

# Optimal Treatment in Parkinson's Disease: Pharmacotherapy and Practical Tips



Kulkantorn K, MD

Kongkiat Kulkantorn, MD<sup>1,2</sup>

## Abstract

Parkinson's disease, a common neurodegenerative disorder, is treatable. The current treatment strategy is focused on dopamine replacement. Every patient will eventually receive levodopa which is the gold standard therapy, but it is associated with motor complication in a later phase. Using other dopaminergic medications as the first line treatment to avoid levodopa usage may reduce motor complication, but they are less efficacious in symptomatic control. However, in the later stage of the disease, patients often need other medications to optimize dopaminergic transmission. Dopamine agonist (DA), monoamine oxidase inhibitor (MAO-BI) and catechol-o-methyl-transferase inhibitors (COMTI) are standard adjunctive medications in patients who have levodopa-induced motor complication.

**Keywords:** Parkinson's disease, levodopa, dopamine agonist, motor complication

## Parkinson's disease and levodopa-induced motor complication

The current diagnosis of Parkinson's disease is based on the UK Parkinson's Disease Society Brain Bank Criteria. The main criterion is bradykinesia and one of the three following criteria, namely rigidity, 4-6 Hz rest tremor and postural instability. Moreover, there are other supporting criteria such as unilateral onset, asymmetrical involvement, progressive course, good response to levodopa, levodopa-induced chorea.<sup>1</sup>

Dopamine deficiency, due to substantia nigra cell loss, is the key pathophysiology in this condition. Therefore, levodopa is the gold standard treatment for this condition. It is needed in virtually every patient in the later stage of the disease. However, after several years of its usage, most patients will suffer from motor complications which are caused by its short half-life and the advanced disease stage. Common issues include the wearing off phenomenon, dyskinesia, on and off stage.<sup>2</sup> Therefore, adjunctive therapy is needed to optimize motor control. Additionally, in later stage of the disease, more psychiatric symptoms will emerge such as dementia, psychosis, and depression. This will further complicate the management of concurrent medications.<sup>3</sup> Further to the aforementioned symptoms there is a question as to which symptom has the most impact upon the patient. In general, bradykinesia is the most troublesome due to its effect on daily activities. However, this is best judged by the patient. Then, their physician needs to address the treatment plan accordingly.

Over the past few years, research has put more emphasis on the initial stage of Parkinson's disease. In fact, non-motor symptoms occur several years before the usual motor symptoms.<sup>4</sup> For example, symptoms include depression, apathy, tiredness, and abnormal movement during rapid eye movement (REM) sleep, constipation, memory loss and sensory disorder. Now these symptoms are collectively referred to as premotor Parkinson's disease.

<sup>1</sup> Neurology Division, Department of Internal Medicine, Faculty of Medicine, Thammasat University, Pathumthani, Thailand.

<sup>2</sup> Neurosciences Center, Bangkok Hospital Medical Center, Bangkok Hospital Group, Bangkok, Thailand.

\* Address Correspondence to author:  
Kongkiat Kulkantorn, MD, Professor  
Associate Dean for Research  
Neurology Division, Department of Internal Medicine  
Faculty of Medicine, Thammasat University  
Email: kongkiat1@gmail.com

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In the future, changes in diagnostic criteria will certainly occur. Many bio-markers will be incorporated, such as cerebrospinal fluid biomarkers and neuroimaging.<sup>5</sup> The disease can be staged as pre-symptomatic stage, pre-motor stage and motor stage.<sup>6</sup> This proposal corresponds to the brain pathology which progresses from lower brainstem level to midbrain and finally to various parts of the brain. Therefore, the patients' symptoms at each stage depend on their brain pathology.<sup>7</sup>

In 2008, a survey conducted in Thai patients from Thammasat University Hospital, Ramathibodi Hospital and Srinagarind Hospital reported the incidence of motor complication at approximately 25%. The risk factors are a younger age of onset, high dose of levodopa, and duration of treatment.<sup>8</sup> For the past few decades, there have been many adjunctive dopaminergic medications available on the market. The most widely-used groups are dopamine agonists (DA), monoamine oxidase B inhibitors (MAO-BI) and catechol-o-methyl-transferase inhibitors (COMTI). Unfortunately, for the past decade, the treatment with new medications has not had much effect on the patient's final outcome. Interestingly, recent research from the Republic of Ghana in Africa and research from Italy puts more emphasis on the duration of disease as a strongest risk factor for motor complication, rather than the length of levodopa treatment.<sup>9</sup> Consequently we have to learn to use levodopa more wisely.

## Dopaminergic drug

### Levodopa

Levodopa is the most effective medication in relieving all major motor symptoms which include tremors, bradykinesia and rigidity. After ingestion and absorption in the small intestine, it is directly converted to dopamine by a dopaminergic cell in both the peripheral and central nervous system. In order to prevent gastrointestinal side effects, mainly nausea and vomiting, dopa-decarboxylase inhibitors (DDCI) are routinely added to levodopa to inhibit this peripheral conversion (Figure 1). Regarding the efficacy, the dose response relationship has been clearly demonstrated in randomized controlled trials, but the higher dose (600 mg per day) is associated with more motor complications, especially dyskinesia and the wearing off phenomenon.<sup>10</sup> From a recent study in newly diagnosed patients comparing regular formulation of levodopa plus DDCI, or the combination of levodopa, DDCI plus COMT inhibitors, the triple combination therapy group had a higher risk of dyskinesia due to higher drug exposure.<sup>11</sup> The threshold seems to be at 400 mg per day.<sup>12</sup>

Regarding its pharmacology, levodopa can be titrated up without ceiling effect. It should be taken on an empty stomach. Levodopa must be converted into dopamine in order to work in the central nervous system. It is always

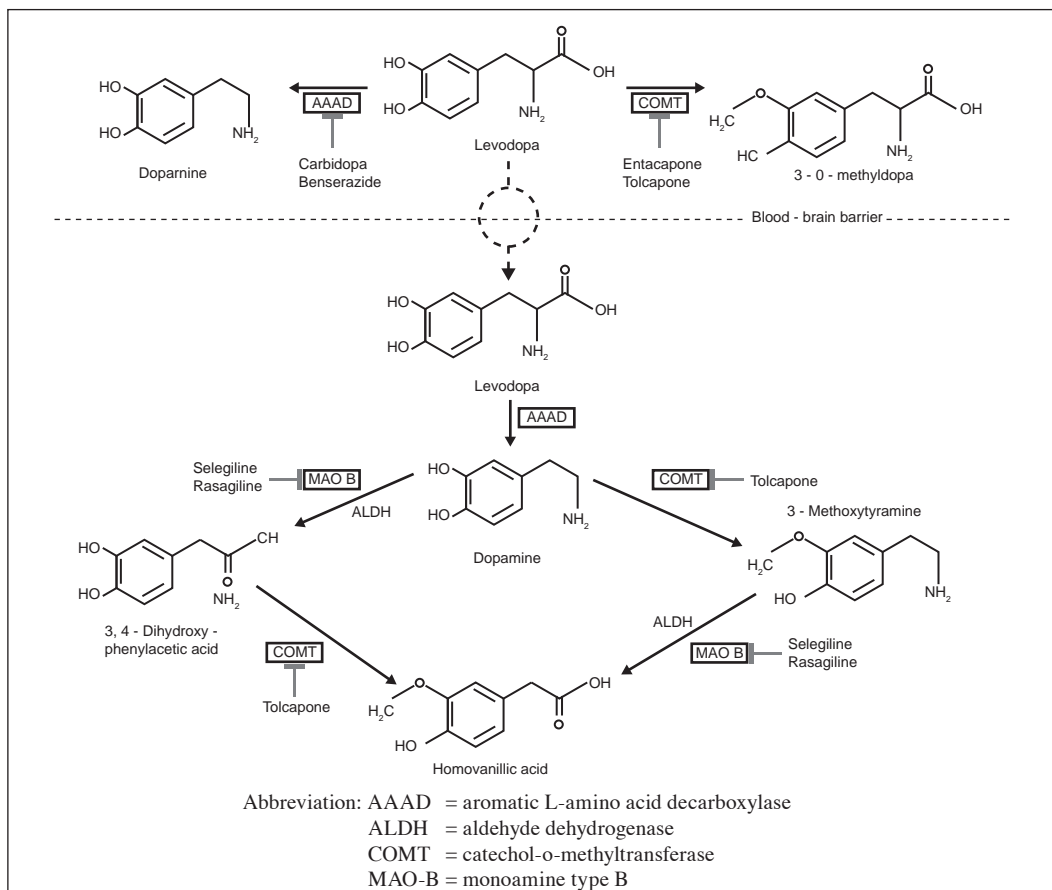


Figure 1: Levodopa pathway and dopaminergic medications

combined with dopa decarboxylase inhibitor in the commercial preparation, such as Madopar® (levodopa plus benserazide) and Sinemet® (levodopa plus carbidopa). There are many preparations and proportions of levodopa and DDCI in each brand. The rapid disintegrating tablet (Madopar DT®) is used for patients who cannot swallow well, on tube feeding or in need of immediate effect of the medication. Controlled released formulation is useful to prolong its half-life, but it is poorly absorbed which leads to unreliable dose adjustment. In general, its half-life is 1-2 hours. But in early cases of Parkinson's disease, it can be used three times a day due to the "buffer" or storage effect of remaining nigral neurons. Common side effects include nausea, vomiting and low blood pressure which are found after the drug is initially absorbed. So, a slow dose adjustment in dose is recommended.

It is commonly used as a monotherapy or a combination therapy with standard adjunctive medication. In addition, other non-dopaminergic drugs, which work with other neurotransmitter systems such as anticholinergic and amantadine, can be used as a supplementary drug to relieve motor complications. In terms of motor symptom control, levodopa gives slightly higher efficacy than dopamine agonist and MAO-B inhibitor as a monotherapy. Due to its mechanism, COMTI cannot be used for monotherapy and will be only used with levodopa as a supplementary drug.<sup>2</sup>

#### Dopamine agonist

Due to many dopamine receptor subtypes, each medication has a different binding affinity to each subtype. All DA binds to D2 receptors to have an anti-parkinsonian effect. Some also had the effect on D1 receptors which may cause certain side effects such as dyskinesia. These are apomorphine and bromocryptine. If the drug works on the D3 receptor, it will enhance emotion and perception. The old DA usually stimulates 5-HT2B receptor, so it can cause valvular fibrosis in long term use. It also has a bind-

ing affinity to the alpha-1 receptor which usually causes drowsiness. In general, bromocryptine and pramipexole will bind with many kinds of receptors, yet ropinirole will bind with D2, D3 only. Therefore, the binding affinities of DA are different and also depend on the dose (Table 1).

It clearly provides an additional benefit when used with levodopa in patients who already experience motor complications which can be measured by reducing off-time, increasing on-time and reducing levodopa dosage.<sup>2</sup> However, some more dyskinesia may occur which needs levodopa dose reduction. When used as a monotherapy, DA is able to delay the use of levodopa which leads to a lower risk of motor complications.<sup>13,14</sup> It can also have a positive effect on depression as well as motor benefit.<sup>15</sup>

The crucial peripheral side effects are orthostatic hypotension and edema due to its action on the D2 receptor and the alpha-1receptor of the blood vessels, and constipation from the alpha-2 receptor action. Other uncommon, but serious side effects in the cardiovascular system are syncope and heart failure. The central nervous system side effects are nausea, vomiting, confusion, psychological symptoms, unusual behavior, sleep disorders and headache.<sup>16</sup> Drowsiness or sleep attacks may cause accidents, falls or injuries in elderly patients who may have Alzheimer's disease or may be on other CNS suppressant drugs. This often occurs during the initial titration period. The notorious side effect of DA is impulse control disorder which can occur up in up to 39% of patients who were on long term DA treatment. It often manifests as pathological gambling, punding, hypersexuality, and compulsion.<sup>17</sup> The risk factors are high dose and oral form of DA, younger age, history of drug or alcohol abuse and underlying psychiatric illness.<sup>18,19</sup>

Liver metabolism is the major route of DA elimination. The most common elimination is through the cytochrome (CYP) P450 system. For example, bromocryptine is metabolized in CYP3A4 enzyme which is also the

**Table 1:** Pharmacology of dopamine agonist.

	Pramipexole*	Ropinirole*	Bromocryptine	Piribedil	Rotigotine	Apomorphine
D1	0	0	0	0	+	+++
D2	+++	+++	++	+++	+++	++
D3	++++	++++	++	++	++++	++++
Type	Nonergot	Nonergot	Ergot	Nonergot	Nonergot	Morphine derived
Routes	oral	oral	oral	oral	transdermal	subcutaneous
Half-life (h)	8-12	5-6	12-14	20	5-7	40 min.
Daily dose (mg)	0.75-4.5	4-24	10-60	150-300	8-16	As needed
Doses/day	3	3	3	3	1	As needed

\* extended release formulation is available with a once daily dose  
D1, D2, D3 denotes receptor affinity

common pathway for most other medications. Therefore, drug-drug interaction needs to be monitored. Ropinirole is metabolized by CYP1A2 which has to be closely adjusted in smokers. Smoking is a potent inducer for CYP1A2 activity and ropinirole may be less effective due to its rapid clearance. Piribidil has both hepatic and renal clearance. The exception is pramipexole which is mainly disposed of by the kidneys. Each drug has a different preparation such as oral form (immediate release and controlled release), transdermal patch and continuous subcutaneous injection. The selection of DA needs to be individualized to maximize the treatment response while minimizing the side effects; therefore, it is a joint decision between the patient and physician.<sup>20</sup>

### MAO-B inhibitor

The MAO-B inhibitor increases dopamine availability by inhibiting the metabolism of dopamine at the synaptic cleft by the MAO-B enzyme. Selegiline has been used for several decades as a monotherapy and adjunctive therapy to levodopa. However, its efficacy was lower than other medications. Insomnia is a common side effect due to its amphetamine-like metabolite and its sympathomimetic action. Therefore, it is recommended to take twice a day, morning and noon time. The new medication in this group is rasagiline which has a higher potency and more efficacy than selegiline. It can be used in both monotherapy and adjunctive therapy settings.<sup>21,22</sup> The side effect is mild and less severe than other drug classes.<sup>23,24</sup>

### COMT inhibitor

The COMT inhibitor will inhibit the metabolism of COMT enzyme which also metabolizes levodopa peripherally and centrally and it is hoped will prolong the half-life of levodopa in the system. Therefore, it must be used with levodopa as an adjunctive therapy in patient who has wearing off phenomenon or motor fluctuation. The older and more effective medication which can inhibit COMT enzyme outside and inside the blood brain barrier is tolcapone, but it was withdrawn from the market due to liver toxicity. Currently, only entacapone is available, and this has been shown to reduce the off-time and increase on-time in wearing off patients.<sup>25,26</sup> The common but unharmed side effect is urine discoloration. Other side effects are mainly from levodopa itself.

### Practical guide for dopaminergic drug usage

In the early disease state, the monotherapy of rasagiline, levodopa or dopamine agonist is recommended as first line treatment.<sup>26,27</sup> Drug selection depends on each patient's profile, desired efficacy and potential side effects. At the late disease stage, almost all patients will need combination therapy to ensure continuous dopaminergic stimulation and to minimize side effects from such usage. For

example, a patient who presents with mild bradykinesia with minimal disability should consider MAO-B inhibitor or DA for first line treatment. In a patient who is more symptomatic with both tremors and bradykinesia, yet still under the age of 60, a dopamine agonist should be used in the first instance. However, if the patient is more than 60 years old and is impaired in daily activities, levodopa should be considered first because of its higher efficacy and rapid onset of action. If monotherapy is not effective or intolerable, combination therapy is recommended.<sup>2</sup>

The use of DA for first treatment will reduce the risk of dyskinesia in 87% of cases, regardless of the dose of DA administered, the length of the illness, the length of treatment or the concurrent use of levodopa.<sup>14</sup> According to a large, practical and long-term study comparing DA, MAO-B inhibitor and levodopa in England, levodopa showed higher efficacy and better quality of life than the other two groups. In terms of delaying the use of levodopa and dyskinesia, DA and MAO-B are both effective and they are not significantly different.<sup>28</sup> However, the use of pramipexole in delayed-start trials did not change the natural course of the disease.<sup>29</sup>

Patients at the advanced stage of Parkinson's disease will use levodopa as a backbone therapy with other drugs as adjuncts. For example, the use of a new form of levodopa which has a rapid onset and longer duration of action will help alleviating motor fluctuation.<sup>30</sup> In the case of changing from one DA to another DA, dose adjustment is required in order to maintain the treatment effect and to hopefully reduce side effects (Table 2). Rotigotine administered via transdermal patch is also effective and provides smoother blood levels, but it is more difficult to use than oral DA. A DA injection, such as apomorphine infusion pump or levodopa jejunal infusion, is recommended in severe cases for patients who do not respond or experience severe side effects from conventional treatment. These drugs are expensive and require expertise in handling.

Based on meta-analysis, the comparison of the three drugs (DA, COMT inhibitor and MAO inhibitor) in terms of efficacy and safety revealed that DA can reduce off-time much better than other medications (1.6 hours compared to

**Table 2:** Dosing guideline for switching DA.

Dose (mg/day)			
Bromocriptine	Pramipexole	Ropinirole	Rotigotine
3	0.375	1.5	2
5	0.5	2	2
7.5	0.75	3	4
10	1	4	4
15	1.5	6	6
20	2	8	6-8
30	3	12	6-8

0.8 and 0.9 hours per day respectively), and the dose of levodopa can be decreased further (110.7 mg per day compared to 52.1 and 29.1 milligrams per day accordingly). However, side effects with dyskinesia are more common in DA and the COMT inhibitor than in the MAO-B inhibitor.<sup>31</sup>

Canadian guidelines suggest that drug selection depends on the natural history of the disease and the patient's profile. Levodopa, MAO inhibitor and dopamine agonist are recommended and graded as level A in a newly diagnosed patient. In the case of patients at the later stage of the disease or for those with issues with levodopa, combination therapy with two or three medications is recommended.<sup>27</sup> The Movement Disorder Society also concurs with this recommendation and provided more supportive evidence for doing so.<sup>32</sup>

## Conclusion

In conclusion, at present, the treatment of Parkinson's disease is focused on symptom control rather than delaying the disease's progression. Optimizing dopaminergic stimulation at its receptor is the key for successful management. At least four drug classes (levodopa, DA, COMT inhibitor and MAOB inhibitor) are available and have solid evidence to support their usage at both early and late stages of the disease. The choice of an appropriate drug for each patient, whilst considering both motor and non-motor symptoms, is recommended in order to provide the best quality of life for the patient.

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