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Revisiting the Medical Management of Parkinson's Disease: Levodopa versus Dopamine Agonist

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Abstract: The optimal treatment strategy for Parkinson's disease has been debated for decades. The introduction of levodopa (LD) treatment is frequently delayed because of theoretical concerns about its toxicity or the risk of drug-induced motor complications. These concerns have resulted in "LD phobia" with clinicians selecting dopamine agonist (DA) over LD as initial therapy. More recently, a shift in the treatment approach towards initial LD use appears to be occurring. It is therefore necessary to review current evidence for the use of LD and DA. This review discusses the medical management of Parkinson's disease with regards to the use of LD versus DA. Pendulum swings in treatment strategies between LD-first and DA-first therapies should be avoided. A balanced perspective is needed as there is a place for both drugs in the management of PD.

Keywords: Dopamine agonists, dyskinesias, levodopa, motor complications, Parkinson's disease, treatment.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease that poses several challenges for neurologists [1]. The selection of treatment strategies depends on the balance between the clinical benefits and side-effects of treatment.

Levodopa (LD) is the classic treatment for PD. Since its introduction in the late 1960s, LD has become the most effective and widely used medication for PD. However, its use has been associated with the occurrence of motor complications in about 80% of younger patients (onset between 21 and 40 years) and 44% in older patients after 5 years of use [2].

There are ten dopamine agonists (DA) that have been marketed for PD. Five are ergot derivatives (bromocriptine, cabergoline, dihydroergocryptine, lisuride, pergolide) and five are non-ergot derivatives (apomorphine, piribedil, pramipexole, ropinirole, rotigotine) [1].

The other medications available for PD include anti-cholinergics (benzhexol), amantadine, Monoamine oxidase B (MAO-B) inhibitors (selegiline, rasagiline), and Catechol-O-methyl transferase (COMT) inhibitors (tolcapone, entacapone). Some of these medications may be used as initial treatment for PD or as combination therapy with other medications in advanced PD.

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The optimal treatment strategy for PD has been debated for decades. The introduction of LD treatment is frequently delayed because of theoretical concerns about its toxicity or the risk of drug-induced motor complications [3, 4]. Around the turn of the millennium in the year 2000, there was a debate about the possible toxic effect of LD. At that time, the fear of LD motor complications among patients and doctors resulted in "LD phobia" [5]. Clinicians resisted the use of LD strategies as many were of the opinion that the initial treatment of PD should be a DA in order to delay the long term complications of LD use [6-8]. As a result, many clinicians chose DA over LD as initial therapy. More recently, a shift in the treatment approach towards initial LD use appears to be occurring [9]. It is therefore necessary to review the current evidence for the use of LD and DA. The purpose of this review is therefore to discuss the medical management of the PD with regard to the use of LD versus DA. This review will attempt to answer some of the following questions. Should patients with early PD be started on DA or LD? What are the short-term and long-term outcomes for each of these medications?

POSSIBLE NEUROTOXIC AND NEUROPROTECTIVE EFFECTS: LD VERSUS DA

As PD is a progressive neurodegenerative disease, an important question is whether LD or DA has neurotoxic or neuroprotective effects. Several studies on MAO-B inhibitors, selegiline and rasagiline, have shown evidence of possible disease modification effects of these drugs [10-12].

Possible Neurotoxic or Protective Effects of LD

The possible neurotoxicity of LD was first suggested in *in-vitro* studies which showed that high doses of LD reduced

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the number of tyrosine hydroxylase (TH)-positive neurons in different dopaminergic cell lines [13-17]. The potential of LD to generate free radicals and other reactive oxygen species to cause oxidative stress was thought to be the reason [4]. However, further studies revealed that only 12% of orally administered LD reached the cerebrospinal fluid (CSF) [18] and at this concentration of LD, it was considered not to be toxic. On the contrary, LD was found to have protective effects on dopaminergic cells that were cultured on a glia-conditioned media [19-21]. It therefore appeared that it was not LD itself but rather the study conditions of the cultured dopamine neurons that determined if LD was toxic or protective to dopaminergic cells *in-vitro* [3].

There is little evidence to suggest that LD is toxic *in-vivo* or in PD patients. High doses of LD for up to 18 months did not induce any reduction in the number of dopaminergic neurons in rats or mice [22-24]. The same results were also found in non-human primates [25, 26] and individuals without PD [27, 28]. Further clinical and imaging data from PD patients, who participated in the ELLDOPA trial, confirmed that LD was not toxic in the short term [29]. There is therefore no definite evidence to indicate that LD has either toxic or protective effects [4].

Possible Neuro-protective Effects of Agonist

Do DA have neuro-protective effects in PD? Both *in-vitro* and *in-vivo* studies in animal models of PD have shown that DA might be protective to dopaminergic neurons [30-33]. The mechanism of action appears to be *via* its antioxidant properties and ability to diminish excitotoxicity by reducing subthalamic nucleus activity [34]. Unfortunately, further clinic trails did not provide evidence that of DA were neuroprotective.

In the CALM-PD study, the neuroprotective effects of pramipexole was evaluated using single photo emission computed tomography and iodine 123[123I]2-β-carboxymethoxy-3-β-(4-iodophenyl)tropane (β-CIT) [35] in 39 early PD patients on LD and 39 patients on pramipexole who were followed up for about 23.5 months. Unfortunately, the decline in striatal β-CIT uptake was similar between subjects treated initially with pramipexole and LD (20.0% vs 24.8%). Based on the results of the functional imaging in this study, no evidence of neuroprotection from pramipexole was found. In another study, the REAL-PET study compared ropinirole with LD using (18)F-dopa PET to follow the loss of nigrostriatal cell density amongst early PD patients [36]. The reduction of (18)F-dopa uptake was significant less in the ropinirole group (14.1%) compared to the LD group (22.9%). The CALM-PD study extended its follow-up to 46 months and found that patients initially treated with pramipexole demonstrated a reduction in loss of striatal β-CIT uptake, compared with those initially treated with LD [37]. However, the results of this study was difficult to interpret as there was no placebo arm in the study [4]. Another study (INSPECT) compared the effects of LD, pramipexole and placebo on striatal beta-CIT uptake and found no evidence of neuroprotection in both pramipexole and LD arms [38]. There is therefore no definite evidence of disease modification effects of DA based on these functional imaging studies [36, 37, 39, 40].

There are currently no established neuroprotective therapies to date [41]. Some traditional Chinese Medicine or herbs, such as green tea [42-44], ginkgo [45] and ginseng [46-49], have been reported to have possible neuroprotective effects. However, the results of studies have not been conclusive [50]. Rasagiline, an MAOB inhibitor, is purported to have possible disease modifying effects [12, 51]. However, no such evidence currently exist for either LD or DA [7].

EARLY PD, INITIAL TREATMENT STRATEGY: LD VERSUS DA

Many factors influence a clinician's decision to initiate treatment with LD or DA. The preference of clinicians and patients to initial DA treatment derives from the fear that early LD exposure leads to disabling dyskinesias and motor fluctuations in long-term [35, 52]. Some patients hold the view that initial therapy for PD should always be a DA as LD will loss efficacy after 5 years and that the initiation of LD is a beginning of slippery downward slope to disease progression [7, 53]. However, such views may not only deprive patients of the most effective therapies, but also increase the likelihood of adverse effects [53]. The key question then is whether initial DA therapy can provide both short-term and long-term advantages.

Short-term Outcomes of DA-first Therapy

A series of randomized, controlled clinic trials that compared the use of LD versus DA in early PD patients were conducted between 1989 and 2006. The DA used in these studies included bromocriptine [54], pramipexole [35], ropinirole [39], cabergoline [55, 56], and pergolide [40]. The study designs for these studies were similar. Early PD patients were randomized to either LD or DA treatment as initial treatment for PD. For the DA arm some studies [40, 54] were restricted to pure DA monotherapy, while in others [35, 39, 55, 56] additional LD was permitted after an initial DA run-in period.

At around the turn of the millennium, there were several studies that showed a reduced incidence of LD-induced dyskinesias when early PD patients were initiated on DA instead of LD. The PKDS009 study [56], a multicenter randomized double blind 3 to 5 years trial, assessed the outcome of therapy with cabergoline in patients with early PD. At the end of the study, the development of motor complications was significantly less frequent in patients treated with cabergoline than with LD (22% vs 34%, $p<0.02$). The relative risk of developing motor complications was more than 50% lower in the cabergoline group than the LD group. However, serious adverse events were more common in cabergoline-treated patients. Another study was a five year clinical trial comparing the initial treatment of ropinirole against LD [39]. The overall incidence of dyskinesias at 5 years was 20% in ropinirole-treated subjects compared with 45% in the LD group. However, the UPDRS motor score was significantly in favor of LD (mean change: 0.8 point vs 4.8 point, $p=0.008$) [39]. In the CALM-PD trial, a 2 year Class I study [35, 57], 51% of all LD treated patients developed motor fluctuations and 31% developed dyskinesias. In pramipexole arm, only 28% of patients developed motor complications and 10% developed

dyskinesias. However, a significant difference in the UPDRS motor score improvement was found in favor of the LD treatment (7.3 point improvement in LD arm vs 3.4 point improvement in pramipexole arm). There was also significantly more leg edema, somnolence and hallucinations in the pramipexole group compared with the LD group. After a further follow-up to 6 years, the motor complications increased in both groups, 68% in initial LD-treated subjects and 50% in initial pramipexole-treated subjects. This difference however remained statistically significant [58]. Following this clinical trial, the PELMOPET study [40] compared initial monotherapy of pergolide with LD in a 3 year trial and also obtained a similar result. In the pergolide group, the severity of motor complications was significantly lower and the onset of dyskinesias was significantly delayed, compared to the LD group. However, the delay in the onset of motor complications was no longer seen after 3 years of pergolide therapy. As in previous studies, the LD group experienced greater symptomatic relief. Adverse events resulted in discontinuation of the drug in 17.6% of patients in the pergolide group compared to 9.6% in the LD group.

The above clinical trials on early PD patients consistently demonstrated the delayed onset of dyskinesias with the initial treatment of DA instead of LD over the period of 3 to 5 years. These evidence resulted in the recommendation by the American Academy of Neurology (AAN) in 2002 [59], that either LD or a DA could be used to initiate therapy. At that time, some experts had recommended that DA should be the initial choice for the treatment of early PD with LD supplemented when DA could no longer provide satisfactory clinical control [8].

A major reason for clinicians preferring to use DA over LD as initial treatment for early PD is based upon the premise that DA delays the onset of LD related motor complications [7]. The question remains if the benefits of initial DA therapy are still present in long-term. In the CALM-PD study, the incidence of motor complication increased from 28% at year 2 to 50% in pramipexole arm after a further follow-up of 4 years. The incidence rate of motor complications remained significantly lower than the group treated initially with LD. However, in the PELMOPET study, the delay in onset of motor complications was no longer seen after 3 years of pergolide therapy.

In terms of symptom relief as measured by the UPDRS motor scores, all DA arms in the above clinical trials had poorer relief of motor symptoms than LD treatment arms. Therefore, the short-term advantage of delaying motor complications by DA needs to be weighed against its poorer efficacy in providing motor symptom relief and its higher incidence of adverse effects [7]. Perhaps the delayed use of LD and development of LD related motor complications can only be justified if the symptoms of PD are adequately controlled [39].

Long-term Outcomes of DA-first Therapy

In 1985, the Parkinson's Disease Research Group (PDRG) of the United Kingdom started its 14 years, randomized multicenter trial which compared the initial treatment of PD with bromocriptine, against LD with selegiline, and LD therapy alone [60]. The results of this study were published in 2008. In the initial four years of follow up, the results showed significantly worse disability ratings but fewer motor complications in the bromocriptine arm [61], which is similar to what has been found in other DA studies. The incidence of dyskinesias and motor fluctuations were significantly lower in bromocriptine group (2% and 5% respectively) than the other 2 groups (range: 27% to 35%). However, after 10 years, the short-term advantage of bromocriptine diminished. The benefits of bromocriptine monotherapy in reducing motor complications observed at 4 years had diminished substantially by 10 years and was no longer present at the final follow-up (14 years) [60]. At the final follow-up, dyskinesias were present in 58% of participants in LD arm, compared with 56% in the bromocriptine arm. Motor complications occurred in 50% in the LD arm compared with 56% in the bromocriptine arm. No significant difference in prevalence of dyskinesias, motor fluctuations, mortality rates and dementia were found at the final follow-up visit. Moreover, motor function (disability scores) and quality of life (physical functioning and physical summary scores) were superior in participants in the LD arm. This study therefore did not support any long-term benefits or clinically relevant disease-modifying effect with initial bromocriptine treatment [60]. The limitations of this study included its prolonged enrollment period (1985-1990), recruitment at 93 different UK hospitals, re-randomized due to the higher mortality of LD plus selegiline, and high dropout rate (only 21% of the original patients were available for 14-year analysis) [7].

Another study published earlier compared low-dose LD with low-dose bromocriptine in 52 surviving patients of 149 PD patients recruited 15-18 years earlier in the Sydney Multicenter Study of Parkinson's disease [62]. The results showed that dyskinesias and dystonia were delayed by the early use of bromocriptine. However, the wearing-off effects of LD appeared at a similar time once LD was added. The rate of disease progression was similar in both arms and almost all surviving patients experienced dyskinesias or wearing off [7].

Both the UK and Sydney studies demonstrated that starting with bromocriptine, a DA, did not affect the final outcome of PD. These studies showed that the long term outcomes of LD-first or DA-first therapy were similar. However, these clinical trials used bromocriptine, an older DA that is now rarely used in clinical practice. Some have argued that the newer DA are different from bromocriptine and would result in different results.

In 2014, the PD-MED study which is a large, pragmatic trial that assessed the long-term outcomes of different therapeutic strategies amongst early PD patients who were followed for a median duration of 3 years and a maximum duration of 7 years was conducted [63]. This study assigned 1620 early PD patients to three different initial treatment regimens: LD (528 patients), DA (632 patients) and MAO-BI (460 patients). The aim was to establish which treatment arm provided the most effective long-term control of symptoms and the best quality of life. The risk of developing dyskinesias in LD and LD-sparing groups was 36% and 33% respectively. There was no difference in the occurrence of motor fluctuations between groups. The results indicated

very small but persistent benefits for patient-rated mobility scores when treatment was initiated with LD compared with LD-sparing therapy. MAOBI as initial LD-sparing therapy was at least as effective as DA [9, 63]. Overall, this study favored LD over LD-sparing therapy as a result of better patient-rated quality of life both in the short and long term [63]. There therefore appears to be no grounds for concern with regard to the use of LD as first-line therapy as these patients are not worse-off in the long-term [63].

Based on these studies, the delay or reduction in the incidence of motor complications through initiation of DA as opposed to LD in the early years did not appear to translate into a better outcomes in the long term [9]. The short term benefits of DA in reducing motor complications may be negated by its poorer efficacy in improving motor function when compared with LD. The STRIDE-PD study [64, 65] recently published its analysis about the predictive factors of motor complication and found that a younger age at onset, higher dose of LD dose, lower body weight, and residing in North American predicted the development of dyskinesias. The correlation between the rate of development of dyskinesias and LD dose was linear, with a marked increase at doses greater than 4mg/kg. The risk of developing dyskinesias or wearing-off was closely linked to the dose of LD [65, 66]. These results suggest that the initial therapeutic dose of LD is important and that motor complications may be reduced if the initial LD treatment dose is lowered.

Side-effect: LD Versus DA

Treatment strategies are always dependent on the balance of drug efficacy and its side effect. The non-motor side-effects are more frequent with DA than with LD. These side-effects include nausea, hallucinations, edema, daytime sleepiness, and sleep disturbance [67-69].

The use of DA has also been associated with the occurrence of impulse control disorders (ICDs) [70, 71]. ICDs in the form of pathological gambling was first reported to be associated with DA in 2003 [72]. Since then, many reports have found ICDs such as pathological gambling [73-75], compulsive buying [76], hypersexuality [73, 76], and impulsive smoking [77] to be associated with the use of DA. DA use and total dose of agonist in particular, have been linked to ICDs [78, 79]. In order to ascertain the prevalence and higher risk of ICDs in subjects with agonist treatment, a cross-sectional study (DOMINION study) of approximately 3000 patients was undertaken [71]. ICDs were more common in patients treated with a DA than in patients not taking agonist (17.1% vs 6.9%), with more than a quarter of ICD patients experiencing 2 or more ICDs. The frequencies of ICDs were similar for pramipexole and ropinirole-treated patients, which suggest that DA as a class are associated with ICDs. DA treatment in PD was associated with 2- to 3.5-fold increased odds of having an ICD [71]. In addition, it has been found that in patients taking DA, concurrent LD use increased the incidence of an ICD by approximately 50% [71].

Advanced PD, Continuous Dopaminergic Delivery: LD Versus DA

In advanced PD patients, motor fluctuations and dyskinesias pose a significant management problem and limit treatment options. These motor complications occurs in about 50% PD patients who have received LD for more than 5 years, and all younger-onset patients will encounter these problems [80, 81]. When these complications occur, deep brain stimulation (DBS) of the sub-thalamic nucleus (STN) or internal globus pallidus (GPi) are proven treatment options. In addition, two different strategies of continuous drug delivery are also available. These include the use of

Table 1. Levodopa vs dopamine agonists.

	Levodopa	Dopamine Agonists
Neurotoxic or Neuroprotective effects	*In-vitro*: high dose: toxic low dose: possible protective *in vivo* or PD patients: no evidence of either toxic or protective effects	*In-vitro* or *in-vivo*: Possible protective effects In PD patients: No evidence of protective effects
Early PD: Initial treatment		
Short-term outcomes (3-5 years)	More motor fluctuations and dyskinesias	Less motor fluctuations and dyskinesias
	Earlier onset of dyskinesias	Delayed onset of dyskinesias
	Better motor efficacy	Lower motor efficacy
Long-term outcomes (>5 years)	Similar prevalence of motor fluctuations and dyskinesias	
	Better motor efficacy	Lower motor efficacy
Advanced PD: CDC choices	Both improve quality of life, motor dysfunction and motor complications.	
	Greater improvement in NMSS total score	Greater improvement in mood and apathy scores of NMSS
Side-effects	More motor complications	More non-motor side-effects

PD, Parkinson's disease; CDC, Continuous dopaminergic delivery; NMSS, the Non-Motor Symptoms Scale.

intrajejunal LD gel infusion (IJLI) and continuous subcutaneous apomorphine infusion (Apo) [82].

Continuous dopaminergic delivery (CDD) is an increasingly available treatment option for advanced PD patients in recent years [83, 84]. Previous clinical trials have shown that continuous infusion of LD or DA(apomorphine) in patients with advanced PD can provide dramatic improvement in patients with established motor complications [85, 86]. These therapies also improve non-motor symptoms, non-motor fluctuations, as well as motor function [87, 88]. A recently published open-labelled, prospective, observational, multicenter study [82] compared infusion apomorphine (Apo, 43 patients) with infusion LD (IJLI, 44 patients) for up to 6 months. Both Apo and IJLI treatment led to beneficial effects on the patients' quality of life, motor dysfunction and motor complications. Compared to Apo, IJLI therapy showed a significantly greater beneficial effect on the Non-Motor Symptoms Scale (NMSS) total score while Apo had a significantly better effect on mood and apathy scores of NMSS [82].

In advanced PD patients, both the infusion of LD and apomorphine appear to provide satisfactory efficacy for non-motor and motor symptoms. Further studies with larger sample sizes will be useful to better compare these two infusional therapies.

COSTS FACTOR, THE BALANCE BETWEEN MONEY AND BENEFIT: LD VERSUS DA

The newer preparations of DA and MAOBIs cost more than LD or selegiline. We are still awaiting the outcome of the full cost-utility analysis from "PD MED STUDY" [9, 63]. However, other outcome measures including major cost drivers such as admissions and dementia have consistently favored LD over LD-sparing therapy. The economic analyses are therefore likely to favor the less expensive LD therapy [63].

There is a need for more studies that evaluate the cost-benefit ratios of different treatment strategies, particularly in the comparison of LD-first versus DA-first therapies. The results of such studies will enable clinicians to factor in cost-benefit considerations when discussing initial treatment options with early PD patients [63, 89, 90].

CONCLUSION

The Table (Table **1**) briefly summarizes the evidence for LD and DA with regards to its possible neurotoxic or neuroprotective effects; its use in early PD and advanced PD; and its side effects. While there is some suggestion of toxic effects of LD and protective effects of DA *in-vitro*, no conclusive neurotoxic or neuroprotective effects of either drug has been shown in clinical studies. The short term benefits of DA have clearly been shown in most DA in delaying the onset of motor complications for up to 3 to 5 years. However, LD is still superior in improving motor function. In the few long-term studies conducted, the prevalence of motor complications was similar with either the LD-first or DA-first treatment strategies after more than 5 years of treatment. In advanced PD, both infusional LD and Apo improved quality of life, motor dysfunction and motor complications, and various aspects of NMSS scores. With regards to side-effects, LD resulted in more motor complications while DA resulted in more non-motor side-effects.

Since the introduction of LD into clinical use from 1967, LD had been the primary drug of choice in the treatment of PD. With the publication of two pivotal clinical trials in 2000 [35, 39], the treatment pendulum swung to DA, and DA became strongly advocated as initial therapy in early PD. It was at about this time that "LD phobia" set in as both clinicians and patients held the belief that levodopa was toxic; levodopa had more side-effects; and that levodopa was associated with motor complications and lose of efficacy in the long term. Over time, as more long-term studies revealed that the rate of motor complications are similar with either the LD-first or DA-first strategy, and the realization of the many side-effects of DA coupled with its lower efficacy, the treatment pendulum appears to be shifting back to LD therapy. Rather than having a pendulum swing from one extreme to another, we believe that a balance is needed between the use of LD and DA. There is a place for both LD and DA, and clinicians need to recommend treatment based on the patient factors, disease factors, and the co-morbid conditions present.

DA-first strategy should be considered for younger patients who present early with mild symptoms as DA would be able to alleviate these motor symptoms while at the same time delay the use of LD and its complications for which this group of patients are vulnerable to [91, 92], at least in the short term. In this group of patients, clinicians should not hesitate to use LD if side-effects to DA occur or if motor symptoms warrant a second agent to be added. On the other hand, LD-first strategy may be applied to older patients, patients who present with moderate to severe motor symptoms, patients with multiple comorbidities, and patients with an addictive personality. When using LD, the minimum dose that results in a good functional outcome should be used, as a lower dose has been shown to reduce the risk of developing dyskinesias [65]. In suitable patients, combination therapy with DA or other PD medications should be considered so as to minimize the dose of LD needed [93].

Each individual patient will also have their own values and treatment preference which must be respected when treatment strategies and options are considered. The cost of treatment is also an important consideration and may differ from one country to another. Ultimately, the decision of which PD strategy or medication to use rest with the patient who has to be guided by a well-informed clinician with a balanced perspective [57].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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