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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).

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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

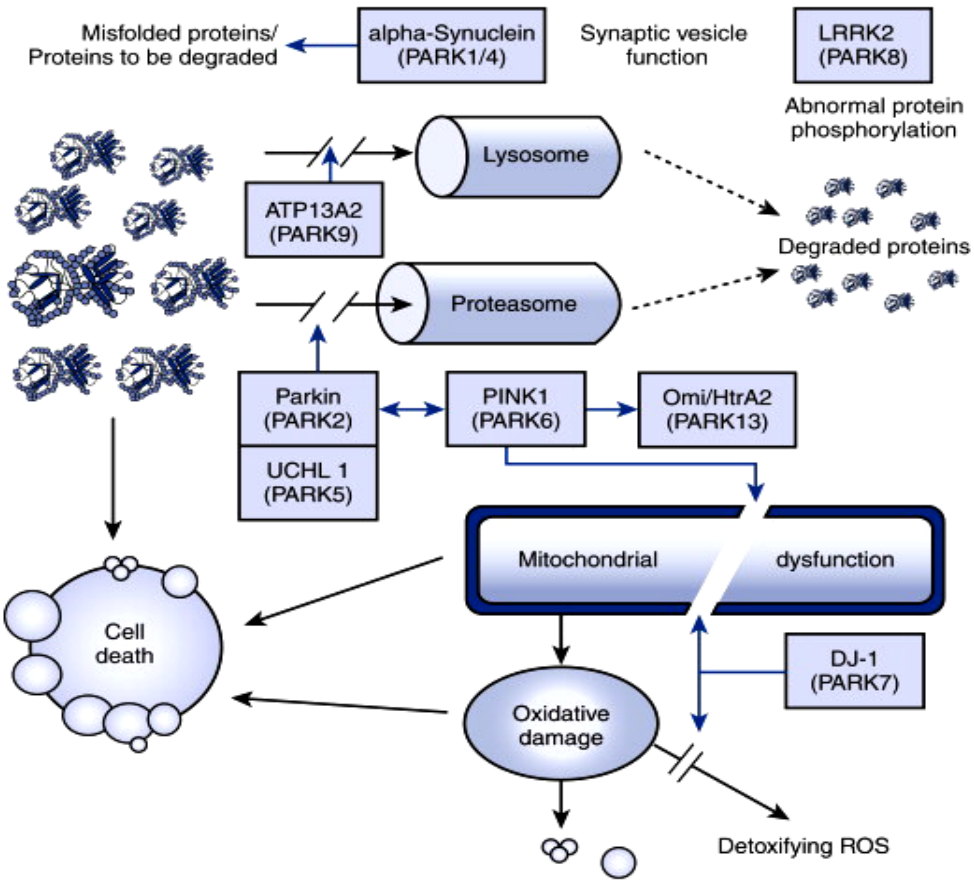

Figure 1. Model for common pathways underlying genetic and idiopathic PD.

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 catecholaminesBiosynthesis

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*., 1911).

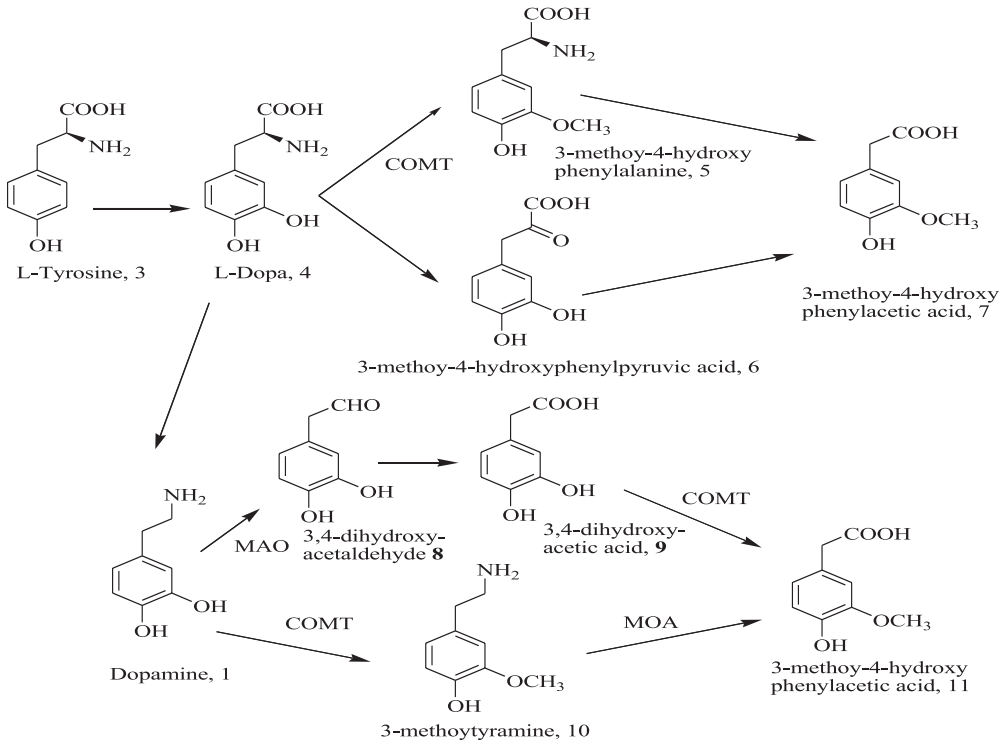

Figure 2. Pathways of the biosynthesis and catabolism of L-dopa and dopamine.

$$RCH_2CH_2NH_2 + O_2 + H_2O \longrightarrow RCH_2CHO + NH_3 + H_2O_2 \qquad \text{(Equation 1)}$$

$$H_2O_2 + O_2^{\bullet\ominus} \longrightarrow O_2 + OH + OH^{\ominus\bullet} \qquad \text{(Equation 2)}$$

Figure 3. Formation of hydroxyl radical from the autoxidation of DA by MAO enzyme.

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 once 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).

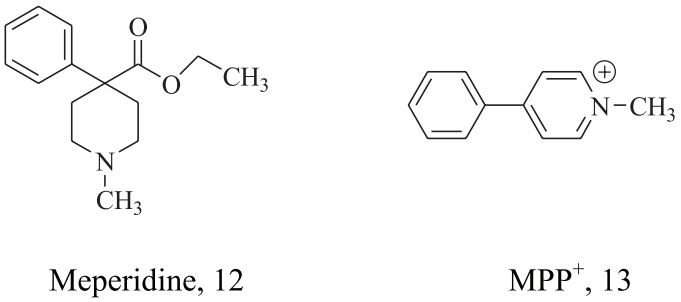

Figure 4. The structure of meperidine and MPP+.

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).

Figure 6. The structure of dopamine and levodopa.

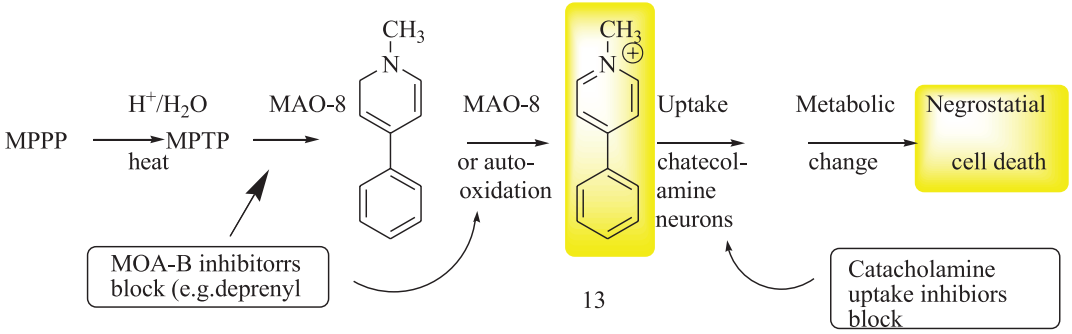

Figure 5. Biosynthesis of MPP+ in human body from MPPP.

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

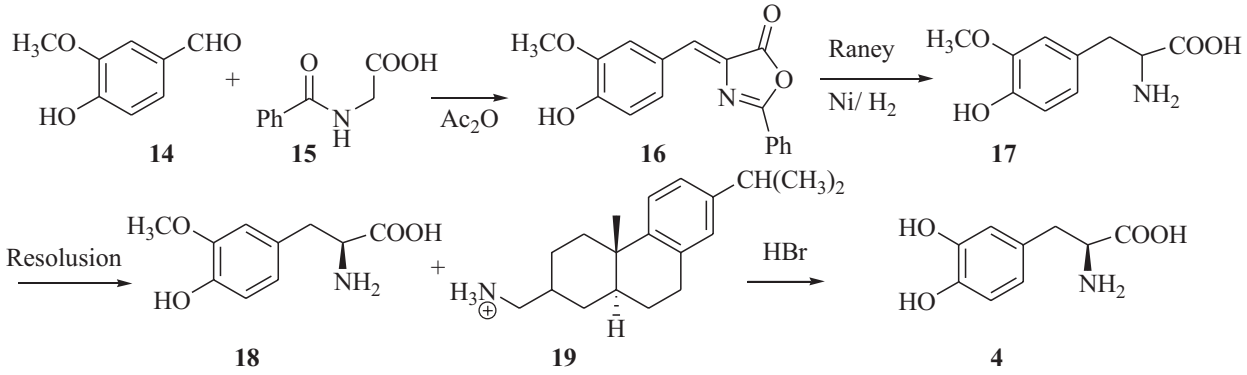

Figure 7. Hoffmann La-Roche synthesis.

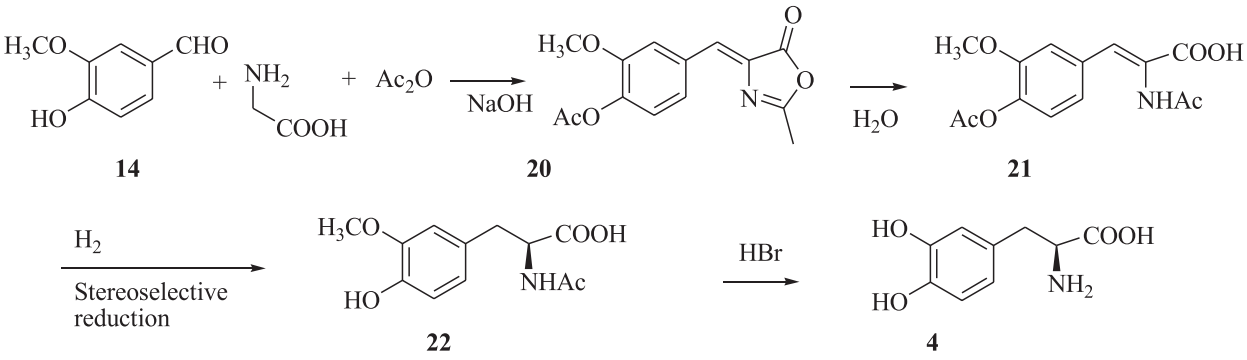

Figure 8. The Monsanto synthesis.

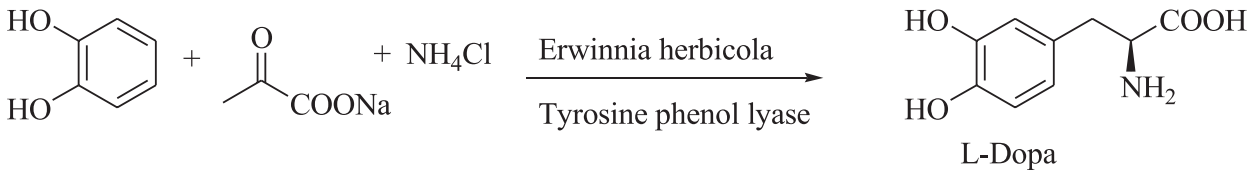

Figure 9. The Ajinomoto synthetic route.

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

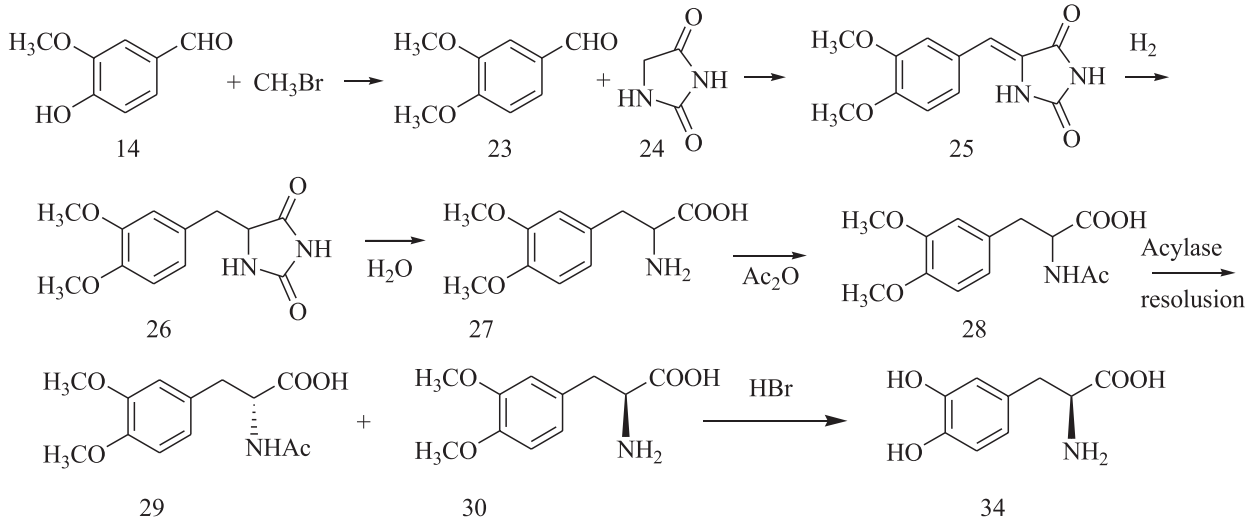

Figure 10. The Sankyo synthesis.

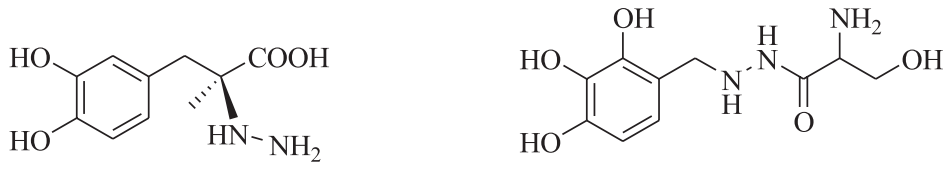

Figure 11. The structure of carbidopa and benserazide.

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 semisynthetized 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 $NaBH_4$ 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

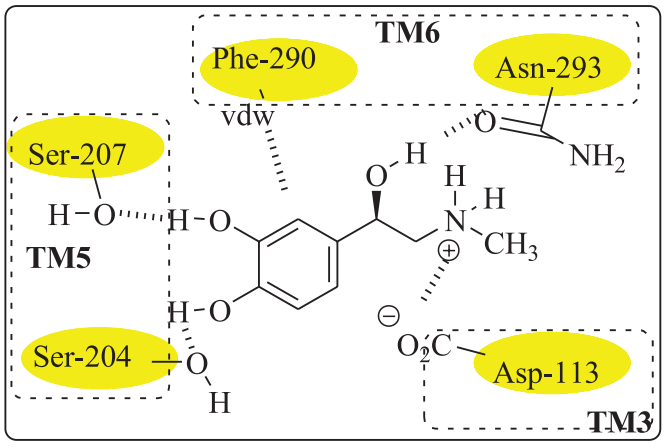

Figure 13. Catecholamines binding groups involved with the receptor.

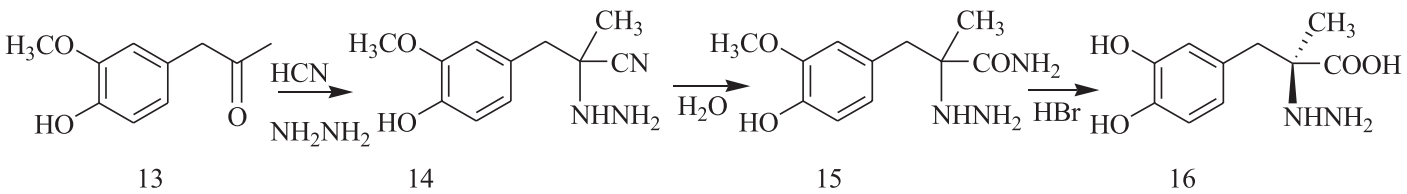

Figure 12. Synthesis of L-carbidopa.

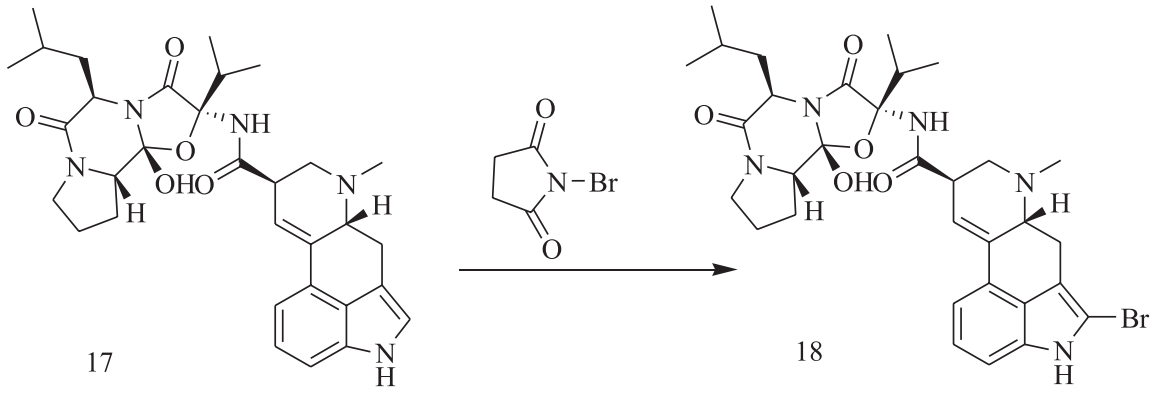

Figure 14. Semisynthesis of bromocriptine.

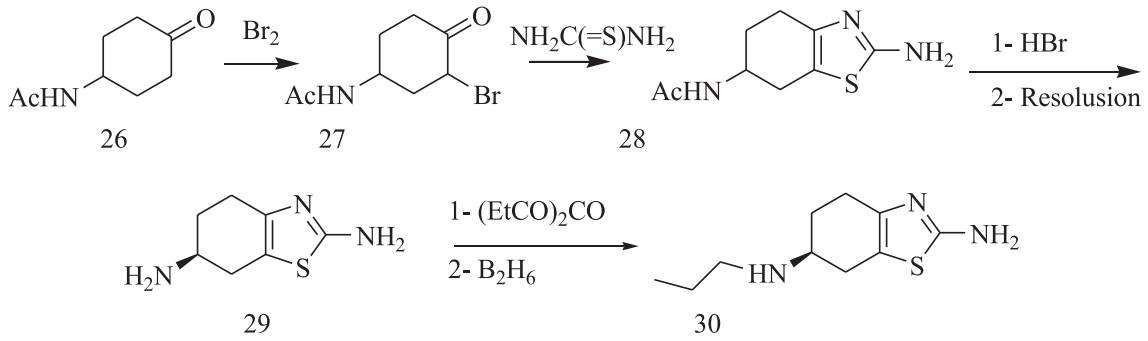

Figure 16. Synthesis of pramipexole.

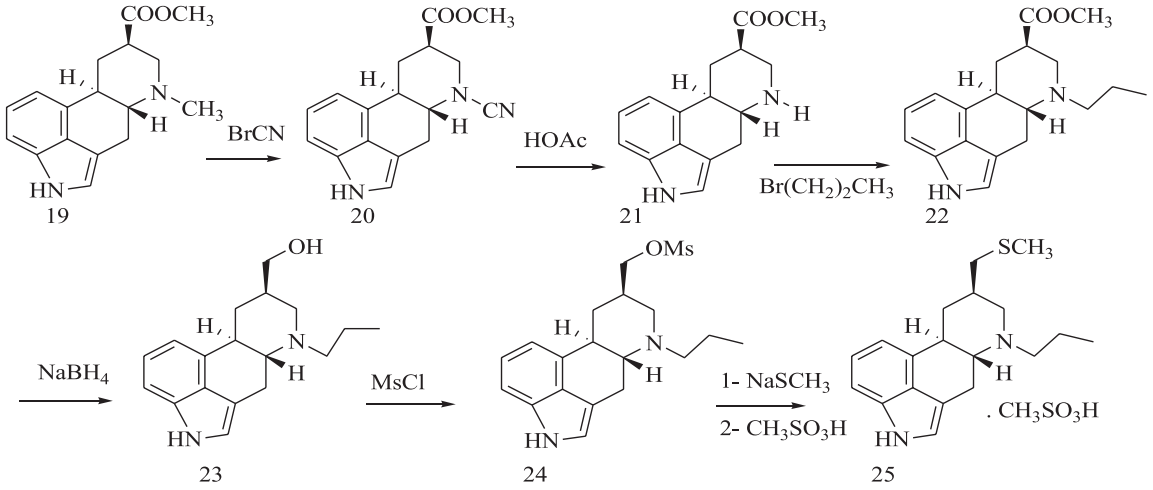

Figure 15. Synthesis of pergolide.

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 (Kalgutkar *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 (Kalgutkar *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:

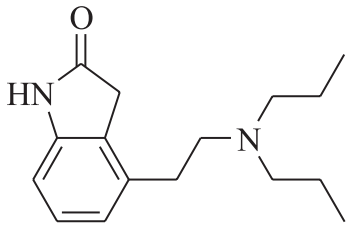

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Figure 17. The structure of ropinirole.

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

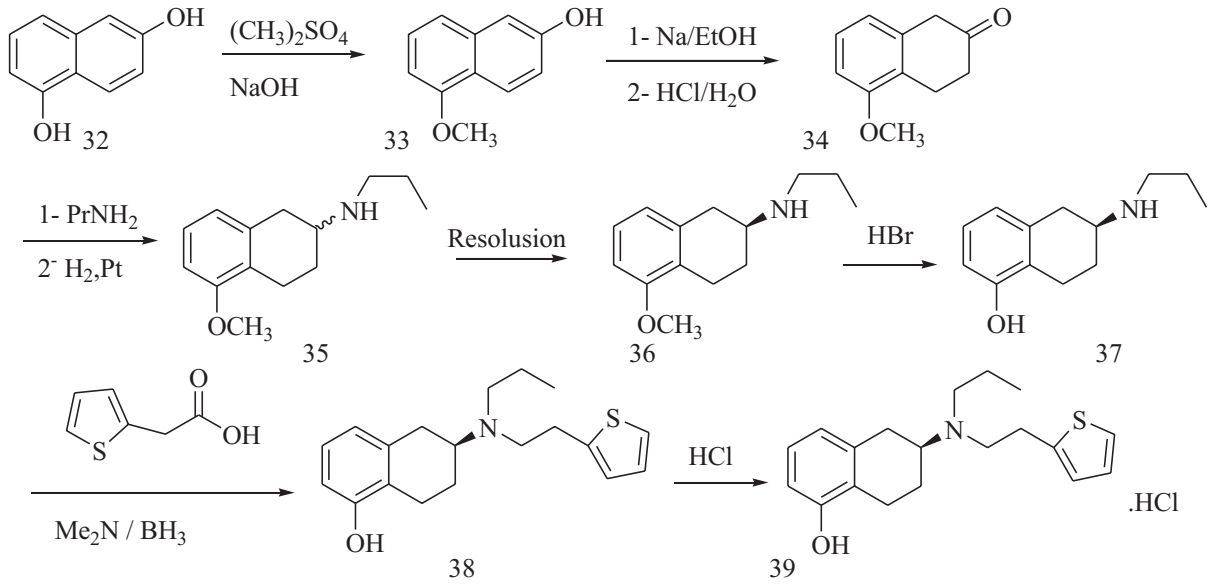


Figure 18. Synthesis of rotigotine.

increase the risks of having Parkinson's symptoms in human and animals (Reynolds *et al*., 1978; Tetrud 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).

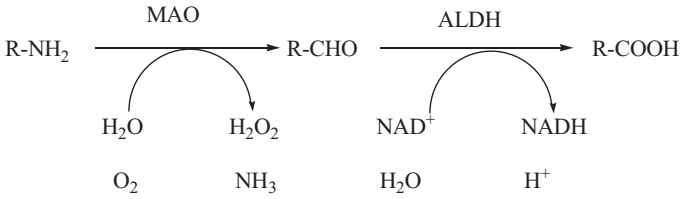


Figure 19. Breakdown of monoamines substrates by MAO to aldehydes and by ALDH to carboxylic acid.

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,

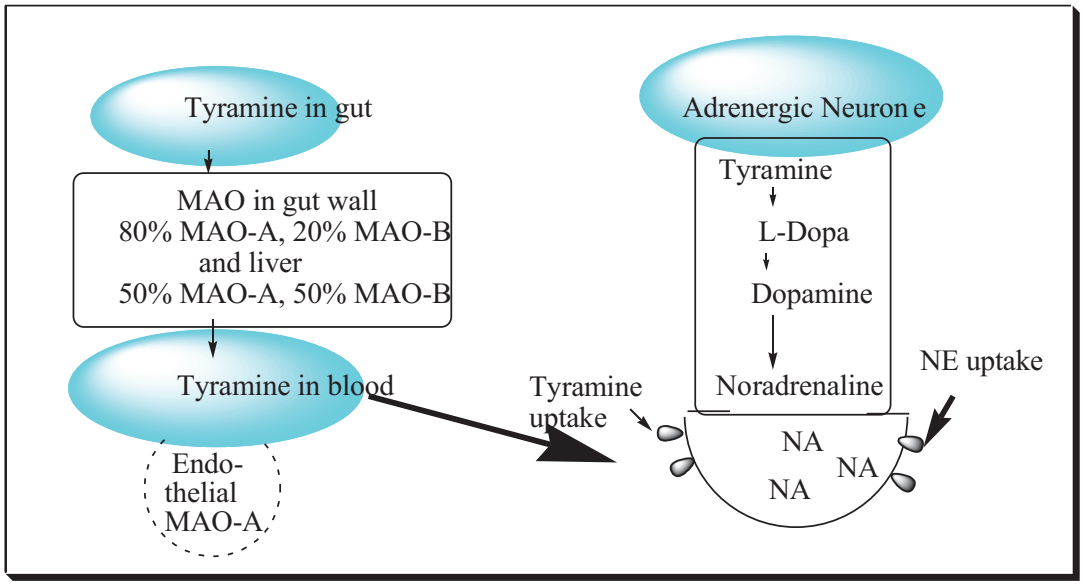


Figure 20. Mechanism of hypertensive crisis caused by MAO-A inhibitors.

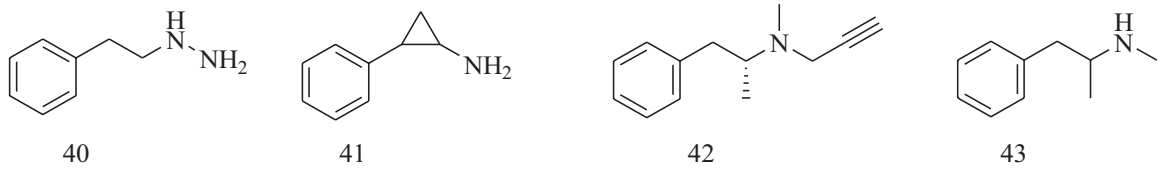


Figure 21. Structure of phenelzine, tranylcypromine, selegiline, and 1-methamphetamine.

2010; Olanow *et al*., 1995). 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 mg^{2+} 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).

Therefore, the development of COMT inhibitors was initiated. These drugs are used as adjunctive therapy with levodopa in the treatment of PD. They can act centrally and peripherally as they show positive results in the treatment of neurological and psychiatric disorders (Ericsson, 1971).

The first generation of COMT inhibitors (Fig. 27) was developed back in the late 1950s; all of these drugs contained catechol groups, such as gallic acid (58), caffeic acid (59), U-0521 (60), 2-hydroxyoestrogen (61), and flavonoids like quercetin (62). However, there are numerous reports available, revealing the inhibition of COMT by some plant-derived alkaloids and phenolics (Abdel-Moty *et al*., 1998; Chaudhary *et al*., 2016, 2018a, 2018b, 2019, 2020; El-Shorbagi *et al*., 2015, 2019; Mohamed *et al*., 1993; Soliman *et al*., 2019; Vieira-Coelho *et al*., 1996). These drugs have undergone insufficient clinical trials, so they are not actually used as medicines due to unsatisfactory selectivity, toxicity, and disadvantageous pharmacokinetics (Backstrom *et al*., 1989; Ruottinen and Rinne, 1998).

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).

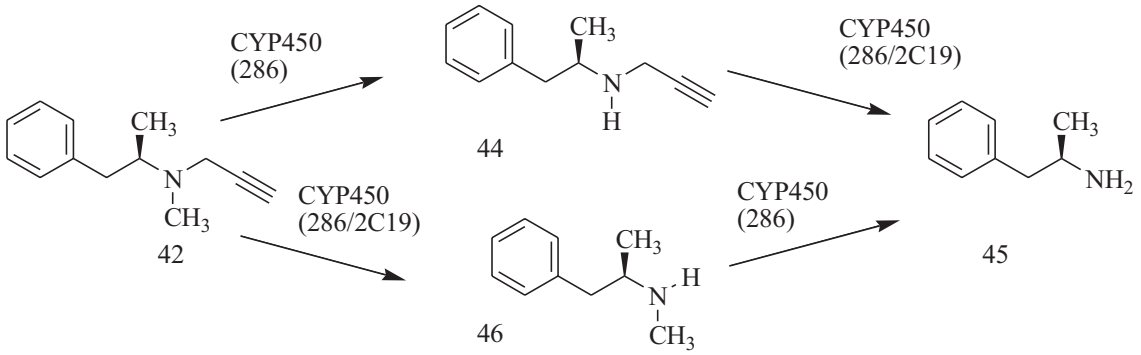


Figure 22. Metabolism of selegiline to the toxic metabolite amphetamine.

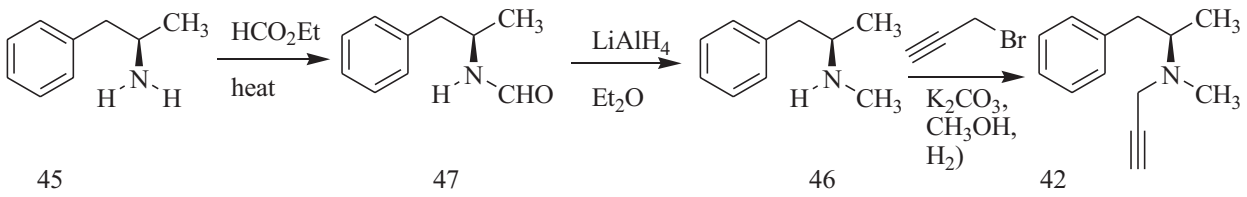


Figure 23. Chemical synthesis of Selegiline.

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).

48 49

Figure 24. Metabolites of rasagiline and selegiline.

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-methoxy tyramine (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

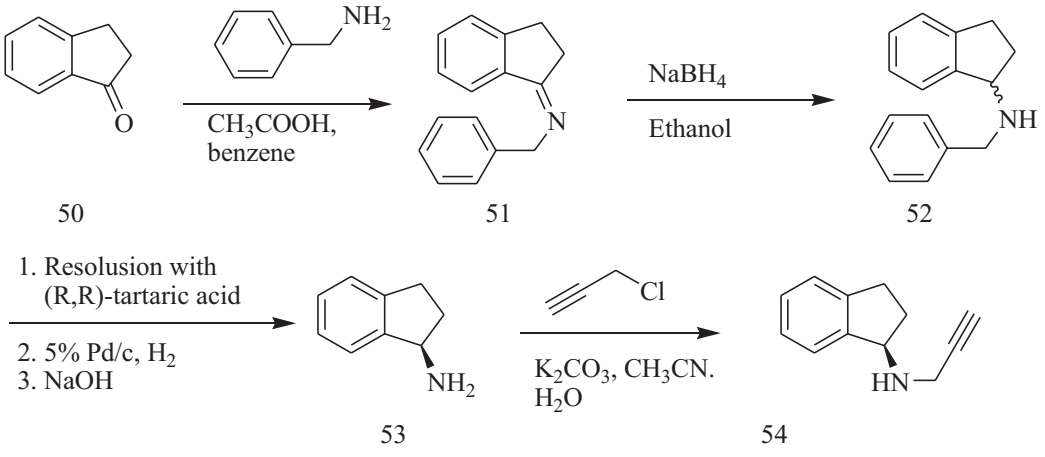


Figure 25. Chemical synthesis of rasagiline.

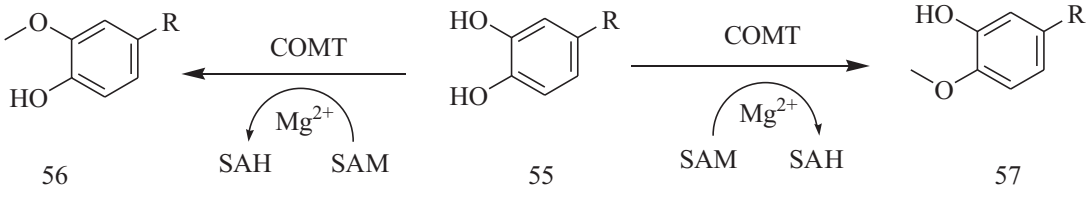


Figure 26. O-Methylation mechanism of COMT enzyme to catechol neurotransmitters like dopamine.

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-dihyroxy-5-nitrobenzaldehya 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 (CH_2CH_2) 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 (CH_3CO) group. The conversion of acetoxy into carbamoyl (NH_2CO) 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,

63 64

Figure 28. Structure of 3-O-methyldopa and HVA.

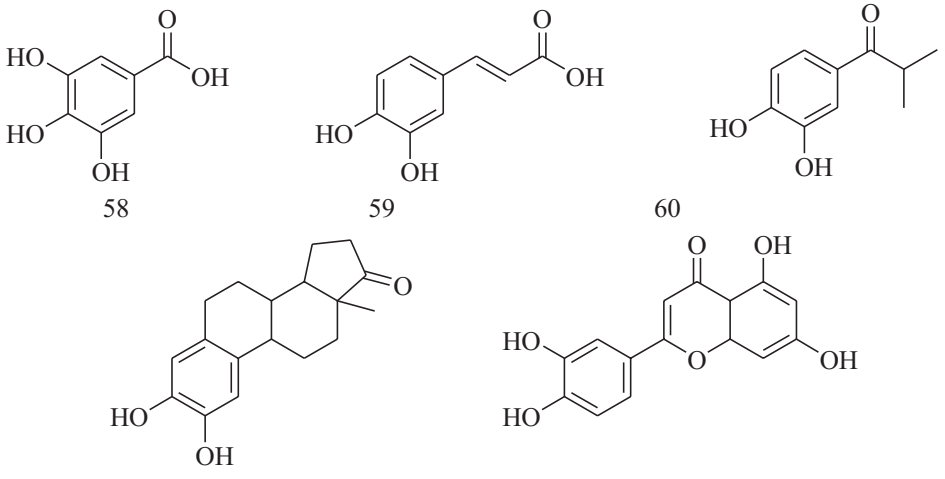


Figure 27. First-generation COMT inhibitors.

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.

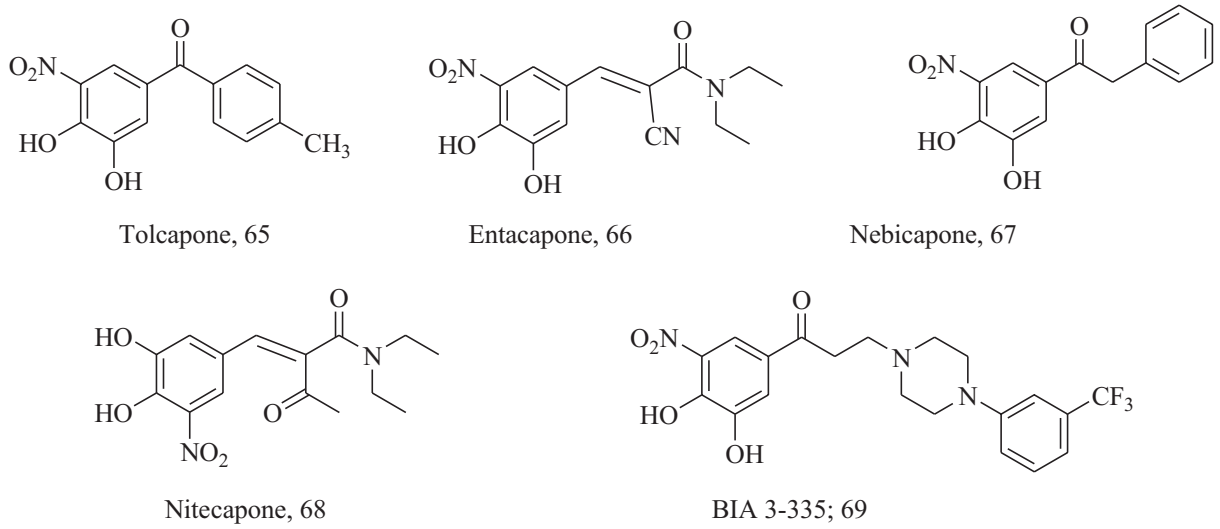


Figure 29. Nitrocatechol derivatives as COMT inhibitors (second generation).

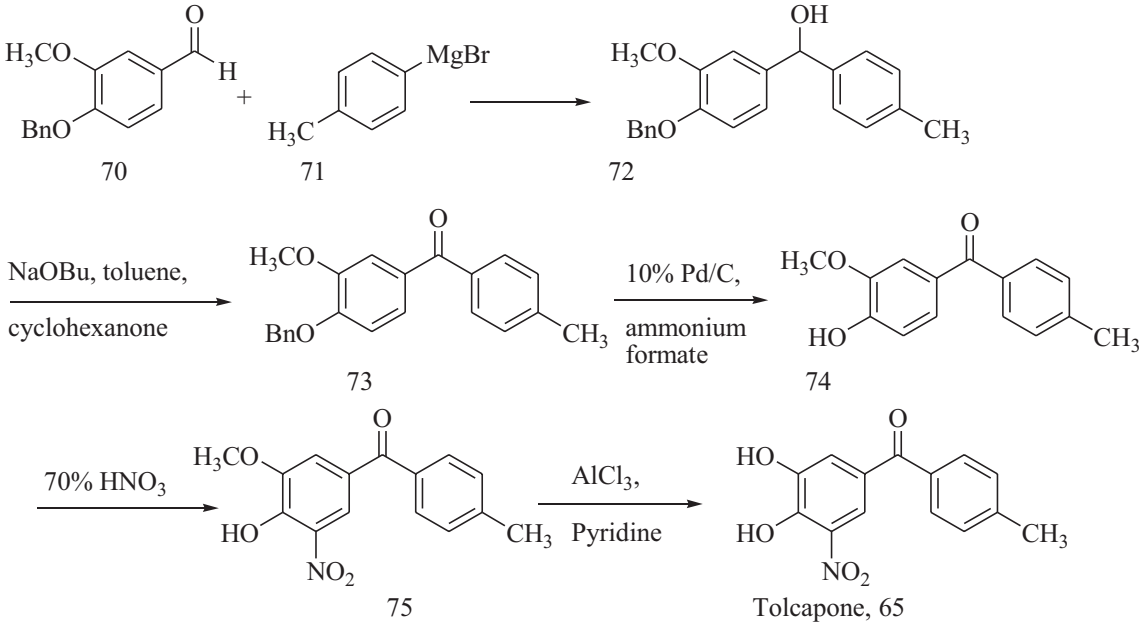


Figure 30. Chemical synthesis of tolcapone.

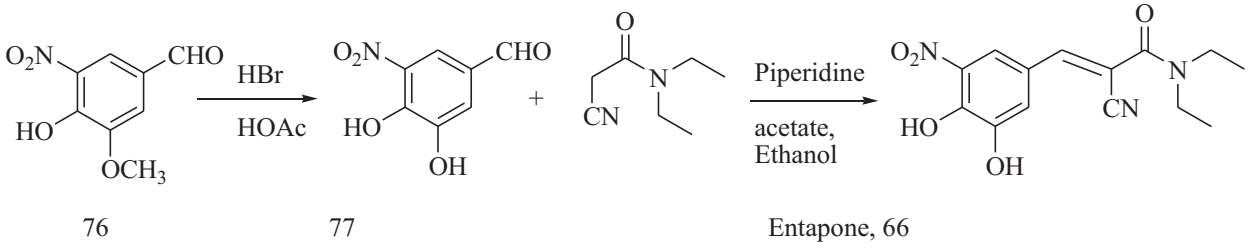


Figure 31. Chemical synthesis of tolcapone.

Anticholinergic drugs

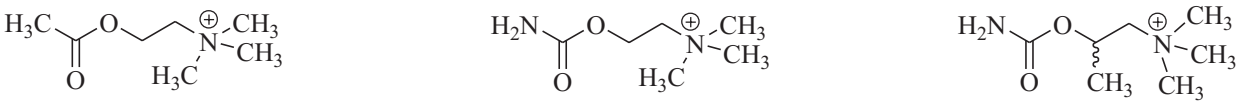
Serval drugs fall under the anticholinergics class, like benztropine (83), biperiden (86), and benzhexol (89). The design of anticholinergic drugs relies on the shape of the active site of the muscarinic cholinergic receptor and the binding interactions include acetylcholine. Therefore, there is a need 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 (Br_2) (Fig. 34). The intermediate (82) reacts with tropine and work-up results in the formation of benztropine (83) (Pedersen *et al*., 2004).



Acetylcholine, 78 Carbachol, 79 Bethanichol, 80

Figure 32. Structures of acetylcholine and cholinergic drugs.

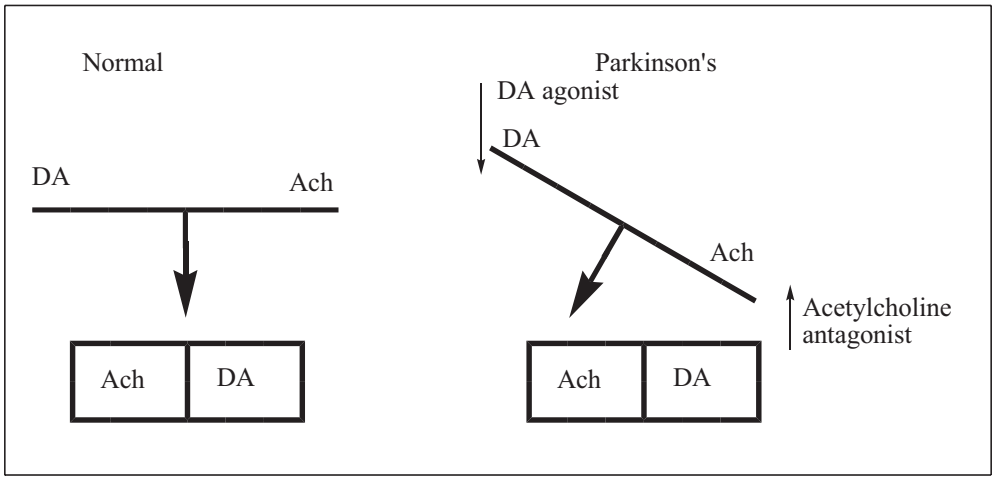


Figure 33. Imbalance between acetylcholine and dopamine.

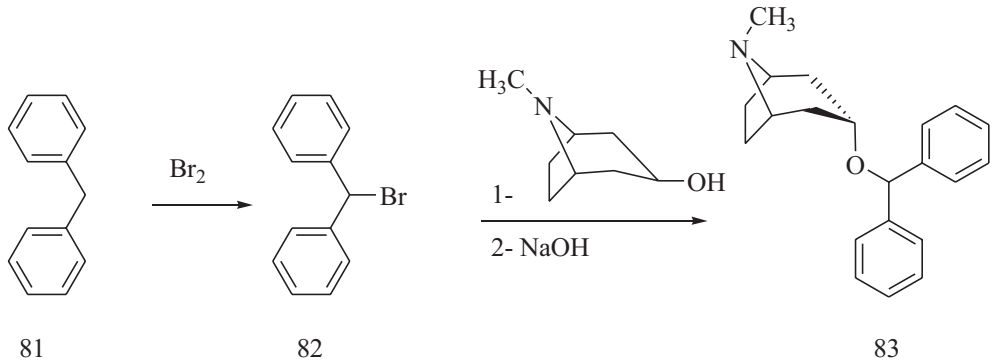


Figure 34. Synthesis of benztropine.

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-piperdino) 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).

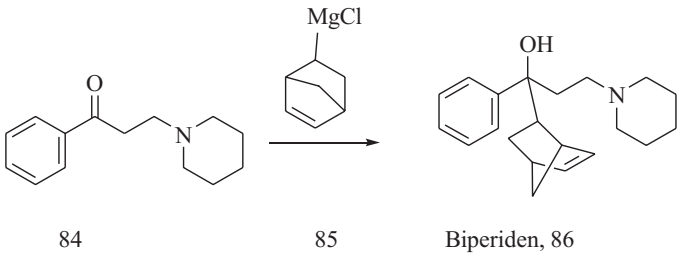


Figure 35. Synthesis of biperiden.

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

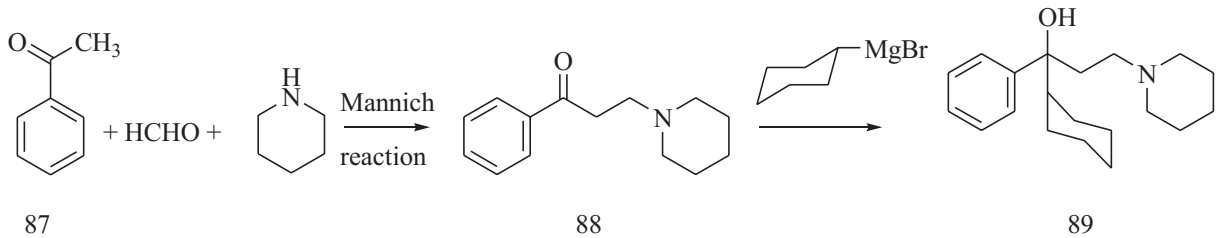


Figure 36. Synthesis of benzhexol.

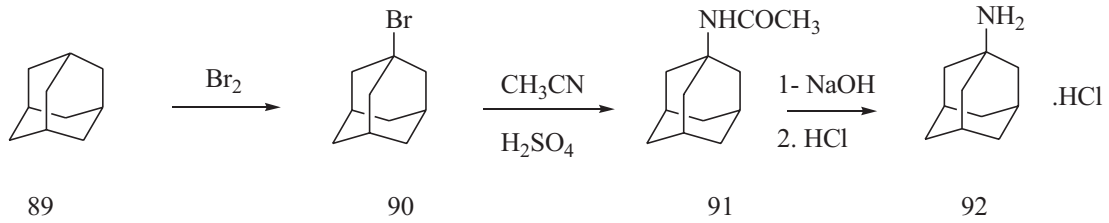


Figure 37. Synthesis of amantadine.

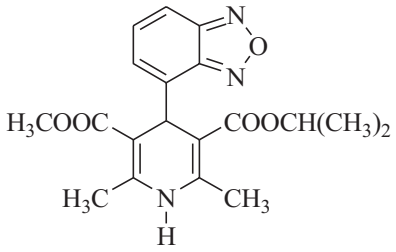


Figure 38. Structure of isradipine.

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro- Pro- Pro-Ser-NH2

Figure 39. Amino acid arrangement of exendin-4.

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

The authors declare no conflicts of interest, financial or otherwise, with this work.

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REFERENCES

Abdel-Moty SG, Sakai S, Aimi N, Takayama H, Kitajima M, El-Shorbagi A, Ahmed AN, Omar NM. Synthesis of cytotoxic 1-polyhydroxyalkyl-β-carboline derivatives. Eur J Med Chem, 1998; 32(12):1009-1017.

Aboukarr A. Interaction between monoamine oxidase B inhibitors and selective serotonin inhibitors. Can J Hosp Pharm, 2018; 71(3):196–207.

Abu-Raya S, Tabakman R, Blaugrund E, Trembovler V, Lazarovici P. Neuroprotective and neurotoxic effects of monoamine oxidase-B inhibitors and derived metabolites under ischemia in PC12 cells. Eur J Pharmacol, 2002; 434(3):109–16.

Aellig WH, Nuesch E. Comparative pharmacokinetic investigations with tritium-labeled ergot alkaloids after oral and intravenous administration man. Int J Clin Pharmacol Biopharm, 1977; 15(3):106–12.

Arotcarena ML, Teil M, Dehay B. Autophagy in synucleinopathy: the overwhelmed and defective machinery. Cells, 2019; 8(565):1–24.

Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, Hibbert S, Budnik N, Zampedri L, Dickson J, Li Y, Aviles-Olmos I, Warner TT, Limousin P, Lees AJ, Greig AJ, Tebbs S, Foltynie T. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet, 2017; 390(10103):1664–75.

Awad O, Sarkar C, Panicker LM, Miller D, Zeng X, Sgambato JA, Lipinski MM, Feldman RA. Altered TFEB-mediated lysosomal biogenesis in gaucher disease iPSC-derived neuronal cells. Hum Mol Genet, 2015; 24(20):5775–88.

Axelrod J. Methylation reactions in the formation and metabolism of catecholamines and other biogenic amines. Pharmacol Rev, 1966; 18(1):95–113.

Axelrod J, Tomchick R. Enzymatic O-methylation of epinephrine and other catechols. J Mol Biol, 1958; 233(3):702–5.

Backstrom R, Honkanen E, Pippuri A, Kairisalo P, Pystynen J, Heinola K, Nissinen E, Linden IB, Mannisto PT, Kaakkola S. Synthesis of some novel potent and selective catechol-O-methyltransferase inhibitors. J Med Chem, 1989; 32(4):841–6.

Bertilsson G, Patrone C, Zachrisson O, Andersson A, Dannaeus K, Heidrich J, Kortesmaa J, Mercer A, Nielsen E, Roonnholm H, Wikstrom L. Peptide hormone exendin-4 stimulates subventricular zone neurogenesis in the adult rodent brain and induces recovery in an animal model of Parkinson's disease. J Neurosci Res, 2008; 86(2): 326–38.

Birkmayer W, Hornykiewicz O. The l-dioxyphenylalanine (Dopa) effect in parkinson-akinesia. Wien Klin Wochenschr, 1961; 10(73):77–88.

Borgulya J, Bruderer H, Bernauer K, Zurcher G, Da PM. Catechol-O-methyltransferase-inhibiting pyrocatechol derivatives-synthesis and structure activity studies. Helv Chim Acta, 1989; 72(5):952–68.

Bortolato M, Chen K, Shih JC. Monoamine oxidase inactivation: from pathophysiology to therapeutics. Adv Drug Deliv Res, 2008; 60(13–14):1527–33.

Brannan T, Prikhojan A, Yahr MD. Peripheral and central inhibitors of catechol-O-methyl transferase: effects on liver and brain COMT activity and L-DOPA metabolism. J Neural Transm, 1997; 104(1):77–87.

Brenna D, Pirola M, Raimondi L, Burke AJ, Benaglia M. A stereoselective, catalytic strategy for the in-flow synthesis of advanced precursors of rasagiline and tamsulosin. Bioorg Med Chem, 2017; 25(23):6242–7.

Brooks DJ. Dopamine agonists: their role in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry, 2000; 68(6): 685–90.

Bruno A, Bruno SC. Effects of L-2, 4-dihydossifenilalanina (L-Dopa) in parkinsonian patients. Riv Sper Freniatr, 1966; 90:39.

Cabri W, Roletto J, Olmo S, Fonte P, Ghetti P, Songia S, Mapelli E, Alpegiani M, Paissoni P. Development of a practical high-yield industrial synthesis of pergolide mesylate. Org Process Res Dev, 2006; 10(2):198–202.

Caccia C, Maj R, Calabresi M, Maestroni S, Faravelli L, Curatolo L, Salvati P, Fariello RG. Safinamide: from molecular targets to a new anti-Parkinson drug. Neurology, 2006; 67(7):S18–23.

Casimir F. LXV-synthesis of dl-3:4-dihydroxyphenylalanine. J Chem Soc Trans, 1911; 99:554–7.

Castillo SO, Baffi JS, Palkovits M, Goldstein DS, Kopin IJ, Witta J, Magnuson MA, Nikodem VM. Dopamine biosynthesis is selectively abolished in substantia nigra/ ventral tegmental area but not in hypothalamic neurons in mice with targeted disruption of the Nurr1 gene. Mol Cell Neurosci, 1998; 11(1–2):36–46.

Cavanaugh JH, Griffith JD, Oates JA. Effect of amphetamine on the pressor response to tyramine: formation of p-hydroxynorephedrine. Clin Pharmacol Ther, 1970; 11(5):656–64.

Cedarbaum JM. Clinical pharmacokinetics of anti-parkinsonian drugs. Clin Pharmacokinet, 1987; 13(3):1411–78.

Chase TN. The significance of continuous dopaminergic stimulation in the treatment of Parkinson's disease. Drugs, 1998; 55(1):1–9.

Chaudhary S, Gupta RK, Gupta MK, Verma HC, Kumar H, Kumar A, Swain SR, El-Shorbagi AN. Hepatoprotective response of Cordia sebestena L. fruit against simvastatin induced hepatotoxicity. J Pharm Pharmacogn Res. 2020; 8(4):327–35.

Chaudhary S, Gupta RK, Kumar A, Tarazi H. Hepatoprotective and antitubercular potential of *Nyctanthes* arbor-tristis L. leaves against antitubercular drug induced hepatotoxicity. J Pharm Pharmacogn Res, 2018a; 6(3):205–15.

Chaudhary S, Hisham H, Mohamed D. A review on phytochemical and pharmacological potential of watercress plant. Asian J Pharm Clin Res, 2018b; 11(12):102–7.

Chaudhary S, Semwal A, Kumar H, Verma HC, Kumar A. *In-vivo* study for anti-hyperglycemic potential of aqueous extract of basil seeds (*Ocimum basilicum* linn) and its influence on biochemical parameters, serum electrolytes and haematological indices. Biomed Pharmacother, 2016; 84:2008–13.

Chaudhary S, Verma HC, Gupta MK, Kumar H, Swain SR, Gupta RK, El-Shorbagi AN. Antidiabetic aptitude of *Cordia sebestena* and its outcome on biochemical parameters, serum electrolytes, and hematological markers. Pharmacogn J, 2019; 11(2):418–23.

Churchyard A, Mathias CJ, Boonkongchuen P, Lees AJ. Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson's disease. J Neurol Neurosurg Psychiatry, 1997; 63(2):228–34.

Clarke A, Brewer F, Johnson ES, Mallard N, Corn TH, Johnston A, Boyce M, Warrington S, MacMahon DG. A new low-dose formulation of selegiline: clinical efficacy, patient preference and selectivity for MAO-B inhibition. J Neural Transm, 2003b; 110(1):1257–71.

Davis GC, Williams AC, Markey SP, Ebert MH, Caine ED, Reichert CM, Kopin IJ. Chronic parkinsonism secondary to intravenous injection of meperidine analogues. Psychiatry Res, 1979; 1(3):249–54.

de Hemptinne C, Swann NC, Ostrem JL, Ryapolova-Webb ES, San Luciano M, Galifianakis NB, Starr PA. Therapeutic deep brain Stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. Nat Neurosci, 2015; 18(5):779–86.

de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. Lancet Neurol, 2006; 5(6):525–35.

Ebersbach G, Baas H, Csoti I, Mungersdorf M, Deuschi G. Scales in parkinson's disease. J Neurol, 2006; 253(4):iv32–5.

Eden RJ, Costall B, Domeney AM, Gerrard PA, Harvey CA, Kelly ME, Naylor RJ, Owen DA, Wright A. Preclinical pharmacology of ropinirole (SK&F 101468-A) a novel dopamine D2 agonist. Pharmacol Biochem Behav, 1991; 38(1):147–54.

El-Shorbagi AA, Abdel-Moty S.G, Ahmed AN, Takayama H, Kitajima M, Aimi N, Sakai S. The antiviral (RNA & DNA) profile of some incomplete C-nucleosides inspired from natural β-carboline (pyrido [3,4-b] indole) scaffold; pharmacology of the intermediates in the total synthesis. Der Pharma Chemica, 2015; 7(11):87–92.

El-Shorbagi AN, Chaudhary S. Monobactams: a unique natural scaffold of four-membered ring skeleton, recent development to clinically overcome infections by multidrugresistant microbes. Lett Drug Des Discov, 2019; 16(12):1305–20.

Ericsson AD. Potentiation of the L-dopa effect in man by the use of catechol-O-methyltransferase inhibitors. J Neurol Sci, 1971; 14(2):193–7.

Finberg JP, Update on the pharmacology of selective inhibitors of MAO-A and MAO-B: focus on modulation of CNS monoamine neurotransmitter release. Pharmacol Ther, 2014; 143(2):133–52.

Finberg JPM. Pharmacology of rasagiline, a new MAO-B inhibitor drug for the treatment of parkinson's disease with neuroprotective potential. Ramban Maimonides Med J, 2010; 1(1):1–10.

Firestone JA, Smith-Weller T, Franklin G, Swanson P, Longstreth WT, Checkoway H. Pesticides and risk of Parkinson disease: a population-based case-control study. Arch Neurol, 2005; 62(1):91–5.

Fuller RW, Clemens JA. Pergolide: a dopamine agonist at both D1 and D2 receptors. Life Sci, 1991; 49(13):925–30.

Giachetti A, Giraldo E, Ladinsky H, Montagna E., Binding and functional profiles of the selective M1 muscarinic receptor antagonists trihexyphenidyl and dicyclomine. Br J Pharmacol, 1986; 89(1):83–90.

Gil M, McKinney C, Lee MK, Eells JB, Phyillaier MA, Nikodem VM. Regulation of GTP cyclohydrolase I expression by orphan receptor Nurr1 in cell culture and *in vivo*. J Neurochem, 2007; 101(1):142–50.

Gilks WP, Abou-sleiman, PM, Gandhi S, Jain S, Singleton A, Lees AJ, Shaw K, Bhatia KP, Bonifati V, Quinn NP, Lynch J, Healy DG, Holton JL, Revesz T, Wood NW. A common LRRK2 mutation in idiopathic Parkinson's disease. Lancet, 2005; 365(9457):415–6.

Gill JR, Mason DT, Bartter FC. Effects of hydroxyamphetamine on the function of the sympathetic nervous system in normotensive subjects. J Pharmacol Exp Ther, 1967; 155(2):288–95.

Goetz CG, Diederich NJ. Dopaminergic agonists in the treatment of Parkinson's disease. Neurol Clin, 1992; 10(2):527–40.

Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins, GT, Stern MB, Tilley BC, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, Lewitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, Van Hilten JJ, LaPelle N. Movement disorder of society-sponsored revision of the unified parkinson's disease rating scale (MDS-UPDRS): process, format, and clinimetric testing plan. Mov Disord, 2007; 22(1):41–7.

Goldwurm S, Zini M, Mariani L, Tesei S, Miceli R, Sironi, F, Clementi M, Bonifati V, Pezzoli G. Evaluation of LRRK2 G2019S penetrance: relevance for genetic counseling in Parkinson disease. Neurology, 2007; 68(14):1141–3.

Guerra de Souza AC, Prediger RD, Cimarosti H. SUMO-regulated mitochondrial function in Parkinson's disease. J Neurochem, 2016; 137(5):673–86.

Guldberg HC, Marsden CA. Catechol-O-methyl transferase: pharmacological aspects and physiological role. Pharmacol Rev, 1975; 27(2):135–206.

Harrison ST, Poslusney MS, Mulhearn JJ, Zhao Z, Kett NR, Schubert JW, Melamed JY, Allison TJ, Patel SB, Sanders JM, Sharma S, Smith RF, Hall DL, Robinson RG, Sachs NA, Hutson PH, Wolkenberg SE, Barrow JC. Synthesis and evaluation of heterocyclic catechol mimics as inhibitors of catechol-o-methyltransferase (COMT). ACS Med Chem Lett, 2015; 6(3):318–23.

Hunot S, Brugg B, Ricard D, Michel PP, Muriel MP, Ruberg M, Faucheux BA, Agid Y, Hirsch EC. Nuclear translocation of NF-κB is increased in dopaminergic neurons of patients with Parkinson disease. Proc Natl Acad Sci, 1997; 94:7531–6.

Jackson-Lewis V, Przedborski S. Protocol for the MPTP mouse model of parkinson's disease. Nat Protoc, 2007; 2(1):141–51.

Jankovic J. Parkinson's disease therapy: tailoring choices for early and late disease, young and old patients. Clin Neuropharmacol, 2000; 23(5):252–61.

Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Psychiatry, 2008; 79:368–76.

Johnston JP. Some observations upon a new inhibitor of monoamine oxidase in brain tissue. Biochem Pharmacol, 1968; 17(7):1285–97.

Kaakkola S. Clinical pharmacology, therapeutic use and potential of COMT inhibitors in Parkinson's disease. Drugs, 2000; 59(6):1233–50.

Kaakkola S, Mannisto PT, Nissinen E. Striatal membrane-bound and soluble catechol-o-methyl-transferase after selective neuronal lesions in the rats. J Neural Transm, 1987; 69(3–4):221–8.

Kalgutkar AS, Dalvie DK, Jr CN, Taylor TJ. Interactions of nitrogen-containing xenobiotics with monoamine oxidase (MAO) isozymes A and B: SAR studies on MAO substrates and inhibitors. Chem Res Toxicol, 2001; 14(9):1139–62.

Karady S, Ly MG, Pines SH, Sletzinger M. Synthesis of D- and L-alpha-(3,4-dihydroxybenzyl)-alpha-hydrazinopropionic acid via resolution. J Org Chem, 1971; 36(14):1946–8.

Kempster PA, Hurwitz B, Lees AJ. A new look at James Parkinson's essay on the shaking palsy. Neurology, 2007; 69(5):482–5.

Kim JL, Bortan E. The role of rasagiline in the treatment of Parkinson's disease. Clin Interv Aging, 2010; 5:149–56.

Klein C, Westenberger A. Genetics of Parkinson's disease. Cold Spring Harb Perspect Med, 2012; 2(1):1–15.

Knoll J, Magyar K. Some puzzling pharmacological effects of monoamine oxidase inhibitors. Adv Biochem Psychopharmacol, 1972; 5:393–408.Knowles W. Asymmetric hydrogenations (Nobel lecture). Angew Chem Int Ed Engl, 2002; 41(12):1999–2007.

Lai BC, Marion SA, Teschke K, Tsui JK. Occupational and environmental risk factors for Parkinson's disease. Parkinsonism Relat Disord, 2002; 8(5):297–309.

Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. Science, 1983; 219(4587):979–80.

Langston JW, Ballard PA. Parkinson's disease in a chemist working with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. N Engl J Med, 1983; 309(5):310.

Learmonth DA, Vieira-Coelho MA, Benes J, Alves PC, Borges N, Freitas AP, da-Silva PS. Synthesis of 1-(3,4-dihydroxy-5-nitrophenyl)-2-phenyl-ethanone and derivatives as potent and long-acting peripheral inhibitors of catechol-O-methyltransferase. J Med Chem, 2002; 45(3):685–95.

Leegwater-Kim J, Waters C. Tolcapone in the management of parkinson's disease. Expert Opin Pharmacother, 2006; 7:2263–70.

Li T, Li X. Comprehensive mass analysis for chemical processes, a case study on L-dopa manufacture. Green Chem, 2014; 16(9):4241–56.

Li Y, Perry T, Kindy MS, Harvey BK, Tweedie D, Holloway HW, Powers K, Shen H, Egan JM, Sambamurti K. GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism. Proc Natl Acad Sci, 2009; 106:1285–90.

Lieberman AN, Goldstein M. Bromocriptine in Parkinson disease. Pharmacol Rev, 1985; 37(2):217–27.

Lin Y, Li W, Tan C, Liu X, Wang X, Gui Y, Qin L, Deng F, Hu C, Chen L. Meta-analysis comparing deep brain stimulation of the globus pallidus and subthalamic nucleus to treat advanced Parkinson's disease. J Neurosurg, 2014; 121(3):709–18.

Linden IB, Nissinen E, Etemadzadeh E, Kaakkola S, Mannisto P, Pohto P. Favorable effect of catechol-O-methyltransferase inhibition by OR-462 in experimental models of Parkinson's disease. J Pharmacol Exp Ther, 1988; 247(1):289–93.

Ma Z, Liu H, Wu B. Structure-based drug design of catechol-*O*-methyltransferase inhibitors for CNS disorders. Br J Clin Pharmacol, 2014; 77(3):410–20.

Mannisto PT, Kaakkola S. Catechol-O-methyltransferase (COMT): biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. Pharmacol Rev, 1999; 51(4):593–628.

Mannisto PT, Kaakkola S. New selective COMT inhibitors: useful adjuncts for Parkinson's disease? Trends Pharmacol Sci, 1989; 10(2):54–6.

Mannisto PT, Tuomainen P, Tuominen RK. Different *in vivo* properties of three new inhibitors of catechol-O-methyltransferase in the rat. Br J Pharmacol, 1992; 105:569–74.

Marsh L. Neuropsychiatric aspects of Parkinson's disease. Psychosomatics, 2000; 41(1):15–23.

Martin WR, Sloan JW, Sapira JD, Jasinski DR. Physiologic, subjective and behavioral effects of amphetamine, metamphetamine, ephedrine, phenmetrazine and methylphenidate in man. Clin Pharmacol Ther, 1971; 12(2):245–58.

McClure MM, Harvey PD, Goodman M, Triebwasser J, New A, Koenigsberg HW, Sprung LJ, Flory JD, Siever LJ. Pergolide treatment of cognitive deficits associated with schizotypal personality disorder: continued evidence of the importance of the dopamine system in the schizophrenia spectrum. Neuropsychopharmacology, 2010; 35(6):1356–62.

Meissner WG, Frasier M, Gasser T, Goetz CG, Lozano A, Piccini P, Obeso JA, Rascol O, Schapira A, Voon V, Weiner DM, Tison F, Bezard E. Priorities in Parkinson's disease research. Nat Rev Drug Discov, 2011; 10(5):377–93.

Milic D, Demidkina TV, Faleev NG, Matkovic-Calogovic D, Antson AA. Insight into the catalytic mechanism of tyrosine phenol-lyase from x-ray structures of quinonoid intermediates. J Biol Chem, 2008; 283(43):29206–14.

Mohamed MH, El-Shorbagi AN. A. (±)-termisine, a novel lupine alkaloid from the seeds of Lupinus termis. J Nat Prod, 1993; 56(11):1999–2002.

Moors TE, Hoozemans JJ, Ingrassia A, Beccari T, Parnetti L, Chartier-Harlin MC, vandeBerg WD. Therapeutic potential of autophagy-enhancing agents in Parkinson's disease. Mol Neurodegener, 2017; 12(11):1–18.

Nandipati S, Litvan I. Environmental exposure and parkinson's disease. Int J Environ Res Public Health, 2016; 13(9):881.

Nath S, Goodwin J, Engelborghs Y, Pountney DL. Raised calcium promotes α-synuclein aggregate formation. Mol Cell Neurosci, 2011; 46(2):516–26.

Nissinen E, Linden IB, Schultz E, Kaakkola S, Mannisto PT, Pohto P. Inhibition of catechol-O-methyltransferase activity by two novel disubstituted catechols in the rat. Eur J Pharmacol, 1988a; 153(2–3): 263–9.

Nissinen E, Linden IB, Schultz E, Pohto P. Biochemical and pharmacological properties of a peripherally acting catechol-O-methyltransferase inhibitor entacapone. Naunyn Schmiedebergs Arch Pharmacol, 1992; 346(3):262–6.

Nissinen E, Tuominen R, Perhoniemi V, Kaakkola S. Catechol-O-methyltransferase activity in human and rat intestine. Life Sci, 1988b; 42(25):2609–14.Nutt JG, Fellman JH. Pharmacokinetics of levodopa. Clin Neuropharmacol, 1984; 7(1):35–49.

Odekerken VJ, van Laar T, Staal MJ, Mosch A, Hoffmann CF, Nijssen PC, Beute GN, van Vugt JP, Lenders MW, Contarino MF, Mink MS, Bour LJ, van den Munckhof P, Schmand BA, de Haan RJ, Schuurman PR, de Bie RM. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomized controlled trial. Lancet Neurol, 2013; 12(1):37–44.

Oguh O, Videnovic A. Inpatient management of parkinson disease: current challenges and future directions. Neurohospitalist, 2012; 2(1):28–35.

Okun MS, Foote KD. Parkinson's disease DBS: what, when, who and why? The time has come to tailor DBS target. Expert Rev Neurother, 2010; 10(12):1847–57.

Olanow CW, Hauser RA, Gauger L, Malapira T, Koller W, Hubble J, Bushenbark K, Lilienfeld D, Esterlitz J. The effect of deprenyl and levodopa on the progression of Parkinson's disease. Ann Neurol, 1995; 38(5):771–7.

Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease. Neurology, 2009; 72(4):S1–136.

Ovallath S, Sulthana B. Levodopa: history and therapeutic applications. Ann Indian Acad Neurol, 2017; 20(3):185–9.

Pagano G, Rengo G, Pasqualetti G. Cholinesterase inhibitors for parkinson's disease: a systematic review and meta-analysis. Neurol Neurosurg Psychiatry, 2015; 86(7):767–73.

Parkinson J. An essay on the shaking palsy. J Neuropsychiatry Clin Neurosci, 2002; 14(2):223–36.

Pedersen H, Sinning S, Bulow A, Wiborg O, Falborg L, Bols M., Combinatorial synthesis of benztropine libraries and their evaluation as monoamine transporter inhibitors. Org Biomol Chem, 2004; 2(19):2861–9.

Pletscher A, DaPrada M. Pharmacotherapy of parkinson's disease: research from 1960 to 1991. Acta Neurol Scand Suppl, 1993; 146:26–31.

Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL. Mutation in the alpha-synuclein gene identified in families with parkinson's disease. Science, 1997; 276(5321):2045–7.

Priyadarshi A, Khuder SA, Schaub EA, Shrivastava S. A meta-analysis of parkinson's disease and exposure to pesticides. Neurotoxicology, 2000; 21(4):435–40.

Pu J, Keren-Kaplan T, Bonifacino JS. A regulator-BORC interaction controls lysosome positioning in response to amino acid availability. J Cell Biol, 2017; 216(12):4183–97.

Ramaker C, Marinus J, Stiggelbout AM, Van Hilten BJ. Systematic evaluation of rating scales for impairment and disability in parkinson's disease. Mov Disord, 2002; 17(5):867–76.

Rangno RE, Kaufmann JS, Cavanaugh JH, Island D, Watson JT, Oates J. Effects of a false neurotransmitter, p-hydroxynorephedrine, on the function of adrenergic neurons in hypertensive patients. J Clin Invest, 1973; 52(4):952–60.

Rascol O, Brooks D, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. N Engl J Med, 2000; 342:1484–91.

Reynolds GP, Elsworth JD, Blau K, Sandler M, Stern GM. Deprenyl is metabolized to methamphetamine and amphetamine in man. Br J Clin Pharmacol, 1978; 6(6):542–444.

Riederer P, Laux G. MAO-inhibitors in parkinson's disease. Exp Neurobiol, 2011; 20(1):1–17.

Rinne UK. Dopamine agonist as primary treatment in parkinson's disease. Adv Neurol, 1987; 45:519–23.

Rivero-Rios P, Madero-Perez J, Fernandez B, Hilfiker S. Targeting the autophagy/lysosomal degradation pathway in parkinson's disease. Curr Neuropharmacol, 2016; 14(3):238–49.

Ruottinen HM, Rinne UK. COMT inhibition in the treatment of parkinson's disease. J Neurol, 1998; 245(11):25–34.

Saura J, Andres N, Andrade C, Ojuel J, Eriksson K, Mahy N. Biphasic and region-specific MAO-B response to aging in normal human brain. Neurobiol Aging, 1997; 18(5):497–507.

Saura MJ, Kettler R, Da PM, Rochards JG. Molecular neuroanatomy of MAO-A and MAO-B. J Neural Transm Suppl, 1990; 32:49–53.

Scatton B, Cheramy A, Besson MJ, Glowinski J. Increased synthesis and release of dopamine in the striatum of the rat after amantadine treatment. Eur J Pharmacol, 1970; 13(1):131–3.

Schiff Jr PL. Ergot and its alkaloids. Am J Pharm Educ, 2006; 70(5):1–10.

Settembre C, DiMalta C, Polito VA, Garcia Arencibia M, Vetrini F, Erdin S, Erdin SU, Huynh T, Medina D, Colella P, Sardiello M, Rubinsztein DC, Ballabio A. TFEB links autophagy to lysosomal biogenesis. Science, 2011; 332(6036):1429–33.

Shah RS, Chang SY, Min HK, Cho ZH, Blaha CD, Lee KH. Deep brain stimulation technology at the cutting edge. J Clin Neurol, 2010; 6(4):167–82.

Singleton AB, Farrer MJ, Bonifati V. The genetics of parkinson's disease: progress and therapeutic implications. Mov Disord, 2013; 28(1):14–23.

Sletzinger M, Chemerda JM, Bollinger FW. Potent decarboxylase inhibitors. Analogs of methyldopa. J Med Chem, 1963; 6(2):101–3.

Soliman S, Hamoda AM, El-Shorbagi ANA, El-Keblawy AA. Novel betulin derivative is responsible for the anticancer folk use of *Ziziphus spina-christi* from the hot environmental habitat of UAE. J Ethnopharmacol, 2019; 231:403–8.

Spathis AD, Asvos X, Ziavra D, Karampelas T, Topouzis S, Cournia Z, Qing X, Alexakos P, Smits LM, Dalla C, Rideout HJ, Schwamborn JC, Tamvakopoulos C, Folas D, Vassilatis DK. Nurr1: RXRα heterodimer activation as monotherapy for Parkinson's disease. Proc Natl Acad Sci, 2017; 114(15):3999–4004.

Speiser Z, Levy R, Cohen S. Effects of N-propargyl-1-(R) aminoindan (rasagiline) in models of motor and cognition disorders. J Neural Transm Suppl, 1998; 52:287–300.

Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. α-Synuclein in lewy bodies. Nature, 1997; 388(6645):839–40.

Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of parkinson's disease. Science, 1989; 245(4917):519–22.

Tintner R, Manian P, Gauthier P, Jankovic J. Pleuropulmonary fibrosis after long-term treatment with the dopamine agonist pergolide for parkinson disease. Arch Neurol, 2005; 62(8):1290–5.

Trost BM. The atom economy-a search for synthetic efficiency. Science, 1991; 254(5037):1471–7.

Truong DD. Tolcapone: review of its pharmacology and use as adjunctive therapy in patients with parkinson's disease. Clin Interv Aging, 2009; 4:109–13.

Tsao D, Diatchenko L, Dokholyan NV. Structural mechanism of S-adenosyl methionine binding to catechol O-methyltransferase. PloS One, 2011; 6(8):1–5.

Van Hilten JJ, Ramaker CC, Stowe R, Ives NJ. Bromocriptine versus levodopa in early parkinson's disease. Cochrane Database Syst Rev, 2007; 17(4):CD002258.

Vieira-Coelho MA, Soares-da-Silva P. Ontogenic aspects of liver and kindey catechol-*O*-methyltransferase sensitivity to tolcapone. Br J Pharmacol, 1996; 117(3):516–20.

Vrecko K, Birkmayer JG, Krainz J. Stimulation of dopamine biosynthesis in cultured PC 12 phaeochromocytoma cells by the coenzyme nicotinamide adeninedinucleotide (NADH). J Neural Transm Park Dis Dement Sect, 1993; 5(2):147–56.

Wakade C, Chong R, A novel treatment target for parkinson's disease. J Neurol Sci, 2014; 347(1–2):34–8.

Woolverton WL, Ricaurte GA, Forno LS, Seiden LS. Long-term effects of chronic methamphetamine administration in rhesus monkeys. Brain Res, 1989; 486(1):73–8.

Youdim MB, Weinstock M. Therapeutic applications of selective and non-selective inhibitors of monoamine oxidase A and B that do not cause significant tyramine potentiation. Neurotoxicology, 2004; 25(1–2):243–50.

Zetterstroom RH, Solomin L, Jansson L, Hoffer BJ, Olson L, Perlmann T. Dopamine neuron agenesis in Nurr1-deficient mice. Science, 1997; 276 (5310):248–50.

Zhang L, Le W, Xie W, Dani, JA. Age-related changes in dopamine signaling in Nurr1 deficient mice as a model of Parkinson's disease. Neurobiol Aging, 2012; 33(5):1001.e7–e16.

Zheng YJ, Bruice TC. A theoretical examination of the factors controlling the catalytic efficiency of a transmethylation enzyme: catechol-*O*-methyl transferase. J Am Chem Soc, 1997; 119(35):8137–45.

Zorzon M, Capus L, Pellegrino A, Cazzato G, Zivadinov R. Familial and environmental risk factors in parkinson's disease: a case-control study in north-east Italy. Acta Neurol Scand, 2002; 105(2):77–82.

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