muscarinic receptors. The introduction of the methyl group at beta position has more selectivity toward muscarinic than nicotinic receptors. The trials with chains longer than two carbons between nitrogen and oxygen decreased the activity; thus, the distance between nitrogen and oxygen must be two carbon lengths.

(c) The final segment of the acetylcholine (78) is the acetoxy (CH₃CO) group. The conversion of acetoxy into carbamoyl (NH₂CO) group increases cholinergic activity. Carbachol (79) and bethanechol (80) are made up of carbamic acid ester. Both (79) and (80) are more potent than the acetylcholine on cholinergic receptors. Moreover, the replacement of acyl group with aromatic or higher molecular weight esters makes the molecule antagonist at cholinergic receptor.

**Acetylcholine-receptor target interaction**

Acetylcholine binds to the arm of the muscarinic receptor. Binding occurs by three possible interactions that are ionic bond, two hydrogen bond acceptors, and Van der Waals interactions.

Anticholinergics represent the most used treatment for the PD. It is used with other treatments for PD. Anticholinergics work by blocking the action of acetylcholine. As a result,
the activity of the neurons will be decreased and the balance between DA and acetylcholine will be restored (Fig. 33). Normal people who do not suffer from PD have balanced DA and acetylcholine, whereas in people who suffer from PD, the amount of DA released is less than that required. That decrease results in the increase in acetylcholine that causes the imbalance. In order to restore the balance, anticholinergics are given to the patients.

![Chemical structures](image)

**Figure 29.** Nitrocatechol derivatives as COMT inhibitors (second generation).

![Chemical synthesis](image)

**Figure 30.** Chemical synthesis of tolcapone.

![Further chemical synthesis](image)

**Figure 31.** Chemical synthesis of tolcapone.
Anticholinergic drugs

Serval drugs fall under the anticholinergics class, like benztropine (83), biperiden (86), and benzhexol (89). The design of anticholinergic drugs relies on the shape of the active site of the muscarinic cholinergic receptor and the binding interactions include acetylcholine. Therefore, there is a need to consider the SAR of the endogenous neurotransmitter (acetylcholine).

Benztropine

Benztropine is a drug that helps reduce the PD symptoms. Doses verify depending on the patients’ need. Benztropine may cause addiction; therefore, patients must stick with the doctor’s prescription. Like any other drug, benztropine has various side effects, such as dizziness, constipation, nausea, and dry mouth. The mechanism of action of benztropine works by blocking the relative excess of the acetylcholine in the striatum. This will result in restoring the balance between acetylcholine and DA.

Synthesis of Benztropine

Benztropine is synthesized from diphenylmethane (81) combined with bromine (Br₂) (Fig. 34). The intermediate (82) reacts with tropine and work-up results in the formation of benztropine (83) (Pedersen et al., 2004).

![Figure 32. Structures of acetylcholine and cholinergic drugs.](image1)

![Figure 33. Imbalance between acetylcholine and dopamine.](image2)

![Figure 34. Synthesis of benztropine.](image3)
Biperiden

Biperiden (86) helps in reducing the side effects of PD like movements caused by other medications. It works by helping to correct the chemical imbalance. It restores the imbalance at the excitatory system and its function is to block the muscarinic cholinergic receptor to result in decreasing the acetylcholine action. It is classified as competitive antagonist of acetylcholine.

**Synthesis of biperiden**

Figure 35 shows the synthetic steps starting from 2-(1-piperidino) propiophenone (84) which reacts with the Grignard reagent (85) prepared from 5-chloro-2-norbornene yielding biperiden (86).

Benzhexol (Trihexyphenidyl)

Benzhexol (89) is used to improve and control the PD symptoms. The side effects include dryness of mouth, dizziness, disturbing behavior, and weakness. Benzhexol resembles atropine in the effector cells. It also acts on blocking acetylcholine at certain cerebral synaptic sites. When the body fails to respond to medication, other medications are given along with the benzhexol.

The mechanism of action of benzhexol is that it blocks cholinergic activity in the CNS that is responsible for the symptoms of the disease. In addition, it increases DA.

**Synthesis of benzhexol**

Figure 36 shows the initial synthesis of 2-(1-piperidino) propiophenone (88) by aminomethylation using three compounds, which are acetophenone (87), paraformaldehyde, and piperidine which then reacts with cyclohexyl magnesium bromide resulting in the formation of benzhexol (89) (Giachetti et al., 1986).

Dopamine releasers

Amantadine is an antiviral agent which can be used to reduce the symptoms of PD early and in managing some side effects of L-dopa. It works by blocking the DA reuptake and therefore increases the level of DA. The mechanism of action of amantadine remains unclear. The drug is known to be a weak N-methyl-D-aspartate receptor antagonist.

The side effects of amantadine occur rarely. These effects include fainting, lower back pain, swelling of hands and feet, and seeing and feeling things that are not there. In addition, patients may experience anxiety and loss of appetite.

**Synthesis of amantadine**

Figure 37 shows the synthesis of amantadine. The starting material is the tricyclic ring (89), which reacts with bromine to produce (90), followed by acetonitrile in acidic media. The carboxamide intermediate (91) is subjected to alkaline hydrolysis and the final compound is obtained and isolated as hydrochloride salt (92) (Scatton et al., 1970).

New therapeutic strategies to treat PD

Scientists and neurologists are trying to identify new targets of therapy with fewer side effects, such as promoting neuroprotection.

Promoting neuroprotection

Calcium Ca\(^{2+}\)

Calcium plays an important role in protecting neuron cells; reports have suggested that an increase in brain Ca\(^{2+}\) levels promotes the aggregation of α-synuclein (Athauda et al., 2017; Bertilsson et al., 2008; Hunot et al., 1997; Li et al., 2009; Nath et al., 2011). Therefore, using calcium-channel blockers L-type, such as isradipine (93) (Fig. 38), helps to decrease the levels of Ca\(^{2+}\) in the brain and promote neuroprotection in PD. Currently, isradipine is conducted in phase 3 clinical trials for its efficacy in early PD.

Glucagon-like peptide-1 (GLP-1)

Exendin-4 (Fig. 39) is a GLP-1 agonist that acts on the GLP-1 receptors in the brain; exendin-4 suppresses proinflammatory cytokine production, prevents microglia activation, and restores DA activity in MPTP-induced PD models (Castillo et al., 1998; Zetterstroom et al., 1997). In
In addition, transcription nuclear factor (NF) that is responsible for PD pathogenesis is inhibited by exendin-4, resulting in the reduction of inflammation of neurons (Gil et al., 2007). Recently, exendin-4 has proved a positive efficacy in PD but the exact mechanism of action is unknown until now (Zhang et al., 2012).

Nuclear receptor-related 1 (Nurr1)

Nurr1 is a nuclear receptor involved in the synthesis of DA and survival of DA neurons (Okun and Foote, 2010). In addition, Nurr1 enhances in vivo and in vitro transcription of TH which is a rate-limiting enzyme of DA synthesis (Vrecko et al., 1993; Wakade and Chong, 2014). Therefore, a reduction in Nurr1 levels causes a reduction in the DA levels which is a main sign of PD (Shah et al., 2010).

Nurr1 binds with retinoid x-receptor-alpha (RXR-α) in the midbrain DA neurons. Spathis et al. (2017) [134] have designed a selective lead compound RXR-α and have proved its efficacy in protecting DA neurons, which prevents its loss in vivo.

Niacin

Niacin is a precursor of NADH and NADPH required for DA synthesis [135]. PD patients who are receiving L-dopa will suffer from depletion of both NADH and NADPH. Studies show that the administration of niacin receptor agonists has an anti-inflammatory effect via NF, causing protection of DA neurons and delays the progression of the disease (de Hemptinne et al., 2015; Lin et al., 2014).

Deep brain stimulation

Deep brain stimulation (DBS) is a recent therapy that was developed for reducing the potential symptoms of PD. DBS was discovered in the early 1990s. In 2002, the United States Food and Drug Administration (USFDA) approved it as a therapy for PD and many other disorders, some of which are obsessive compulsive disorder and essential tremor (Odekerken et al., 2013; Rivero-Rios et al., 2016). The DBS was developed to target a small nucleus in the brain that is known as subthalamic nucleus (STN). When stimulation occurs, it inhabits the nucleus that results in improving the motor symptoms. DBS is designed to use electrical currents to target abnormal brain activity. This method involves chemical reactions that lead to the release of neuron transmitters. DBS works by implanting electrodes in the STN and the internal part of the globus pallidus (GPI). A wire is attached to these parts of the brain. It runs through the head to the chest and is attached to a battery generator located on the chest area. Then, it is turned on and starts sending electrical currents to the brain. Once the DBS starts working, it delivers continuous electrical stimulations. DBS is not a cure for PD, but it helps to reduce and control the motor symptoms by increasing the DA signaling in the brain (Awad et al., 2015; Moors et al., 2017; Settembre et al., 2011)

Targeting autophagy

Autophagy is an important physiological process that is initiated whenever there are nutrient limitation and cellular stress. In addition, its main role is to regulate the breakdown of long-lived proteins, protein aggregates, and organelles. In PD, a modification in autophagy pathway is highly noticed since α-synuclein aggregates are primarily cleared by this process. Therefore, targeting autophagy with the aid of chemical or genetic procedures could be advantageous to the proper function of neurons. However, it is essential to know which phase of the autophagy process is modified in the disease. If it is the initiation step, then it could be resolved by autophagy inducers, but if the last steps are affected, these autophagy inducers may potentiate very harmful effects (Arotcarena et al., 2019).

One example is modulating the expression of the transcription factor (EB), which is responsible for regulating the gene expression involved in autophagy and lysosomes synthesis.
(Pu et al., 2017), in which the gene’s activity is modified in α-synuclein pathology. Certain studies have demonstrated that genetic or chemical stimulation of TFEB possesses neuroprotective activity in vitro and in vivo models of PD. Another approach to stimulate autophagy is by the use of AMP-activated protein kinase activators, such as metformin and resveratrol, which leads to initiation of autophagy (Guerra de Souza et al., 2016).

CONCLUSION

Therapy for PD focusses on symptomatic relief rather than targeting the pathology of the disease. Such treatment is associated with a high rate of enhancing morbidity and mortality. However, recent clinical trials are conducted interfering with the etiology, pathology, and pathogenesis of PD, such as DBS, targeting autophagy, and neuro-protection. Targeting autophagy may provide greater opportunities to develop therapies targeting the pathology of the disease associated with a greater impact on the disease than did the introduction of L-dopa. In this review, we identified the current therapies used in treating PD patients; in addition, we reviewed the promising therapies for PD, how they work, and their advantages in comparison to the standard treatments for PD. However, some of the novel targets are used in the hospital, and some are still under clinical trial and have not yet reached the market.

DISCLOSURE

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CONFLICT OF INTEREST

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