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REVIEW

Optimizing levodopa therapy, when and how? Perspectives on the importance of delivery and the potential for an early combination approach

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ABSTRACT

Introduction: There is currently a resurgence of levodopa as the initial treatment of choice for most patients with Parkinson's disease, albeit at lower doses than previously used. The addition of adjuvant treatments (including MAO-B inhibitors, COMT inhibitors and dopamine agonists) is an established strategy to reduce motor complications that develop with sustained levodopa therapy.

Areas covered: In this narrative review, the authors discuss the evidence underpinning current levodopa optimization strategies, during early disease and once motor complications occur. To support the discussion, the authors performed a broad PubMed search with the terms 'levodopa/L-dopa/L-Dopa, and Parkinson's disease,' restricted to clinical trials. There is now a wealth of evidence that improving levodopa delivery to the brain improves outcomes and we discuss how agents can be combined earlier in the course of disease to leverage the full potential of this strategy.

Expert opinion: Levodopa remains the cornerstone of antiparkinsonian therapy. Several promising advances in formulation have been made and include novel extended-release oral drugs as well as non-oral delivery systems. However, evidence has long suggested that anti-parkinsonian medications may be better used in combination earlier in the disease, and consequently patients will benefit from low doses of several agents rather than ever larger levodopa doses.

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1. Introduction and a brief history of levodopa therapy

The prevalence of Parkinson's disease (PD) has recently been estimated to be 1 in 800 people, with advancing age being the greatest risk factor. Current estimates suggest that the PD population will double in the next decade [1], and this will be associated with a considerable increase medical costs [2]. While the underlying pathology is now better understood [3,4], accumulating evidence supports the concept that PD neurodegenerative process starts years before the motor symptoms of the disease, including bradykinesia, emerge [5,6]. In the absence of proven disease-modifying therapy, the current goal of treatment is to relieve suffering by helping patients retain functional independence for as long as possible.

Up until the mid-1960s, prior to the advent of levodopa therapy, most patients with PD were severely physically disabled or dead within 10 years of disease onset. The only available treatments were anticholinergic drugs and stereotactic thalamotomy, neither of which improved bradykinesia, the most disabling motor symptom of the disease. The magnitude of improvement seen in many patients with levodopa (Larodopa) led to claims, that were not without some justification, that it was a *'magic bullet'* or '*miracle drug*,' but its shortcomings and unwanted side effects soon became apparent, leading to adverse publicity that delayed its introduction into clinical practice [7]. Soon after, the combination of levodopa with peripheral dopa decarboxylase (DDC) inhibitors allowed for a fourfold reduction in the dosage of levodopa and a substantial reduction in side effects such as anorexia, nausea, and vomiting [8]. By 1972, Madopar® (levodopa/benserazide) and Sinemet® (levodopa/carbidopa) were the treatment of choice for PD, with anticholinergics and amantadine being used as adjuvant therapy in some patients [9].

In the early years of 'levodopa combination' therapy, many patients received high doses of levodopa. NonselectiveNonselective monoamine oxidase inhibitors used to treat depression in the 1960's potentiated the effects of levodopa but could not be used safely because of dangerous elevations of blood pressure [10]. The emergence of motor fluctuations and disabling levodopa-induced dyskinesias (LID) as a

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Article highlights

- After more than 50 years of clinical use levodopa has remained unsurpassed in terms of clinical effects size on PD motor symptoms but is associated with the development of motor complications in the long-term.
- Following a period of 'levodopa-phobia' current treatment algorithms have seen a return to the use of levodopa therapy as the initial treatment of choice for most patients with PD but at lower doses than were used in the 1970's.
- There is a large evidence-base to show that optimizing levodopa delivery, through the development of improved formulations and delivery or via adjunct therapies, improves long-term outcomes.
- Accumulating evidence suggests that the levodopa 'sparing' approach has no long-term therapeutic benefits and may negatively impact on patient quality of life.
- Earlier use of combination therapies may be beneficial by exploiting distinct mechanisms of action that can complement each other.

complication of sustained levodopa therapy led to renewed efforts to improve its bioavailability and reduce its enzymatic breakdown in the peripheral tissues and the brain [9]. In the late 1970s, the first selective MAO-B inhibitor, selegiline was introduced and shown to have mild symptomatic benefits and the capability to reduce the severity of mild wearing-off effects in levodopa treated patients [11]. Two newer MAOB inhibitors – rasagiline and safinamide – are also now available but there is no evidence that they are superior to selegiline [12–14]. The most recent enzymatic refinement to levodopa therapy was the introduction of COMT inhibitors in 1997. Three drugs are currently licensed – tolcapone, entacapone and (the most recently developed) opicapone – all of which smooth out motor fluctuations and reduce the severity of OFF periods.

Developed as levodopa alternatives, orally active dopamine agonists were introduced into clinical practice in the mid-1970s [15]. The first group of drugs were ergoline based, and while highly efficacious, had unwanted serious adverse events including pleuroperitoneal and cardiac valve fibrosis and have now been largely replaced by the non-ergoline compounds ropinirole, pramipexole, and rotigotine [16]. Between 1985 and 2005 dopamine agonists were widely used and promoted as the initial treatment of choice in an attempt to delay the emergence of dyskinesias and disabling OFF periods [17,18] and on a false premise that levodopa may be neurotoxic to brain cells [19]. Long-term follow up over ten years has shown that this levodopa 'sparing' approach has no long-term therapeutic benefits and may negatively impact on patients quality of life [20,21], and dopamine agonists are now less used in part because of concerns about the risk of impulse control disorders including pathological gambling and compulsive sexual disorders [22,23], and excessive daytime somnolence.

2. Areas covered in this review

The last ten years have seen a return to the use of levodopa/DDC inhibitor combinations as the initial treatment of choice for most patients with PD but at lower doses than were used in the early 1970's (300–600 mg/day) [24]. Indeed, the recently updated American Academy of Neurology (AAN) guidelines now recommend levodopa as the initial therapy for *most* patients with early PD seeking treatment for motor symptoms [25]. If adequate control cannot be achieved at these dosages, then addition of MAO-B and/or COMT inhibitors is now a popular strategy. However, there is still little consensus on *when* and *how* to optimize levodopa treatment. In this narrative review, we will discuss the evidence underpinning current levodopa optimization strategies and how agents can be combined earlier on to provide the optimal long-term outcomes. To support our discussion, we performed a broad PubMed search without date or language restrictions with the terms levodopa, L-dopa, L-Dopa, and Parkinson's disease, and restricted to clinical trials. Where relevant, we checked the reference section of prior systematic reviews.

3. Starting PD therapy with levodopa

The so -called 'early' stage of the parkinsonian clinical syndrome is characterized by mild symptoms, minimal to mild disability, without postural instability or marked cognitive decline. For many years, several clinicians advised their patients to wait for functional disability to develop before commencing symptomatic therapy [26,27]. This view was robustly challenged by evidence that:

(i) progression in the initial stages may be slowed by the compensatory mechanisms, which maintain normal motor function while the number of dopamine neurons has fallen to 50% of normal [28,29].
(ii) initiation of therapy with an effective dopamine replacement therapy maintains patient quality of life over 18 months, compared with a worsening in patients who remained untreated [30,31].

Early symptomatic treatment within the first two years after clinical diagnosis is now recommended with either levodopa or other monotherapies such as the MAO-B inhibitors or dopamine agonists [25,32,33]. The UKPDRG trial [20,34,35] and the later PDMed trial [36] assessed the impact of initial choice of therapy on outcomes. The UKPDRG study was conducted in the 1990's and recruited 782 patients with *de-novo* untreated PD who were randomized to either levodopa plus dopa decarboxylase inhibitor; levodopa plus decarboxylase inhibitor and selegiline; or bromocriptine. There were several important observations from this study and long-term follow-up. The study showed that a *'slightly lower incidence'* of motor complications is achieved with dopamine agonist versus levodopa treatment at the expense of worse disability (as assessed using Webster scores) throughout the first years of therapy. However, in the group of patients who made it to the final (14-year) visit, the reduction in motor complications was not maintained and there was no evidence of a long-term benefit or clinically relevant disease-modifying effect with initial dopamine agonist treatment [20]. While the study showed very mild early benefits of early combination (levodopa + selegiline) therapy, such as a non-significantly greater improvement from baseline in Webster disability scores (adjusted difference of 0.51) and a longer time before patients returned to baseline disability, this was tempered by an increased mortality in the

combined therapy group which was thought to be due to increased cardiovascular complications including postural hypotension in elderly patients [34].

At around the same time, the PRADO study also evaluated an early 'combination' approach by comparing the effects of levodopa monotherapy versus levodopa combined with bromocriptine on the development of motor complications in newly diagnosed PD patients. The study showed that the cumulative probability of experiencing motor side effects was higher with monotherapy than with combination therapy (0.43 vs 0.28, respectively, p = 0.025) suggesting that early combination therapy can extend the period of optimal disease control [37]. However, the research impetus at the time focused on the 'either-or' monotherapy approach thereby minimizing the impact of this much overlooked study.

More recently, the PDMed Trial, randomized 1620 newly diagnosed PD patients (2:1) between levodopa-sparing therapies (dopamine agonist or MAO-B inhibitor) and levodopa monotherapy, who were then treated as per routine practice; the median follow-up was three years [36]. Using patient-rated mobility scores as the primary outcome measure, the study confirmed the findings of the UKPDRG trial that there were initial benefits for initiating treatment with levodopa compared with levodopa-sparing therapy and no long-term disadvantages [20,36]. While the main results of this purportedly comparative study were not particularly persuasive to either camp [38], patients initially randomized to treatment with a MAO-B inhibitor or dopamine agonist were significantly more likely to discontinue their allocated drug class and/or add another drug class than those allocated levodopa (and these mostly switched to or added levodopa). Of note, about 40% of patients randomized to levodopa monotherapy required adjunct therapy with a dopamine agonist, COMT inhibitor or MAO-B inhibitor [36].

4. Optimizing levodopa drug delivery to manage motor complications

As the natural precursor to dopamine, levodopa allows the synthesis and regulated release of dopamine, thus replacing the full range of tonic and phasic dopamine actions at pre- and post- synaptic receptors [39]. With continued neurodegeneration, the ability of the surviving nigrostriatal dopamine neurons (and other monoaminergic neurons) to synthesize and store dopamine diminishes, and it has been postulated that patients lose the 'long-duration response' to levodopa (LDR). Recent evidence argues that the LDR to levodopa is present from the first dose and may persist long-term [40] although motor fluctuations start to compromise the therapeutic response [41–43]. Additionally, pulsatile levodopa delivery can occur (or be exacerbated) as a direct consequence of impaired gastric emptying, large dietary neutral amino acids interfering with enteric absorption, as well as competition between amino acids and levodopa for the facilitative amino acid transporter (L1) to cross the blood brain barrier [44,45].

As early as the 1970's, clinico-pharmacological studies showed a *'close temporal relationship'* between wearing-off and troughs in plasma levodopa levels [46,47] and other early studies also supported a temporal relationship of LID with the clinical response single levodopa doses [48,49]. Moreover, a wealth of experimental work indicates a possible causal relationship of pulsatile drug delivery to dyskinesia development [41,50]. A wealth of preclinical evidence suggests that the pulsatile stimulation of dopamine receptors associated with traditional levodopa dosing causes a series of downstream changes in the basal ganglia (including altered receptor expression and firing patterns) linked to the development of dyskinesia [41,51]. Modifying the pharmacokinetics of levodopa and its mode of delivery to achieve more continuous drug delivery is a long-accepted strategy for reducing the severity of end of dose deterioration (wearing-off effects) and may also be useful in reducing the risk of LID.

4.1. Modifying dosing strategies to manage motor complications

Although standard levodopa (with benserazide or carbidopa) has a short half-life of only around 90 minutes, the drug is usually started with three daily doses. This leads to fluctuating plasma levels characterized by a dose dependent peak and trough pattern over the day [51,52]. For reasons still not completely understood, these plasma level oscillations are not associated with clinically apparent fluctuations in motor response until several years after initiation of levodopa.

Once levodopa response fluctuations emerge, the most obvious and common practical strategy is to reduce inter-dose intervals by increasing dosage frequency (with or without modifying the total dose). While moving from 3 to 4 daily levodopa doses seems straightforward, it poses challenges for concordance [53,54] and is only effective for a limited period after which further increases in dosing frequency usually are necessary – running the risk of the emergence of LID. One possible solution to this particular problem is the use of drug-device combinations that enable ultra-frequent (up to hourly) oral levodopa dosing to reduce plasma level oscillations [55]. While most patients in a small study rated the 5-dose dispenser generally favorably [56], the practicality of this approach in a broader population remains to be shown and it does not overcome issues related to erratic gastric emptying. Continually increasing the total levodopa dose often exacerbates LID without any significant effect on the duration of benefit. In addition, levodopa dose has also been shown to be an important risk factor for the development of LID, with studies suggesting that doses should be kept below 400 mg/day for as long as possible [57,58].

4.2. Modifying the pharmacokinetics and delivery of levodopa through new formulations and delivery systems

Attempts to develop novel levodopa formulations with the goal of extending the plasma half-life and duration of effect of oral doses of levodopa also date back to the 1980's [59] but the superiority of the marketed extended-release formulations of levodopa over standard immediate release formulations have not been proven – even for night time use [60]. The newer oral levodopa formulations attempting to achieve smoother plasma dopa levels throughout the day are summarized in Table 1.

Table 1. Oral levodopa formulations developed to provide a more continuous levodopa delivery.

Oral levodopa formulation	Status	Impact on levodopa pharmacokinetics	Impact on motor fluctuations	Citations
IPX066 Capsule containing combined immediate and sustained release pellets of CD/LD (ratio 1:4). The different components dissolve at different rates along the gastrointestinal tract.	FDA approved EMA approval now withdrawn.	• Onset of effect within approximately 20–40 minutes of administration. • Plasma LD concentrations kept ≥50% of C_{max} for around 4 hours with IPX066 compared with average of 1.4 hours for IR-LD/CD. • Relative bioavailability of IPX066 is around 75% of IR-LD/CD. • Administration of IPX066 every 6 hours provided relatively stable plasma concentrations.	Significant reductions in OFF-time during waking hours (1.17–1.4 hours) and increase in ON time without troublesome dyskinesia (0.93–1.4 hours) with IPX066 compared to IR-LD/CD or LCE [107] in PD populations with motor fluctuations.	[61,62,106]
Melevodopa A highly soluble formulation as effervescent oral tablets	Marketed in Italy	More rapid absorption, less apparent drug accumulation, less inter-patient variability and more effective LD delivery after the early morning and early afternoon dose compared to IR-LD/CD	Faster onset of effect in aborting OFF-periods in patients with motor fluctuations.	[63,64]
Levodopa/carbidopa microtablet Micro-tablets which are taken using a dose dispenser	Marketed in certain European countries	Significantly shorter time to Cmax, avoidance of trough plasma levels and a reduced fluctuation index compared to LCE.	Majority (85%) of patients reported symptom improvement.	[55,56]
IPX203 Multiparticulate oral capsule formulation of CD/LD (ratio 1:4). Designed to provide a rapid initial rise in plasma LD followed by prolonged, steady LD concentrations.	Phase III	Levodopa concentrations were sustained above 50% of peak concentration for 4.6 hours with IPX203 versus 1.5 hours with IR CD-LD.	Significant reductions in OFF-time (treatment difference −2.7 hours) and increase in ON time without troublesome dyskinesia (treatment difference 2.6 hours) with IPX203 vs IR-LD/CD.	[65]
Accordion pill® Novel gastric-retention oral delivery platform of LD/CD based on folded multilayer films which are folded in an accordion-shape and then filled into standard-size capsules.	Phase III	More stable LD plasma and significantly decreased C_{max} vs. IR-CD/LD .	Significant improvements in daily OFF time, total ON time, and good ON time vs IR-LD/CD in one phase 2 study, but not in a subsequent phase 3. Another phase 3 study is underway (NCT02605434).	[66]
XP21279 Levodopa prodrug absorbed from the small and large intestine. It is rapidly metabolized to levodopa after absorption and the capacity for colonic absorption provides extended plasma concentrations.	Phase II trials completed	Greater AUC, increased average plasma LD concentration and decreased plasma level variation with XP21279.	XP21279 failed to show statistically significant reductions in daily OFF-time vs. IR-LD/CD.	[67]
ODM-101 LD/CD/entacapone tablets that contain a fixed amount of either 65 or 105 mg of carbidopa (ODM-101/65 and ODM-101/105)	Phase II		Reduced OFF time vs LCE (treatment difference 0.6–0.7 hours) .	[68]
DM-1992 CD/LD bi-layer tablet formulation combining immediate- and extended-release layers. Capsules are taken with food and swells after contact with gastric content and remain in the stomach for prolonged periods.	Phase II	Smoother plasma levodopa concentration profile vs. IR-LD/CD.	Reduction in % OFF-time vs. IR-LD/CD.	[69]

Non-oral levodopa delivery bypasses issues with gastrointestinal transport and absorption that may compromise oral treatment and have been developed along two main rationales:

(1) to provide stable plasma concentrations via continuous drug delivery, or
(2) to provide rapid onset of effect suitable for use as an on-demand ('rescue') medication.

Pilot studies of intravenous levodopa infusions provided 'proof of concept' for the efficacy of continuous drug delivery in patients with motor fluctuations already in the 1980s [70,71] but it took another 20 years before enteric dopa administered through a gastro-jejunostomy entered clinical practice [72]. The efficacy of levodopa/carbidopa intestinal gel infusions (LCIG) in reducing motor fluctuations is well established (treatment difference of −1.91 hours in OFF time vs IR-levodopa therapy [73]) and recent evidence suggests that LCIG significantly reduced dyskinesia compared with oral optimized medical treatment [74]. A new intestinal formulation including entacapone is also now available in Europe [75]. However, this approach is limited to later 'advanced' disease by its need for abdominal surgery (insertion of PEG tubes) as well as mechanical complications including tube dislocation and block and infection. Subcutaneous delivery of levodopa is a

less invasive alternative to enteral infusions and three formulations (ABBV-951, ND0612 and DIZ 102) are in clinical development [76–78], with ABBV-951 and ND0612 having promising results regarding reduced OFF-time [76,77]. Results from the Phase 3 RCT with ABBV-951 reported an increase in ON-time without troublesome dyskinesias of 1.75 hours over optimized oral therapy [76].

Rapid reversal of individual OFF-episodes are another therapeutic need for patients experiencing motor fluctuations that has been difficult to achieve with oral levodopa formulations. An inhaled levodopa formulation (CVT-301) has been developed to provide intrapulmonary levodopa delivery using a pocket-sized inhaler. In a double-blind placebo-controlled Phase 3 study, UPDRS motor scores were significantly improved over placebo at 30 minutes post dose (treatment difference of −3.92 points vs placebo) [79]. The drug has meanwhile been approved for clinical use by both the FDA and EMA.

5. Adjuvant combination therapy

Dopamine receptor agonists were developed to directly stimulate post-synaptic dopamine receptors on striatal neurons. Because the dopamine agonists alone rarely cause dyskinesia, physicians sometimes think that they will not increase dyskinesia when added to levodopa. However, careful experimental studies with pramipexole indicate that agonists also augment the levodopa pharmacodynamic response (potentially increasing dyskinesia) [80]. Thus, as with the other classes of PD drugs, the decision to combine agonists and levodopa requires striking an appropriate balance between gain of motor function versus worsening of dyskinesia. In addition, the lack of phasic release in the ventral striatum (important for reward and punishment learning) coupled together with the selective receptor profile of the dopamine agonists (particularly those with high affinity at D3 receptors) has been associated with a higher frequency of impulse control disorders, particularly pathological gambling in susceptible patients [81,82], and has tempered enthusiasm for their use. Nevertheless, while they are less used as initial monotherapy, dopamine agonists remain a popular choice for augmentation of levodopa [83].

MAO-B inhibitors act by interfering with one of the catabolic pathways for dopamine and thereby prolonging the synaptic availability of dopamine. The MAO-B inhibitors selegiline and rasagiline have mild antiparkinsonian effects when used as monotherapy (a meta-analysis reported standardized mean differences [SMD] for total UPDRS scores of −0.53 for rasagiline and −0.33 for selegiline [84]) but are less efficacious than oral dopamine agonists and levodopa [85]. The most recent MAO-B inhibitor safinamide is described as a dual action drug because it combines selective MAO-B inhibition with antiglutamatergic actions (via voltage-gated sodium channel) and is licensed in many countries as an adjunct to levodopa but there is no evidence to point to its superiority over selegiline or rasagiline [86]. The evidence that selective MAO inhibitors are neuroprotective is not persuasive and in elderly patients they may increase mortality as a result of cardiovascular side effects [34].

While MAO-B inhibitors are used as adjunct to levodopa and have been reported to improve wearing-off effects (by prolonging exogenous dopamine availability) they have no effect on levodopa pharmacokinetics and thus do not address one of the key underlying causes of wearing-off [87]. For this reason, COMT inhibitors (entacapone and opicapone) are often preferred as first-line therapy for wearing-off as they act directly to reduce the peripheral metabolism of levodopa increasing the half-life of levodopa and avoiding the deep troughs in levodopa plasma levels that are associated with motor fluctuations [88]. The earliest available COMT inhibitor, tolcapone is now only used when other COMT inhibitors have not been helpful due to the small risk of severe liver toxicity [32]. Work with entacapone and opicapone shows that there is an important interplay between the frequency of levodopa dosing and COMT inhibition [52,89,90], with a recent study suggesting that adding opicapone 50 mg may be considered as an alternative option to increasing the dosing frequency and total daily levodopa dose [91]. Importantly, preclinical work with entacapone and opicapone confirm that the changes in plasma levodopa pharmacokinetics are translated into changes in central dopamine availability [92,93].

5.1. Evidence for a combination approach in stable PD

The FIRST-STEP study compared the efficacy of levodopa/carbidopa/entacapone (LCE, Stalevo) with levodopa/carbidopa in patients with early, stable PD. While not a study in *de novo* patients, only about a third of patients were receiving other antiparkinsonian therapy at baseline (amantadine, anticholinergics, MAO-B inhibitors) and less than 10% in each group had previously tried a dopamine agonist. Statistically significant benefits were seen favoring 'combination therapy' for Unified Parkinson's disease Rating Scale (UPDRS) Parts II+III (primary endpoint, treatment difference of 1.7 points) and Part II (activities of daily living [ADL]) vs standard levodopa/carbidopa therapy. Of note, wearing-off was observed in 13.9% of patients in the LCE group versus 20.0% in the levodopa/carbidopa group ($P = 0.099$). However, rates of LID were not significantly different (5.3% vs. 7.4%, respectively; $p = 0.367$). Unfortunately, the observable benefits of early combination therapy in FIRST-STEP study were eclipsed by the failure of LCE to delay or reduce the frequency of LID compared to levodopa in the much-anticipated STRIDE-PD study [94]. In fact, although there was a non-significant trend towardtowards a lower incidence of wearing-off, LCE was associated with a shorter time to onset and increased frequency of LID compared to levodopa [94].

A small number of trials have also investigated the earlier addition of adjunct therapy when patients are in a 'honeymoon' period (*i.e.* before the patient experiences the overt expression of motor complications). Studies with the COMT inhibitors tolcapone [95] and entacapone [96] evaluated the effects of COMT inhibition versus placebo as adjunct to levodopa in stable, non-fluctuating patients with PD. In these studies, treatment with a COMT inhibitor improved ADL scores versus placebo, and these benefits were accompanied by a significant reduction in levodopa requirement [95,96]. A levodopa 'sparing' effect was also seen in the UK-PDRG selegiline

study which allowed clinicians the flexibility to adjust doses. Whereas the median daily dose of levodopa in the combined levodopa plus selegiline arm remained stable over 4 years of sustained follow up, daily levodopa doses in the monotherapy arm increased from a median of 375 mg/day after one year of treatment to 625 mg/day after 4 years. Additionally, the ropinirole 228 study specifically compared the early addition of adjunct prolonged release ropinirole as a means of delaying LID versus continually increasing doses of levodopa [97]. During the study, 3% of the ropinirole prolonged-release group and 17% of the levodopa group developed LID, and the difference was statistically significant ($P < 0.001$). There were no significant differences in UPDRS scores, suggesting comparable efficacy between the two strategies but with benefits once again favoring the combination approach [97].

5.2. Potential of levodopa combination therapy to prevent or delay motor complications

Motor complications can develop as early as 0.5–2 years after starting chronic use of levodopa [18,24], and the STRIDE-PD study suggest that lowest dose of levodopa that provides satisfactory clinical control should be used [98]. While STRIDE-PD failed to demonstrate a delay in the development of LID with combination therapy, later analyses suggested that this was because of higher levodopa dose equivalents in the LCE group and the fact that treatment with LCE did not provide continuous levodopa delivery [98]. More recently, it has been suggested that the combination of levodopa/DDCI with opicapone may provide a better pharmacokinetic profile for such an investigation [99]. The length and costs of repeating a STRIDE-PD like study with opicapone are likely to be prohibitive [99]. An alternative could be to look at how opicapone compares with entacapone in patients with stable, non-fluctuating disease where both older COMT inhibitors have been shown to improve UPDRS ADL scores [95,96]. With hindsight, it is likely that at least some of those patients in those early 1990's studies had signs and symptoms of early wearing-off, which is common already at the early stages of PD and is underestimated by routine neurological clinical evaluation. Previous studies with combination therapy in patients with mild motor fluctuations indicate that levodopa combined with COMT inhibition is more efficacious than levodopa monotherapy, both in terms of UPDRS ADL and motor scores [100]. Since COMT and MAO-B inhibitors act via different mechanisms (the first increasing levodopa delivery to the brain and the latter by prolonging striatal dopamine availability) these two adjunctive enzyme inhibitors might also be synergistic in their pharmacological effects. Early studies with entacapone and selegiline showed that the addition of selegiline increased the response to levodopa/DDCI and entacapone treatment [101].

6. Conclusions

As of today, levodopa remains the cornerstone of antiparkinsonian therapy, and the pendulum has swung firmly back in its favor as the initial treatment for people diagnosed with PD. Several promising advances in formulation have been made and include novel extended-release oral drugs as well as non-oral delivery systems. However, evidence has long suggested that anti-parkinsonian medications may be better used earlier in combination at lower doses than we have traditionally used, and consequently patients will benefit from low doses of several agents rather than ever larger doses of just levodopa/DDCi.

7. Expert opinion

Earlier use of combination therapies may take advantage of the fact that antiparkinsonian medications have overlapping indications, but distinct mechanisms of action that can complement each other. Indeed, implementation of these treatment strategies and the broader use of invasive treatments has already reduced the reduced the risk of troublesome dyskinesia and improved quality of life in advanced PD [102,103]. According to our current understanding, the decision of when to combine medications will need to be individualized to patient needs and preferences [104]. For some patients who are worried about the risks of motor complications, combination therapy may be introduced while they are still in their 'honeymoon' period, while other patients may simply find it easier to remain on monotherapy until the first signs of wearing-off. Future work may consider how novel forms of levodopa delivery can be used in combination with other drug classes for tailored therapy.

7.1. Five-year view

In recent years, there has been considerable commercial interest in developing more efficacious levodopa formulations that address the pharmacokinetic limitations of the oral immediate-release formulation [105]. Although they are primarily being developed as 'one-stop' solutions, these therapies can also be combined with other PD medications. The first of these new formulations to reach the market was IPX066 (Rytary/Numient) which is described as an extended-release levodopa capsule containing combined immediate- and sustained-release pellets of levodopa/carbidopa. IPX066 has been shown to provide a greater reduction of OFF time and a greater increase in ON time without troublesome dyskinesia when *compared* to the LCE formulation [106,107], however as with all current medications for motor fluctuations, treatment does not fully abolish OFF time and further improvements could be expected. Aside from a small subgroup of patients who are recorded as taking adjunct medications in the long-term IPX066 trials, little work has been done to look at the benefits of combining IPX066 with COMT or MAO-B inhibitors. Such prospective work may also be of interest with IPX203 [108] and other novel levodopa delivery systems in development.

The idea of combining levodopa infusion therapies with oral COMT inhibitors was already being tested in 2012, where addition of either entacapone or tolcapone allowed levodopa dose reductions of 20% while maintaining stable levodopa plasma levels and motor function [109]. Together with the success of intestinal infusion, this led to the development of a levodopa–entacapone–carbidopa intestinal gel

(LECIG) [110]. Treatment with the 'triple combination' levodopa/carbidopa/entacapone infusion therapy is now available in certain European markets and early user experience indicates that patients can be switched directly from traditional jejunal levodopa infusion [75]. Other levodopa infusion products in development have also considered the idea of combined therapy. Reports from an early Phase II pharmacokinetic study of the subcutaneous infusion therapy ND0612 suggest that combining ND0612 with entacapone also increased the steady state levodopa levels achieved with both ND0612 regimens tested [111]. In that study entacapone was given every 4 hours, and it would be of interest to observe how once daily administration with opicapone would compare. As these new levodopa formulations become embedded in the marketplace, it is almost inevitable that prescribers will look to individualize care by combining treatments, making collection of real-world data in registries such as the GLORIA registry study of intrajejunal levodopa infusion [112] a priority.

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