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Levodopa Versus Levodopa Sparing in Early Parkinson's Disease: Can we Meet Halfway?

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ABSTRACT

Monotherapy is the recommended initial treatment for early Parkinson's disease. The pharmacological options for initial treatment include dopaminergic agonists, monoamine oxidase B inhibitors, and levodopa formulations. Several factors should be considered when selecting the optimal treatment, such as disease severity, disease duration, age, activity level, and the risk of developing motor and non-motor complications. Early evidence on the potential role of levodopa formulations in the risk of dyskinesia led to levodopa aversion in the late 1990s and early 2000s, favoring the use of levodopa-sparing options like dopamine agonists. This shift resulted in an increase in behavioral adverse effects, such as impulse control disorders, leading to a subsequent dopamine agonist aversion in the mid-2000s. This review aims to provide a comprehensive evaluation of the existing literature regarding the benefits and drawbacks of levodopa versus levodopa-sparing strategies in drug-naive early-stage Parkinson's disease. (REV INVEST CLIN. 2024;76(3):133-44)

Keywords: Dopamine agonists. Levodopa. Parkinson disease. Therapeutics.

INTRODUCTION

In early Parkinson's disease (PD), monotherapy is the recommended starting treatment option. Among the pharmacological drugs available for the initial treatment are dopaminergic agonists (DAs), monoamine oxidase b inhibitors (MAOBIs), and levodopa (L-dopa) formulations (LD-DDis). Several factors should be taken into account when deciding on the best treatment, including disease severity, disease duration, age, activity level, and the risk of developing motor and non-motor complications[1]. Early evidence on the potential role of LD-DDis on the risk of dyskinesia led to "levodopa phobia" in the late 1990s and early 2000s[2]. The latter favored the use of L-dopa-sparing options, such as DAs, in turn leading to an increase in behavioral adverse effects such as impulse control disorder and a consequent "dopamine agonist phobia" in the mid-2000s[3].

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The current review seeks to provide a thorough evaluation of existing literature concerning the merits and drawbacks associated with the use of L-dopa or L-dopa sparing in drug-naive early-stage PD.

LEVODOPA AS INITIAL TREATMENT IN EARLY-STAGE PARKINSON'S DISEASE: MOTOR RESPONSE

The classic study of Earlier versus Later L-dopa (ELLDOPA) was a randomized, double-blind, placebo-controlled study assessing whether L-dopa slows the progression of PD[4]. A total of 361 participants were included and allocated to receive LD-DDi (plus carbidopa) at a dose of 50, 100, or 200 mg 3 times a day (150, 300, and 600 mg/day, respectively) or placebo. After a 42-week follow-up, LD-DDi reduced the worsening of symptoms in a dose-response pattern. Change from baseline was 1.9 points in the total Unified PD rating scale (UPDRS) score in the groups receiving LD-DDi at 150 and 300 mg/day. The 600 mg/day group showed an improvement of 1.4 points. Conversely, the placebo group had a worsening of 7.8 points. On the other hand, the adverse events were significantly more common among those receiving LD-DDi at 600 mg/day. The authors concluded that doses < 600 mg/day and adjusted individually were more effective than doses > 600 mg/day, which were associated with more frequent adverse effects. Other lessons learned included that the placebo effect seemed to fade after 2 weeks and that the 300 mg/day group reached its greatest benefit at approximately week 8. In summary, ELLDOPA showed that LD-DDi at a dose of 300 mg/day was superior to placebo (8 points in the total UPDRS) and that doses of 600 mg/day were deemed a higher risk of adverse effects. It should be pointed out that the study population had disease duration of roughly 6 months and a Hoehn-Yahr (HY) stage of 2.

The PD MED study assessed the long-term effectiveness of DAs and MAOBIs compared with LD-DDis as the initial treatment for PD. The study was a pragmatic, open-label, randomized trial carried out between 2000 and 2009. The primary outcome was patient reported using the mobility subscale score of the 39-item PD Questionnaire (PDQ-39). The sample size was based on a six-point minimum clinically meaningful difference between groups in the PDQ-39. A total of 1620 people with early-stage PD were assigned (1:1:1) to receive either LD-DDis, DAs, or MAOBIs. PDQ-39 mobility scores averaged 1.8 points better in participants randomly assigned to L-dopa than those with the L-dopa-sparing therapy[5].

Nevertheless, caution is needed when interpreting these results. For instance, the median follow-up was 3 years (with only 109 participants reaching the 7-year follow-up at the time of publication). Due to the pragmatic nature of the study and the possibility of allowing investigators to start open-label treatment with whichever drug they preferred within the allocated class, participants assigned to DAs and MAOBIs had less severe disease and were younger than the LD-DDi group. Other points to consider are the fact that only immediate-release pramipexole was used, and only 1.5% and 24% of the participants allocated to L-dopa sparing received rotigotine or rasagiline, respectively. Regarding the L-dopa equivalent daily dose (LEDD), the LD-DDi group received approximately 350 and 500 mg/day at years 1 and 7, respectively. Otherwise, the DAs and MAOBIs groups averaged 96 and 131 mg at year 1, respectively. At 7 years, LEDD rose to 526 mg for DAs and 489 mg for MAOBIs after adding LD-DDis in up to 76% of the participants allocated to the L-dopa-sparing groups. These data are in line with the doses used in the ELLDOPA study. Finally, the PD MED study was negative since it did not reach the a priori minimum clinically meaningful difference.

The LEAP study, a more recent trial, was a randomized delayed-start double-blind placebo-controlled study assessing disease-modifying effects of early L-dopa. The primary outcome was the mean change in the UPDRS scores between the early- and delayed-start groups at 80 weeks. During Phase 1 (first 40 weeks), participants received LD-DDi or placebo; in Phase 2 (second 40 weeks), participants in both groups received LD-DDi[6]. A total of 445 patients were randomly distributed to the early-start group or the delayed-start group in a 1:1 ratio. The change in UPDRS score from baseline to week 80 was −1.0 ± 13.1 points and −2.0 ± 13.0 points, respectively. At 40 weeks, the mean UPDRS difference between the early- and late-start groups was five points in favor of the group receiving LD-DDi. A subsequent sub-analysis evaluated the responsiveness of cardinal motor symptoms, demonstrating improvement in bradykinesia,

rigidity, and tremor to the same order of magnitude for both early and late-start groups. The authors report that the symptomatic effect of LD-DDi did not increase after 22 weeks, possibly due to the long-duration response of 300 mg/day of LD-DDi reaching its peak between 4 and 22 weeks, again in line with the ELLDOPA findings.

Regarding other LD-DDi, the APEX-PD study evaluated the safety and efficacy of IPX066 in L-dopa-naive people living with PD (PwP). While the study did not focus specifically on early-stage PD, the sample had mean disease duration of < 2 years and almost 80% were on HY stages 1-2. In this randomized, double-blind, placebo-controlled study spanning 30 weeks, 381 L-dopa-naive PwP was assigned to receive either a placebo or IPX066, which included doses of 145, 245, or 390 mg of LD-DDi 3 times a day. The results indicated that all IPX066 doses exhibited superiority over the placebo. Notably, there was a substantial improvement in UPDRS II and III scores between baseline and 30 weeks for all three IPX066 doses, with increments of 11.7 points, 12.9 points, and 14.9 points, in contrast to a mere 0.6 points observed in the placebo group. Furthermore, no serious adverse effects were reported[7].

A recent meta-analysis including 4913 participants (2364 with LD-DDi alone group and 2549 with L-dopa-sparing therapy) reported a mean difference of 4.71 points in the UPDRS III score in favor of the LD-DDi alone group[8].

DOPAMINE AGONISTS AS INITIAL TREATMENT IN EARLY-STAGE PARKINSON'S DISEASE: MOTOR RESPONSE

The comparison of the DA pramipexole with L-dopa on motor complications of PD (CALM-PD) was a randomized, double-blind, controlled clinical trial comparing initial treatment with pramipexole versus LD-DDi in early symptomatic PD. Participants were randomly assigned to receive (a) pramipexole 0.5 mg 3 times a day plus LD-DDi placebo or (b) carbidopa/L-dopa 25/100 mg 3 times a day plus pramipexole placebo[9]. A total of 301 participants were included, with a mean age of 61 years and mean disease duration of 1.5 years. Overall, the mean improvement in UPDRS I, II, III, and total scores from baseline to 24 months was more significant in the L-dopa group. The L-dopa group had a mean difference in the total UPDRS of around nine points versus 4.5 points in the pramipexole group, with similar results in Part III (mean difference of 7.3 vs. 3.4 points, respectively).

The PROUD study, a delayed-start trial in PD, assessed whether early initiation of pramipexole improved the UPDRS total score at 15 months compared to a delayed start. Pramipexole was up-titrated over 4 weeks from 0.125 to 0.25 mg 3 times a day, with a final dose of 0.5 mg 3 times a day. At 15 months, UPDRS scores, clinical global impression ratings, and quality of life (QoL) ratings did not differ significantly between those given early and delayed pramipexole. During the first period (pramipexole vs. placebo), the mean difference in the UPDRS total score was −0.5 points for the early start group in comparison to an increase of 4.8 points in the placebo group, similar to the change reported in the CALM-PD[10].

In addition, pramipexole extended-release (ER) has been shown to be non-inferior to pramipexole immediate release (IR). The adjusted mean UPDRS III change after a 33-week follow-up was −6.4 for IR, −6.1 for ER, and −1.1 in the placebo group[11]. The mean pramipexole dosage was 2.9 mg/day in both groups.

Regarding ropinirole, an improvement of about 4.5 points in the UPDRS motor score compared to placebo has been initially reported at a mean dose of 15.7 mg/day (LEDD 314 mg)[12]. As in the case of pramipexole, non-inferiority between ropinirole ER and ropinirole IR was reported, with a UPDRS total motor score change of −0.1 for ropinirole ER (mean dose of 9.6 mg/day, LEDD 192 mg) and 0.6 for ropinirole IR (mean dose of 18.8 mg/day, LEDD 376 mg)[13].

In the REAL-PET study, a 2-year, randomized, double-blind comparison of ropinirole versus L-dopa in early-stage PD, the UPDRS motor score exhibited a 0.70-point increase from baseline in the ropinirole group and a notable 5.64-point decrease in the L-dopa group after 2 years. Furthermore, the daily doses were 12.2 mg for ropinirole (LEDD 244 mg) and 558.7 mg for LD-DDi. While data for other periods were not presented, visual representations indicate a smaller difference favoring LD-DDi from the beginning of the study through week 24, with the advantage of LD-DDi becoming more evident thereafter[14].

In a randomized, double-blind, placebo-controlled trial, rotigotine demonstrated efficacy in early-stage PD. A total of 242 participants were randomly assigned to receive 4.5, 9.0, 13.5, or 18 mg of rotigotine or placebo for 11 weeks. Active treatment commenced with 4.5 mg and was titrated weekly to the designated dose. The mean change in UPDRS motor score for each active drug group compared to the placebo group was −0.9, −1.88, −3.91, and −3.82, respectively[15].

An observational (n = 2195), real-life study of rotigotine in comparison to other treatments, including L-dopa as monotherapy, reported a change from baseline in UPDRS motor score at month 15 of −5.0 points for rotigotine, −4.4 for LD-DDi, and −5.7 for rotigotine plus LD-DDi. No data on the dosage were provided in the paper[16].

MONOAMINE OXIDASE-B INHIBITORS AS INITIAL TREATMENT IN EARLY-STAGE PARKINSON'S DISEASE: MOTOR RESPONSE

The study deprenyl and tocopherol antioxidative therapy of parkinsonism (DATATOP) was a double-blind, placebo-controlled trial that assessed selegiline (10 mg/day) in early-stage PD for prolonging the need for L-dopa therapy[17]. A total of 800 participants with early-stage PD were randomized to one of four groups (placebo, selegiline plus placebo, selegiline plus tocopherol, or placebo plus tocopherol). At 18 months, selegiline delayed the onset of disability, requiring the use of LD-DDi (HR 0.50). The annual rate of UPDRS motor score worsening was around 4.9 points for those participants receiving selegiline compared to 8.9-9.8 points for those not receiving selegiline.

A randomized, placebo-controlled, double-blind, parallel trial assessed the effect of selegiline 10 mg/day on the time until L-dopa therapy became necessary in 157 *de novo* PwP. As in DATATOP, selegiline significantly delayed the need to start LD-DDi in early-stage PD. At 6 months, the change in UPDRS motor score was −1.5 in the selegiline group compared to 2.5 in the placebo group[18].

A more recent 12-week controlled trial randomized a total of 292 participants with *de novo* early-stage PD to either selegiline (5 mg twice a day) or placebo. The difference in the UPDRS motor score between the groups from baseline was 4.9 points in the selegiline group versus 2.7 in the placebo group[12].

The TEMPO study was a randomized, double-blind, placebo-controlled, parallel-group trial evaluating the efficacy and safety of rasagiline in untreated participants with early-stage PD. Participants (n = 404) were randomly allocated to receive either 1 or 2 mg of rasagiline or a placebo. At 26 weeks, the change of the UPDRS motor score from baseline was −2.71 for rasagiline 1 mg compared to placebo[19]. Another double-blind, randomized, placebo-controlled, parallel-group, dose-ranging study trial assessing rasagiline as monotherapy at doses of 1, 2, or 4 mg once daily over 10 weeks in participants with early-stage PD reported a change from baseline of the total UPDRS score of −1.8 for rasagiline 1 mg in comparison to −0.5 points in the placebo group[20]. Another study with participants randomized to receive either placebo or rasagiline 1 mg/day showed a statistically significant between-group difference in the MDS-UPDRS motor of 3.98 points in favor of rasagiline (−0.48 and −4.47 for the placebo and rasagiline, respectively) at week 26[21].

The attenuation of disease progression with azilect given once-daily study was an 18-month, double-blind, placebo-controlled, delayed-start design trial in which PwP was randomly assigned to one of four study groups: rasagiline 1-2 mg/day (early-start groups) or corresponding placebo followed by rasagiline (delay-start groups). The change in the total UPDRS score in relation to baseline in Phase 1 was 1.26 points for rasagiline 1 mg/day compared to 4.27 in the placebo group[22]. *Post hoc* analyses reported a change from baseline in UPDRS motor score at week 36 of −1.88 in favor of rasagiline 1 mg versus placebo[23]. Moreover, the treatment effect was better for bradykinesia and tremor than for rigidity, postural instability, and gait difficulties scores.

LEVODOPA AS INITIAL TREATMENT IN EARLY-STAGE PARKINSON'S DISEASE: NON-MOTOR RESPONSE

There are very few studies on the effect of L-dopa on non-motor symptoms in early-stage PD. A small study on the effect of long-term L-dopa therapy on depression in *de novo* PwP reported that it did not alter the

depression level measured by the Beck Depression Inventory after 28 months of treatment (mean LEDD 569 mg)[24]. Overall, published findings suggest that the effects of chronic L-dopa on affective symptoms of PD are limited, with no specific randomized clinical trials performed so far. On the other hand, effects on non-motor symptoms occurring during medication "off" times (non-motor fluctuations) may be prone to respond to L-dopa dosing adjustments since it has been reported that the development of motor fluctuations is closely related to the burden of non-motor symptoms[25].

DOPAMINE AGONISTS AS INITIAL TREATMENT IN EARLY-STAGE PARKINSON'S DISEASE: NON-MOTOR RESPONSE

In contrast to L-dopa, there is more extensive evidence regarding the impact of DAs on non-motor symptoms. Pramipexole, for instance, has demonstrated an improvement in depression and is superior to placebo[26]. It shows a comparable efficacy to citalopram[27] or escitalopram[28].

However, the effect of rotigotine on depression is still a subject of debate. A recent trial indicated that low-dose rotigotine (8 mg/day) significantly improved trait anxiety but did not show notable effects on apathy or depression when compared to the placebo in participants with early-stage PD[29]. The randomized evaluation of the 24-h coverage: efficacy of rotigotine study, on the other hand, reported positive effects on other non-motor symptoms, including nocturnal sleep disturbances and fatigue[30].

MONOAMINE OXIDASE-B INHIBITORS AS INITIAL TREATMENT IN EARLY-STAGE PARKINSON'S DISEASE: NON-MOTOR RESPONSE

A recent systematic review of MAOBIs concluded that these drugs may potentially improve depression and pain[31]. The AzileCt in COgnitive-impairment Related DepressiOn study was a 12-week, double-blind, placebo-controlled trial to assess the effects of rasagiline 1 mg/day on depressive symptoms and cognition in PwP without dementia. The study failed to show significant differences between groups in the BDI-IA at week 12, although there was a significant difference in favor of the rasagiline group at week 4[32]. A *post hoc* analysis of the data from safinamide (100 mg/day) studies 016 and 018 reported a significant improvement in the PDQ-39 "Emotional well-being" domain and on the GRID-HAMD score after 6 months and 2 years, compared to placebo. It is crucial to emphasize that these studies were conducted in participants with mid-late-stage PD, both as monotherapy and as an add-on therapy.

No RCTs have shown significant benefits of MAOBIs based on the sleep-specific rating scales in early PD.

LEVODOPA AS INITIAL TREATMENT IN EARLY-STAGE PARKINSON'S DISEASE: ADVERSE EFFECTS

As mentioned before, the ELLDOPA study showed that doses of 600 mg/day were associated with more adverse effects, including dyskinesia.

The PD MED study reported that participants in the L-dopa group were more likely to develop dyskinesias than those in the L-dopa-sparing group (hazard ratio of 1.5, 95% CI 1.16-2.00, p = 0.003), but there was no difference in motor fluctuations. On the other hand, the 7-year discontinuation risk due to side effects was 72% for MAOBIs, 50% for DAs, and 7% for L-dopa. The LEAP study showed that 23% in the early-start group experienced early motor fluctuations at 80 weeks, compared to 38% in the delayed-start group.

Arguably, the most concerning adverse effect linked to the selection of an initial antiparkinsonian is dyskinesia, commonly recognized as L-dopa-associated dyskinesia.

In a study by Cilia et al., a comparison of motor fluctuations and dyskinesias was conducted between Italian and Ghanaian populations. Despite similar disease duration between the two populations, L-dopa therapy was introduced nearly 2 years later in Ghana. The primary observation indicated that the occurrence of motor fluctuations and dyskinesias was comparable, suggesting that the onset of motor complications is not intricately tied to the duration of exposure to L-dopa therapy but is rather associated with the progression of the disease[33].

A recent meta-analysis comparing L-dopa alone versus L-dopa-sparing therapy for early-stage PD revealed that participants treated with LD-DDi faced a higher risk of experiencing wearing off (RR = 1.41) and dyskinesia (RR = 2.05). Notably, the risk for dyskinesia decreased after the 2-year follow-up[8]. This stands in contrast to an earlier meta-analysis that indicated a reduced risk of dyskinesia and wearing-off phenomenon with L-dopa-sparing therapy[34]. Furthermore, it has been noted that the duration between the L-dopa-first or DA-first treatment is not significantly associated with motor complications to the extent that would prompt consideration of deep brain stimulation (DBS) in terms of the time elapsed from the first treatment to DBS surgery. Participants in the DA group exhibited a statistically significant younger age at onset and at the time of surgery, along with a longer disease duration[35].

The Cambridgeshire Parkinson's Incidence from GP to Neurologist study also revealed that early L-dopa use did not act as a determinant for the development of motor complications. However, those who eventually developed motor complications had a higher baseline UPDRS total score, a measure employed by the authors as a proxy for the severity of nigrostriatal pathology[36].

Addressing this issue, Chung et al. conducted a longitudinal study examining the impact of L-dopa sparing on the development of L-dopa-induced dyskinesia. The L-dopa-sparing group exhibited a reduced risk of developing dyskinesia compared to participants in the L-dopa group, even after adjusting for confounding factors, such as age at onset and dopamine transporter availability in the posterior putamen[37]. This supports the idea that the severity of striatal damage plays a significant role in the risk of developing dyskinesia. Notably, when LD-DDi was initiated in the L-dopa-sparing group, participants tended to experience an earlier onset of dyskinesias.

Finally, evidence indicates that a swift escalation in L-dopa dosage or LEDD is linked to an early onset of dyskinesia. Hong et al. conducted a study revealing a correlation between the time to dyskinesia onset and the initial titration dose of L-dopa and the rate of dose increases for both L-dopa and LEDD[38]. Consistent with other research, PwP who developed dyskinesia early exhibited more severe motor symptoms at the initiation of L-dopa, emphasizing the potential role of more pronounced dopaminergic denervation.

A less-explored association pertains to the choice between benserazide and carbidopa as a decarboxylase inhibitor. While L-dopa/benserazide is not inferior to L-dopa/carbidopa in terms of UPDRS reduction, L-dopa/carbidopa therapy (at a ratio of 1:10) has demonstrated the ability to delay the onset of motor fluctuations by approximately a year when compared to L-dopa/benserazide (at a ratio of 1:4)[39]. This could be attributed to the fact that the mean maximum plasma concentration and area under the plasma concentration-time curve (0 to 3 h) are higher after L-dopa/benserazide intake when compared to L-dopa/carbidopa[40].

DOPAMINE AGONISTS AS INITIAL TREATMENT IN EARLY-STAGE PARKINSON'S DISEASE: ADVERSE EFFECTS

A 5-year, prospective, randomized, controlled trial compared the incidence of dyskinesias in PwP receiving initial ropinirole or L-dopa monotherapy. An HR of 2.56 was calculated for the L-dopa group. Similar to other studies, younger age, greater motor severity, and higher L-dopa dose were significant predictors[41]. The mean LEDD at 5 years was 427 mg in the ropinirole plus LD-DDi supplemented group compared to 753 mg in the L-dopa group. The 10-year follow-up showed that those randomized to LD-DDi had more than 3 times the risk of developing dyskinesia than those participants previously randomized to ropinirole (HR = 0.4). Again, those originally randomized to ropinirole had a mean LEDD of 631 mg versus 800.2 mg in those in the L-dopa group. The REAL-PET study favored ropinirole with a lower risk of dyskinesia (OR = 0.09) and a longer time to develop dyskinesia when compared to L-dopa (HR = 8.28). As pointed out before, the L-dopa group had 2 times the dose in terms of LEDD.

The SP702 study assessed the long-term effects of rotigotine in early-stage PD. At 6 years, the mean dose of rotigotine was 7.2 mg daily (LEDD 216 mg), and 74% required LD-DDi as an add-on treatment (LEDD 373 mg). A total of 25% of the PwP developed dyskinesia, with 83% of them reporting it after the initiation of L-dopa[42].

An open-label extension of SP512 and SP513 studies assessed the risk of dyskinesia (measured using UPDRS IV) with rotigotine. The mean dose of rotigotine at the end of the study ranged between 7.2 and 8.2 mg/day (LEDD of 216-246 mg). In addition, 71% of the participants received LD-DDi as an add-on at some point, with a mean dose of 318 mg/day. At 6 years, 19% of the participants developed dyskinesias. Furthermore, in 78% of the cases, these appeared after LD-DDi was added[43].

LEVODOPA AS INITIAL TREATMENT IN EARLY-STAGE PARKINSON'S DISEASE: QOL AND COST-EFFECTIVENESS

The PD MED study reported that initial treatment with L-dopa is cost-effective compared with L-dopa-sparing therapies over 4 years, with an adjusted difference of 0.17 quality-adjusted life years (QALYs). Although the difference in QALYs is minimal, the higher cost of L-dopa-sparing therapy was the primary factor affecting cost-effectiveness[44].

The LEAP study did not identify any differences in mean QALYs between the early-start and the delayed-start groups, both having a mean of 1.30 QALYs[45].

DOPAMINE AGONISTS AS INITIAL TREATMENT IN EARLY-STAGE PARKINSON'S DISEASE: QOL AND COST-EFFECTIVENESS

The CALM-PD study revealed that PDQUALIF mean change scores were notably better in the L-dopa group at the 2-year follow-up. However, no significant differences were observed in the mean changes at any other time points. The mean difference between groups was approximately two points and given that the PDQUALIF has a theoretical range from 0 to 128, a 2-point difference corresponds to less than a 1% variation. While statistically significant, this difference may not hold clinical significance.

In a study comparing pramipexole ER and IR versus placebo, improvements in PDQ-39 scores were noted as 3.8 (ER) and 6.5 (IR), in contrast to a worsening of 1.5 points in the placebo group[11].

Regarding costs, DAs are considered the most expensive among L-dopa-sparing therapies. Pramipexole daily dose cost and LEDD cost have been reported to be up to 10 times higher than that of LD-DDi[12].

MAOBIS AS INITIAL TREATMENT IN EARLY-STAGE PARKINSON'S DISEASE: QOL AND COST-EFFECTIVENESS

Few of the rasagiline or safinamide placebo-controlled RCTs for advanced PwP reported statistically significant QoL improvement as measured by PDQ-39 or PDQUALIF[31]. The PD MED study estimated the cost-effectiveness of L-dopa-sparing therapies; costs were significantly lower for those allocated in MAOBIs compared to DAs with similar QALYs[46].

DISCUSSION

Over the past two decades, the false dilemma of choosing between a lower incidence of motor complications achieved at the cost of poorer motor scores, particularly during the initial years of anti-parkinsonian treatment, has significantly influenced prescription patterns in drug-naïve PwP starting treatment.

Earlier studies, such as ELLDOPA, focused on the rate of PD progression as the primary endpoint, while others, like DATATOP, defined their primary outcome as reaching a threshold of disability necessitating L-dopa therapy. Subsequently, investigator-reported outcomes, utilizing scales such as UPDRS and MDS-UPDRS, became the norm. However, various issues arise; for example, using combined scores such as total UPDRS or UPDRS II + III introduces complexities when comparing studies. Reporting practices also vary, with some studies comparing mean UPDRS/MDS-UPDRS scores between groups, while others examine mean changes from baseline or the percentage change between groups. In addition, patient-reported outcomes, encompassing QoL or functional status, lack standardization across studies and employ different assessment tools. Finally, although the conversion of individual data from UPDRS Parts II and III to MDS-UPDRS scores is feasible[47], to the best of our knowledge, this method has not been employed for cross-study comparisons.

However, the utmost importance lies in the minimum clinically important difference (MCID), representing the smallest improvement deemed worthwhile by PwP, crucial for practical interpretation, and decision-making.

The MCID estimates for the MDS-UPDRS Part III indicate a significance threshold of −3.25 points for improvement and 4.63 points for worsening[48]. Regarding MDS-UPDRS Parts I and II, improvement exceeding 2.64 and 3.05 points, respectively, or worsening surpassing 2.45 and 2.51 points, respectively, are considered clinically relevant[49]. MCDI values for composite scores based on MDS-UPDRS have also been documented[50].

Recently, the MCID for the unified dyskinesia rating scale has been published[51]. In addition, for PDQ-39-i, the reported MCID is −4.72 for improvement and +4.22 for worsening. Corresponding values for PDQ-8-i are −5.94 and + 4.91[52]. As for EQ-5D scores, MCID estimates range from 0.09 to 0.10 (EQ-5D score) and from 9.1 to 11.40 in the Visual Analog Scale score[53]. Overall, it has been suggested that a relative change of 10% or more or an effect size of 0.20 can likely be deemed clinically meaningful54.

A network meta-analysis comparing DAs to LD-DDi monotherapy in early-stage PD revealed that L-dopa exhibited superior improvement in UPDRS-II, UPDRS-III, and UPDRS-II + III, as anticipated. Conversely, no statistically significant differences were observed among the various DAs. However, pramipexole, ropinirole, bromocriptine, and pergolide, when used as monotherapy, demonstrated a lower incidence of dyskinesia compared to L-dopa. In contrast, the use of DAs was associated with higher incidences of total withdrawals[55].

The 2018 update on motor symptoms treatment of the International Parkinson and Movement Disorder Society states that pramipexole, rotigotine, ropinirole IR, selegiline, and rasagiline remain efficacious and clinically useful as monotherapy. Likewise, recommendations on LD-DDi being as efficacious and clinically useful have remained unchanged since the first evidence-based review in 2005[56]. The 2021 American Academy of Neurology early-stage PD practice guidelines suggest LD-DDi as the initial preferential dopaminergic therapy when the main objective is motor symptom treatment. Nevertheless, it is crucial to consider additional factors in the decision-making process, including age, the risk of dyskinesia, susceptibility to impulse control disorders, pre-existing cognitive impairment, sleep disorders, and hallucinations[57].

Regarding non-motor symptoms, different neurotransmitters are involved in their pathophysiology. Those hypothesized to be linked exclusively to dopamine disruption are alteration of the vision of colors, hallucinations, and early cognitive impairment. Non-motor symptoms involved with dopamine and norepinephrine include depression and anxiety. Pain has been associated with dopamine, norepinephrine, and serotonin, while bladder hyperreactivity has been linked to dopamine and acetylcholine.

The IPMDS Update on Treatments for Non-motor Symptoms of PD does not consider LD-DDis and focus mainly on DAs and MAOBIs. The practice implications range from possible to clinically useful depending on the drug and non-motor symptom, and in most cases, with acceptable risk without specialized monitoring[58].

From a clinical perspective, LD-DDis are typically initiated with three doses a day, and adjustments involve reducing interdose intervals by increasing the dosage frequency, with or without modifying the total dose. Research by Bovenzi et al. indicated that LEDD adjustments follow a non-linear trend, displaying rapid increases (approximately 527 mg) in the first 0-5 years, followed by slower increments (around 167 mg) in the subsequent 5-10 years. This suggests a projected overall LEDD of 693.73 mg at the 10-year mark from onset[59].

Both LD-DDis and DAs should undergo gradual titration to attain the desired therapeutic effect while minimizing side effects. In the case of L-dopa, the most common titration schedule involves initiation with the lowest possible dose (i.e., 50 mg 3 times a day) and incrementing by 100 mg, divided into three or more doses, at least every 3-4 days based on the clinical symptomatic response. Notably, a higher rate of dose increase (LEDD increase exceeding 100 mg/day/year) is significantly linked to the early onset of dyskinesia.

Tables 1 and 2 provide essential considerations and direct comparisons for prescribing levodopa, which are crucial for informed clinical decision-making (Table 1) and understanding the relative efficacy and safety of LD-DDi, DA, and MAO-Bi (Table 2).

Table 1. Considerations when prescribing levodopa

Initial evaluation
Before starting levodopa therapy, conduct a thorough assessment of the patient's medical history, current symptoms, daily life activities impairments, and overall health status. This evaluation helps determine the appropriate starting dose of levodopa.
Starting dose
The initial dose of levodopa is usually set at a low level to minimize the risk of side effects. This allows the person to gradually adjust to the medication. Common starting doses are determined based on the patient's age, weight, severity of symptoms, and any existing medical conditions.
Dose titration and frequency
The recommended initial frequency is 3 times daily. The initial recommended dose is 50 mg and may be increased by 50 mg daily every 3-4 days according to the response. Increase frequency as needed. Consider that motor clinical response is usually seen at a minimum dose of 300 mg/d.
Titration schedule
The titration schedule is developed based on the patient's needs and response. The dose adjustments are typically made over weeks to months, allowing time for the body to adapt and minimizing the risk of sudden adverse reactions. Consider the dose maximum benefit can take up to 8 weeks, especially at low doses.
Maintenance dose
Ideally up to 600 mg daily in divided doses to avoid increasing the risk of motor complications. If in polytherapy with other dopaminergic drugs, consider the levodopa equivalent daily dose.
Regular monitoring
After initiating treatment, the patient is closely monitored for both therapeutic effects and potential side effects. This involves assessing changes in motor symptoms, mood, cognition, and any adverse reactions.
Symptom response
Depending on the patient's response, it may be needed to increase the dose gradually. If the patient experiences inadequate symptom control (insufficient improvement in motor symptoms), the dose may be increased in small increments. Do not rush; maximum motor benefit can take up to 8 weeks. Consider both PRO and CRO. When using rating scales consider the MCID.
Monitoring side effects
As the dose is increased, the patient is closely monitored for potential side effects, such as nausea, vomiting, dyskinesias, and changes in blood pressure. If side effects occur, adjust the dose or provide additional medications to manage them. If relevant comorbidities are present, a multidisciplinary team approach is always recommended.
Patient feedback
The patient's feedback is crucial during the titration process. Open communication about changes in symptoms, side effects, and overall well-being helps guide the dose adjustments and ensures that the treatment plan is aligned with the patient's goals and needs. Promote patient empowerment and shared decision-making to enhance engagement and adherence.
Optimal dose finding
The titration process aims to find the lowest effective dose that provides optimal symptom control while minimizing side effects. This can involve finding the right balance between levodopa and other medications used to manage Parkinson's disease.
Long-term monitoring
Parkinson's disease is a chronic condition, and the patient's needs may change over time. Regular follow-up appointments are important to continue monitoring the patient's response to the medication and making any necessary adjustments to the treatment plan. Carry out follow-up consultations preferably every 3-6 months but at least once a year.

CRO: clinician-reported outcomes; MCID: minimum clinically important difference; PRO: patient-reported outcomes.

Table 2. Head-to-head comparisons between LD-DDi, DA, and MAO-Bi

Aspect	LD-DDi	DA	MAO-Bi
Advantages			
Efficacy	Provides rapid and effective improvement of motor of symptoms	Offers modest symptomatic improvement	Offers modest symptomatic improvement
Symptom control	Can effectively manage a wide range of motor symptoms	Provides some improvement of motor symptoms	Provides some improvement of motor symptoms
Motor fluctuations	Can lead to motor fluctuations ("on-off" periods)	Lower risk of motor fluctuations	Lower risk of motor fluctuations
Dyskinesias	May increase the risk of dyskinesias (daily dose > 600 mg/d)	Lower risk of dyskinesias	Lower risk of dyskinesias
Cost-effectiveness	Generally less expensive than dopamine agonists	Can be more expensive	Cost-effective option
Disadvantages			
Long-term efficacy	Effectiveness may decrease over time ("wearing off")	Long-term efficacy may be limited	Long-term efficacy can be challenging
Side effects	Higher risk of side effects, especially at higher doses	In general, better tolerated at lower doses	Risk of hypertensive crisis with certain foods/medications (selegiline)
Nausea/vomiting	Can cause nausea and vomiting, especially at the initiation	Lower risk of nausea/vomiting	Potential for dietary restrictions (selegiline)
Impulse control disorders	Lower risk of impulse control disorders	Associated with a higher risk of impulse control issues	Lower risk of impulse control disorders
Hallucinations	May worsen hallucinations in some cases	Increased risk of hallucinations in some patients	May worsen hallucinations in some cases
Cardiovascular effects	May cause blood pressure changes in some cases	In general, has fewer cardiovascular effects	Risk of hypertensive crisis with certain medications
Onset of action	Rapid onset of action for symptom relief	Slower onset of action compared to levodopa	Variable onset of action slower onset of action compared to levodopa
Clinical considerations			
Individualized approach	Requires careful titration and monitoring	In general, easier to titrate and manage	Requires monitoring and dietary restrictions (selegiline)
Treatment duration	Often considered as a long-term treatment option	Can be considered as an initial treatment	Long-term use may be limited due to side effects

DA: dopamine agonists; LD-DDi: levodopa with dopa-decarboxylase inhibitor; MAO-Bi: monoamine oxidase B inhibitors.

CONCLUSION

This review highlights the intricate balance between the benefits and adverse effects associated with levodopa and levodopa-sparing therapies in the early management of PD. The historical apprehension toward levodopa, stemming from fears of dyskinesia, juxtaposed with the behavioral side effects of dopamine agonists, underscores the complexity of optimizing treatment for early-stage PD subjects. Studies such as ELLDOPA, PD MED, and LEAP have contributed significantly to our understanding, demonstrating that while levodopa remains a highly effective treatment for motor symptoms; its use is not without risks, particularly concerning the development of dyskinesias. Conversely, levodopa-sparing

options, including dopamine agonists and MAO-B inhibitors, offer alternatives that may delay the onset of these motor complications but not without their own set of adverse effects and impact on QoL.

Crucially, the decision-making process in the clinical setting must account for individual patient characteristics, including age, disease severity, and the potential for developing motor and non-motor complications.

Moreover, the discussion around cost-effectiveness and QoL considerations emphasizes the need for broader perspective on treatment choices, taking into account not only the clinical but also the economic impacts of PD therapies. As the field progresses, the ongoing challenge will be to integrate new evidence into clinical practice, ensuring that patients receive the most effective, safe, and patient-centered care possible.

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