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Review

Editor's comment: Levodopa has now been available for the treatment of Parkinson's disease for over 40 years and most neurologists are very familiar with its use. Familiarity may, however, lead to a somewhat cavalier attitude toward the potential problems that can be encountered with the use of levodopa. I suspect that very few neurologists, me included, have been acutely aware of the potential for levodopa to produce peripheral neuropathy and of the frequency with which it does so. In this review, Müller and colleagues provide a tremendously valuable service by bringing this to our attention and discussing approaches to treat and potentially avoid this surprisingly common and sometimes dangerous adverse effect of what is still the most effective treatment available for Parkinson's disease.

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Peripheral neuropathy in Parkinson's disease: Levodopa exposure and implications for duodenal delivery ***[Universally Available]***

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ABSTRACT

In advanced Parkinson's disease (PD) patients, continuous intra-duodenal infusion of levodopa/carbidopa intestinal gel (LCIG) is an established approach in the management of motor complications that cannot be further improved by conventional oral therapy. In general, tolerability of LCIG has resembled that of oral dopaminergic therapy; however, cases of symptomatic peripheral neuropathy (PN), sometimes severe, have been reported in patients receiving LCIG. Cases are generally a sensorimotor polyneuropathy with both subacute and chronic onsets, often associated with vitamin B12 and/or B6 deficiency. Rare cases clinically resemble Guillain-Barré syndrome. In the absence of prospectively collected data on possible associations between LCIG and PN, it is prudent to explore potential mechanisms that may explain a possible relationship. The PN may be linked to use of high-dose levodopa, promoting high levels of homocysteine and methylmalonic acid or reduced absorption of vitamins essential for homocysteine metabolism. Cases of LCIG-associated PN often have responded to vitamin supplementation without need for LCIG cessation, although LCIG cessation is sometimes necessary. It may be advisable to monitor vitamin B12/B6 status before and after patients start LCIG and be vigilant for signs of PN. Prospective, large-scale, long-term studies are needed to clarify whether vitamin supplementation and routine use of a catechol-*O*-methyltransferase inhibitor may help prevent PN in LCIG recipients and whether these measures should be routine practice in patients with PD on high-dose oral levodopa.

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1. Introduction

Half a century after its introduction, levodopa continues to be the most effective pharmacotherapeutic option for ameliorating the motor symptoms of Parkinson's disease (PD) [1,2]. In advanced PD with severe complications that cannot be controlled by oral or transdermal adjuncts to oral levodopa, invasive pharmacologic and surgical options have included the continuous subcutaneous infusion of the dopamine agonist apomorphine [3,4] and deep brain stimulation (DBS) of the bilateral subthalamic nucleus or internal globus pallidus [5–7]. Continuous intra-duodenal infusion of levodopa/carbidopa intestinal gel (LCIG), a carboxymethylcellulose (carmellose sodium) gel suspension of levodopa plus the dopa-decarboxylase inhibitor (DDI) carbidopa [8], is another recent continuous drug delivery approach for advanced PD.

Tolerability resembles that of oral dopaminergic therapy [9–12], except for surgical and delivery-system events (e.g. tube dislocation) [10,11,13]. LCIG uses a carboxymethylcellulose/water vehicle, an agent that is frequently used as a food thickener [14]. Cases of symptomatic peripheral neuropathy (PN)—some severe—have been reported in LCIG recipients [12,15,16]; however, overall incidence cannot be estimated from these case reports. PN also has been reported in long-term recipients of oral levodopa, in whom signs or symptoms develop in as many as 12% [17,18].

This review describes the reported cases, surveys the mechanisms hypothesized for subacute and chronic cases and offers interim suggestions for management and possible prevention.

2. Methods

A thorough and systematic literature search of PubMed used multiple combinations of the following search terms: "advanced Parkinson", "advanced Parkinson's disease", "levodopa", "duodenal levodopa infusion", "levodopa/carbidopa intestinal gel", "LCIG", "polyneuropathy", "peripheral neuropathy", "neuropathy", "vitamin B" and "homocysteine". We subsequently reviewed abstracts for relevance and then searched the reference lists of appropriate articles to obtain any other pertinent references or search terms that were not captured during the original PubMed search.

3. Results: review of the literature

3.1. PN in PD in the absence of LCIG therapy

PN occurs in patients with PD (Table 1). PN was identified clinically and by electromyography (EMG) in 10 (43%) of 23 patients

Table 1
PN and related findings in PD case series and other studies.

Authors/year	Type of study (patient groups)	PN prevalence	Clinical findings	Interventions/outcomes
Taly et al., 1992 [19]	Case series (29 juvenile-PD patients)	Abnormal sensory conduction in 31%; abnormal motor conduction in 14%	–	–
Khan et al., 2003 [20]	Genetic case series (24 patients with *parkin* mutation)	Symptomatic PN in 1 levodopa-naïve patient	Axonal PN	"Dramatically" responsive to trihexyphenidyl initially; moderate motor response at 7 years
Müller et al., 2004 [21]	Pharmacokinetic/pharmacodynamic (31 patients on oral levodopa/DDI; 27 non-PD controls)	–	Sural-nerve action potentials were lower in PD patients than in controls (in association with homocysteine elevation), but conduction velocity was no different	–
Ohsawa et al., 2005 [22]	Case–control study (9 PD patients with *parkin* mutation; 8 idiopathic PD patients)	Sensory symptoms in 2 *parkin*-mutation patients and 2 idiopathic PD patients	Reduced sural-nerve action-potential amplitude in 8 *parkin*-mutation patients but not in idiopathic PD patients	–
Nolano et al., 2008 [23]	Case–control study (18 PD patients; 30 healthy controls)	Paresthesia or "burning feet" in 33%	Across the PD group, abnormal sensation thresholds plus epidermal nerve-fiber and Meissner corpuscle loss	–
Toth et al., 2008 [17]	Case–control study (34 PD patients with symptomatic idiopathic PN; 22 PD-only patients; 258 non-PD PN patients)	All cases (by study design)	Elevated homocysteine or MMA	Intra-muscular B12 led to PN stabilization at 24 and 36 months
Chovancova et al., 2009 [24]	Case series (23 PD patients)	PN signs in 43%	–	–
Capuano et al., 2010 [12]	ADR-database search	PN in 7 patients on LCIG (among an undescribed number of ADR reports)	Neuropathy in 2, polyneuropathy in 3, GBS in 2	LCIG cessation or interruption led mostly to at least gradual improvement
Gondim et al., 2010 [25]	Case series (10 PD patients with PN)	All subjects (by study design)	Primarily axonal PN but demyelinating features in 2 patients; low B12 and/or elevated homocysteine in 6 patients; all patients on oral levodopa	Intra-muscular B12 and oral folate led to PN improvement (time frame not specified)
Montastruc et al., 2010 [26]	ADR-database search	PN in 3 patients on oral levodopa (among 174,341 ADR reports)	PN was reported as ADR, but levodopa role was excluded or doubtful	–
Toth et al., 2010 [18]	Case–control study (58 PD patients; 58 community controls)	PN signs in 55% of patients and 9% of controls; symptomatic PN in 41% of patients and 5% of controls	Predominantly axonal PN, associated with levodopa exposure; elevated homocysteine and MMA	–
Nolano et al., 2011 [27]	Case series (21 PD patients)	–	Meissner corpuscle loss found only in levodopa recipients	–
Rajabally et al., 2011 [28]	Cross-sectional, case–control study (37 PD patients and 37 controls)	PN in 38% of PD patients and 8% of controls	Associated B12 deficiency in 50% of patients with PD + PN and 14% of non-PD controls; significant correlation among cumulative levodopa exposure, B12 level and PD duration in patients with PD + PN	–

ADR = adverse drug reaction; DDI = dopa-decarboxylase inhibitor; GBS = Guillain-Barré syndrome; LCIG = levodopa/carbidopa intestinal gel; MMA = methylmalonic acid; PD = Parkinson's disease; PN = peripheral neuropathy.

with PD [24]. Rajabally et al. [28] studied 37 patients with PD and 37 controls; PN was diagnosed in 14 (38%) patients with PD and 3 (8%) controls. When the 14 patients with PD and PN were compared with 28 age- and gender-matched controls with PN but not PD, B12 deficiency was found to be the sole cause in 7 (50%) patients with PD versus 4 (14%) controls. In the patients with PN, B12 levels were significantly lower in patients with PD than without PD (286.8 versus 413.2 ng/L). In the total cohort of patients with PD, there were no correlations between cumulative levodopa exposure, vitamin B12 levels, neuropathy status or Utah Early Neuropathy Scale scores, although significant correlations existed in patients with PD and PN between cumulative levodopa exposure and both disease duration and vitamin B12 levels.

In a prospective, unblinded case–control study of PN in which 500 patients with PD were screened for PN and compared with 258 patients with idiopathic PN but not PD [17], "idiopathic" PN was diagnosed in 34 (7%) patients with PD. Of these 34 patients with idiopathic PN, 32 (94%) had abnormal serum levels of B12, homocysteine and/or methylmalonic acid (MMA). In comparison, 26 (10%) patients with idiopathic PN but not PD had abnormal serum levels of B12, homocysteine and/or MMA. For B12 deficiency alone (defined by levels $\leq$250 pg/mL), the percentage was 44% versus 10%, respectively. Among the 22 patients with PD with neuromuscular conditions other than PN, none were B12 deficient. In the PD-plus-PN group, cumulative levodopa exposure correlated with PN severity. The mean levodopa exposure and mean PD duration were significantly greater in the PD-plus-PN group, compared with the PD-without-PN group. Exposure to other PD drugs, including catechol-*O*-methyltransferase (COMT) inhibitors, was similar between groups. Intra-muscular B12 for 1–2 years (at 1000 μg once per month) led to PN stabilization accompanied by normalization of B12 deficiency and statistically significant decreases of homocysteine and MMA elevation in all patient groups.

In another case–control study [18], PN was diagnosed in 32 (55%) of 58 randomly selected patients from a movement disorder clinic, compared with 5 (9%) of 58 age- and sex-matched controls. Of note, the mean age of patients with PD and PN exceeded that of patients with PD without PN by approximately 9 years, leading to possible bias by inclusion of relatively young patients and not severely ill patients with long durations of exposure.

Teodoro et al. [29] reviewed published clinical trials of PD drugs versus placebo in search of a possible signal linking PN with the use of levodopa or other PD pharmacotherapy. In 79 studies encompassing 10,620 recipients of active agents and 6710 recipients of placebo (with a total of 12,543 patients exposed to levodopa), no subjects experienced neuropathy as a reported adverse event. Frequencies of event types "suggestive of neuropathy" showed no significant differences between active treatment and placebo in any trial. Only 7 of the trials followed subjects for more than a year; thus, duration of exposure and route of administration were not adequately studied as potential factors in PN development, and none of the trials assessed LCIG.

Genetic studies suggest that the prevalence of asymptomatic PN in PD might be high in patients with *parkin* (PARK2) mutations [19,20,22]. In a study of 29 patients with juvenile PD [19], 9 (31%) patients had abnormal conduction findings in the sural nerve and 4 (14%) had abnormal findings in the peroneal nerve, independent of individual PD duration, severity, pharmacotherapy, and age at PD onset. In a subsequent study of 24 patients with identified *parkin* mutations [20], symptomatic PN accompanied by autonomic dysfunction was present in 1 (4%) patient.

In a study of 9 patients with PD with *parkin* mutation (PD onset at ages of 20–52 years) and 8 patients with idiopathic PD (onset at ages of 47–59 years) [22], a strong association was seen between asymptomatic axonal PN and presence of *parkin* mutation. In the *parkin*-mutation group, 2 (22%) patients had subjective sensory symptoms and 8 (89%) had objective evidence of sensory loss or abnormal nerve conductions. In the idiopathic PD group, 2 (25%) patients reported foot dysesthesia, but no patients had abnormal sural-nerve action potentials. The authors concluded that sensory axonal PN might be sufficiently common in PD patients with *parkin* mutation to serve as a distinguishing diagnostic indicator.

3.2. LCIG-associated PN

Reported cases of PN in recipients of LCIG therapy (Table 2) do not reflect a single type of polyneuropathy. Two general profiles of PN have been observed in LCIG patients: a less severe sensory axonal subtype that is slowly progressive, and a less common subtype that clinically resembles Guillain-Barré syndrome and causes severe deficits. Disease onset ranges from a few weeks [35] to up to 3 years after initiation of LCIG [31]. Nerve conduction studies show both axonal and demyelinating features [30,38]. In most cases, there are vitamin B12 deficiencies [12,15,33,35,36] and an increase in serum homocysteine levels. Vitamin B6 and folate (B9) deficiencies also have been reported [33,35,36]. Symptoms generally improve after discontinuation or dose modification of LCIG, B-vitamin supplementation, or both [12,15,16,33,35,36].

4. Hypothesized levodopa-related mechanisms

Chronic levodopa therapy is associated with homocysteine elevation, caused by levodopa serving as a co-enzyme in the breakdown of methionine [39]. Homocysteine levels in recipients of long-term levodopa therapy have been reported to be elevated by 30–80%, compared with levels in levodopa-naïve patients with PD or healthy controls [40–48]. Hyperhomocysteinemia is hypothesized to affect neurologic function via oxidative stress, mitochondrial dysfunction, inflammation, loss of DNA repair systems, and glutamatergic excitotoxicity [17,18,49,50]. A study of 31 patients with PD on long-term oral levodopa/DDI found a significant difference in sural action-potential amplitude between patients with homocysteine levels exceeding 15 μmol/L and patients with normal levels [30].

Co-administration of levodopa and DDI increases levodopa metabolism by a pathway (Fig. 1) whereby COMT mediates its conversion by methylation into 3-*O*-methyldopa [51]. COMT requires S-adenosylmethionine (SAM) as the methyl-group donor, which converts into S-adenosylhomocysteine, a short-lived intermediary that is cleaved almost immediately into homocysteine.

Homocysteine is metabolized by its reversible re-methylation to methionine or by an irreversible transsulfuration that converts it to cysteine, a sulfhydryl-containing amino acid with chemical properties similar to those of homocysteine (Fig. 1) [52,53]. Total plasma homocysteine accumulation can reflect an altered intra-cellular scenario that encourages reduced ability for methyl-group transfers [54].

Chronic *O*-methylation of levodopa may hypothetically weaken the capacity for other de-toxification processes that add methyl groups to endogenous and exogenous toxins [55]. As a result, vulnerability to toxins and pesticides increases.

In vitro, cysteine has cytotoxic effects against neurons and vascular endothelial cells, mediated partly by its formation of an adduct with nitric oxide [52]. In a study of 30 patients with PD, blood was sampled at 1 h after levodopa/DDI intake and showed increased levels of plasma cysteine in only the 18 patients with baseline plasma homocysteine levels exceeding 15 μmol/L [56]. This group's daily and morning levodopa/DDI intake also was significantly higher than that of the other patients with PD.

Table 2
Published and presented descriptions of PN in LCIG recipients.

Authors/year	Type of study	Number of PN cases	Case presentation	Interventions/outcomes
Antonini et al., 2007 [16]	12-month, open-label trial	1 patient on LCIG (among 9 such patients)	Acute, GBS-like PN at 7 months	LCIG was discontinued; plasmapheresis was performed; had "some benefit" (time frame not specified)
Manca et al., 2009 [15]	Individual case report	1 patient on LCIG	Severe axonal PN at 4 months; elevated homocysteine and MMA; low-normal B12	LCIG was discontinued; B12 supplementation led to improvement in limb strength at 2 weeks and ability to walk with a cane at 3 months
Carrillo F. unpublished data (described and cited in Santos-García et al. [30])[a]	Individual case report	1 patient on LCIG	Acute, severe axonal PN at 5 months; "borderline" B12; elevated urinary MMA	LCIG discontinued and replaced with oral levodopa; parenteral B12 supplementation
Gusmaroli et al., 2010 [31]	Individual case report	1 patient on LCIG	Axonal PN at 3 years; low 25-OH vitamin D	LCIG was continued; vitamin D supplementation and hypercaloric diet led to improvement (time frame not specified)
Palasí et al., 2010 [32]	Individual case report	1 patient on LCIG	Small-fiber autonomic-sensitive PN at 15 months; normal B12 and folate levels; elevated MMA	B12 and folate supplementation; PN improved
Urban et al., 2010 [33]	Individual case reports	2 patients on LCIG	Subacute axonal PN at 13 months; elevated homocysteine; low-normal B12; low B6; high-normal or elevated MMA	LCIG was continued; parenteral B12/B6 supplementation led to stabilization at 10 months
Valldeoriola et al., 2010 [34]	Individual case reports	2 patients on LCIG	Axonal PN at 2 and 8 months; low B12	B12 and folate supplementation; PN did not worsen
Klostermann et al., 2012 [35]	Case series	2 patients on LCIG (among 20 such patients)	Severe axonal PN at "a few weeks"; elevated homocysteine; low-normal B12; low B6 and folate	LCIG was continued; B12, B6 and folate supplementation led to motor (but not sensory) improvement over "several" months
Meppelink et al., 2011 [36]	6-month, open-label trial	2 patients on LCIG (among 15 such patients)	Axonal PN (with time to onset not described); borderline B12	LCIG dose reduction and B12 supplementation led to PN improvement (time frame not specified)
Santos-García et al., 2011 [37]	Individual case report	1 patient on LCIG	Axonal PN at 6 months; reduced serum B12 and folate levels	LCIG dose reduction; folate and B12 supplementation; later presented with slight paresthesia in both feet without pain but normal folate and B12 levels

25-OH = 25-hydroxy vitamin D; GBS = Guillain-Barré syndrome; LCIG = levodopa/carbidopa intestinal gel; MMA = methylmalonic acid; PN = peripheral neuropathy.
[a] This unpublished case was presented by Fátima Carrillo as a brief talk in the *LVII Reunión Anual de la Sociedad Española de Neurología* in Barcelona, Spain.

To date, there is no evidence that normalization of hyperhomocysteinemia is clinically beneficial [40]. Nevertheless, to prevent or reverse hyperhomocysteinemia in patients with PD, physicians should consider vitamin B supplementation and adjustment of a patient's levodopa adjuncts.

In theory, the demands of levodopa metabolism on the body's stores of B vitamins might lead to B vitamin depletion [35]. Malnutrition and/or weight loss might be an exacerbating factor [57], and in recipients of LCIG, intestinal vitamin malabsorption might be another factor [58].

B12 and folate support the metabolism (re-methylation) of homocysteine to methionine, and B6 supports the conversion of homocysteine to cysteine. Thus, supplementation of B12, folate, and/or B6 will reduce homocysteine levels [53].

5. Discussion

Evidence from case–control studies suggests that PN in PD is associated with a cumulative dose of levodopa during treatment, as well as vitamin B12, B6, and/or folate deficiencies, and with dysfunction of homocysteine metabolism [17,25,28]. These findings, however, have yet to be corroborated in clinical trials. A genetic cause may also play a role, supported by studies indicating that idiopathic axonal PN in PD might be associated with *parkin* gene mutation [19,22]. Although the literature on PN in patients receiving LCIG is currently limited, an association with vitamin B deficiency also has been reported [15,31–33,35–37]. In both oral levodopa and LCIG settings, the PN has been variable; onsets have ranged from acute—like Guillain-Barré syndrome—to chronic, as is more typical of vitamin deficiencies. The PN has usually been sensory and motor, but physiology has suggested both an axonal and a demyelinating component. Vitamin B12, B6, and/or folate deficiency is the most common feature, and clinical improvement frequently follows multi-vitamin replacement.

The available data have raised questions concerning whether and to what extent PN is an inherent feature of PD, whether PN is an iatrogenic outcome of intensive levodopa exposure and/or an effect specific to levodopa as a gel delivered directly to the small intestine (LCIG), how PN might best be prevented and managed when it occurs, and whether LCIG plays a role in vitamin B malabsorption, leading to development of PN.

In clinical practice, when a patient is being evaluated for LCIG therapy and in order to help gauge pre-disposing risk factors for PN, we recommend that special attention be devoted to body mass index, nutritional status, vitamin supplement usage, medication usage (for cytochrome P450 interaction), and conditions that could lead to gastrointestinal malabsorption. A detailed neurologic examination as well as nerve conduction studies and a needle EMG should be conducted to detect a possible pre-existing neuropathy.

Baseline laboratory assessments might include plasma values for vitamins B6 and B12, folic acid, homocysteine, and MMA with evaluation of current use of vitamin B supplements, levodopa dosage, and levodopa equivalent dosages.

In the presence of laboratory abnormalities, decisions about whether and when to start LCIG should be made clinically. However, patients with acute PN symptoms or severe chronic PN, as determined by the above workup, should not start treatment with LCIG. Patient-specific factors could include availability and efficacy of alternative treatment options, co-morbidities, and patient preferences. Methylenetetrahydrofolate reductase (MTHFR) genotyping may be considered; however, its utility in clinical practice is still subject to debate.

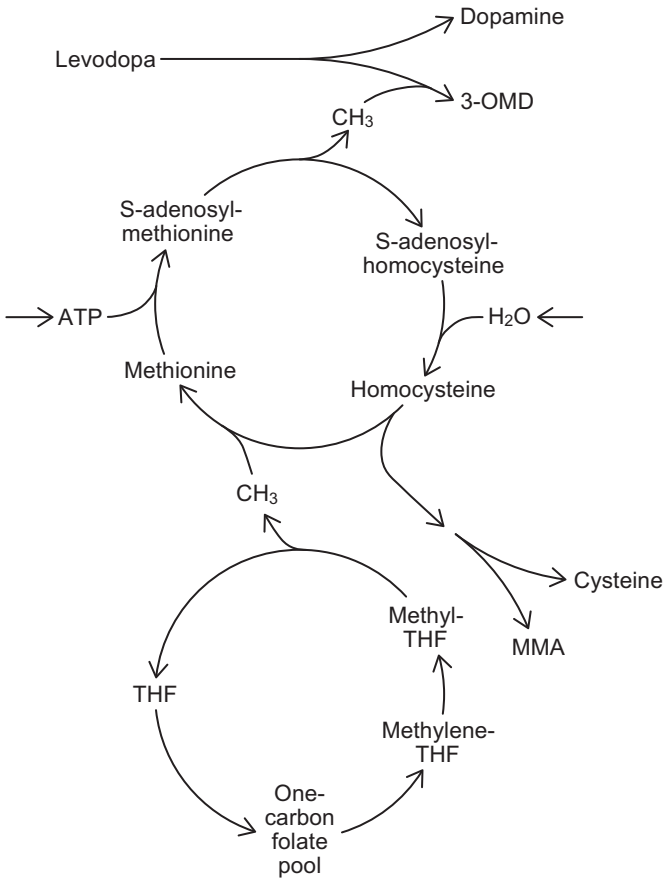

Fig. 1. Facets of levodopa and homocysteine metabolism hypothesized to be relevant to peripheral neuropathy in patients with Parkinson's disease. Conversion of levodopa into 3-*O*-methyldopa (3-OMD) depletes methyl-group (CH_3) reserves and leads to homocysteine production. Subsequent homocysteine re-methylation (into methionine) requires vitamin B12 (cobalamin) as a co-factor and obtains its CH_3 from the one-carbon folate pool. Involvement of methylenetetrahydrofolate (methylene-THF) in supplying the CH_3 makes polymorphism in methylene-THF reductase an important determinant of plasma homocysteine level. Homocysteine trans-sulfuration (into cysteine) requires vitamin B6 (pyridoxine). A pathway leading to methylmalonic acid (MMA) makes MMA as well as homocysteine a marker of functional vitamin B12 deficiency. ATP = adenosine triphosphate.

In LCIG recipients (as well as in patients receiving oral levodopa), the potential benefit of vitamin supplementation should be evaluated. Vitamin status can change rapidly after levodopa therapy starts and PN has been seen within weeks to months of levodopa initiation. The evaluation of vitamins B6 and B12, folate, and homocysteine monthly for the first 6 months, and then every 6 months thereafter, should be considered [28], with patients receiving vitamin supplementation as needed, based on determined deficiencies.

For patients with vitamin deficiency associated with homocysteine elevation, oral folate and vitamin B6 supplements can be given daily and parenteral vitamin B12 supplementation can be administered monthly. No standardized recommendations are available for B12 supplementation and regimens vary, although daily or weekly administration is sometimes suggested for up to 8 weeks before establishing the monthly regimen [59–61]. High-dose oral vitamin B12 (2000 μg/day tapered to 1000 μg/day and then 1000 μg/day weekly segueing to monthly) also has been recommended [61,62].

Because levodopa metabolism is influenced by the enzymatic activities of DDI and COMT inhibitors, administration of levodopa plus an inhibitor of either enzyme might reduce hyperhomocysteinemia [47,63], although findings regarding the effect of levodopa plus entacapone on homocysteine levels have been inconsistent [18]. COMT inhibitors also may provide an opportunity to reduce the LCIG dose [64] and, thus, reduce a presumably dose-dependent potential of levodopa to induce PN.

Visiting a neurologic center every 3–4 months (rather than only if complications occur) should be routine practice, as it is already for patients with advanced PD.

In patients with chronic PN, the decision to continue or stop LCIG should depend on the clinical picture of the individual patient. If deficient or marginal laboratory values are determined, vitamin supplementation is recommended.

In patients with acute PN, LCIG should be stopped and oral levodopa should be re-instituted, if possible at a lower levodopa equivalent dose/day. Specific conditions, such as vitamin deficiency and hyperhomocysteinemia, should be treated, and further diagnostic evaluation and treatment should follow local standards for the treatment of PN.

The development of a structured assessment that includes a standardized questionnaire and standardized batteries of clinical neurophysiologic and laboratory tests would facilitate the collection and analysis of data in both clinical practice and research. Ongoing LCIG studies could incorporate such an assessment and possible PN symptoms and precursors could be reported as adverse events of special interest.

In addition to epidemiologic analyzes of existing databases, prospective studies should assess the incidence of PN and seek its causes in populations of patients with PD, related to vitamin levels, homocysteine metabolism, genetics, and influence of cumulative levodopa dosages.

Documentation of author roles

Manuscript conception: Drs Müller, van Laar, Cornblath, Odin, Klostermann, Grandas, Ebersbach, Urban, Valldeoriola and Antonini.

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Potential conflicts of interest

Dr Müller has served on the advisory boards of Orion Corporation; GlaxoSmithKline; Merck Serono; Lundbeck; Teva Pharmaceutical Industries Ltd; Meda Pharmaceuticals Inc; Abbott Laboratories (now AbbVie, Inc); and Merz Pharmaceuticals, LLC. Dr Müller has received industry honoraria from Orion Corporation; GlaxoSmithKline; Merck Serono; Lundbeck; Teva Pharmaceutical Industries Ltd; Meda Pharmaceuticals Inc; Boehringer Ingelheim; and Abbott Laboratories (now AbbVie, Inc).

Dr van Laar has served on the advisory board of Abbott Laboratories (now AbbVie, Inc) and has received industry honoraria from Abbott Laboratories (now AbbVie, Inc).

Dr Cornblath has served as a consultant for Abbott Laboratories (now AbbVie, Inc); Acorda Therapeutics, Inc; Ardea Biosciences, Inc; Astellas Pharma US, Inc; Avigen, Inc; AxelaCare Health Solutions, LLC; Baxter International, Inc; Biogen Idec; Bionevia Pharmaceuticals Inc; Bristol-Myers Squibb Company; CaridianBCT, Inc; Cebix Incorporated; CSL Behring GmbH; DP Clinical, Inc; Eisai Co, Ltd; Exelixis, Inc; FoldRx Pharmaceuticals, Inc; Genzyme Corporation; Geron Corporation; Gerson Lehrman Group, Inc; GlaxoSmithKline plc; Impeto Medical SAS; Johnson & Johnson; Merck &

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Dr Odin has served as a consultant for Abbott Laboratories (now AbbVie, Inc) and has served on the advisory boards of Abbott Laboratories (now AbbVie, Inc); Boehringer Ingelheim; Cephalon, Inc; GlaxoSmithKline; Nordic Infucare; Orion Corporation; and UCB Pharma, Inc. Dr Odin has received honoraria for lectures from Abbott Laboratories (now AbbVie, Inc); Cephalon, Inc; Ever Pharmaceuticals; Nordic Infucare; Orion Corporation; and UCB Pharma, Inc.

Dr Klostermann has been an investigator in Abbott-sponsored (now AbbVie, Inc) studies. He received honoraria for advisory activities from Archimedes, UCB, and Abbott (now AbbVie, Inc), and holds grants from the German Research Foundation (Kl 1276/4 and Kl 1276/5).

Dr Grandas has served on the advisory boards of Abbott Laboratories (now AbbVie, Inc) and Allergan, Inc, and has received honoraria for lectures from GlaxoSmithKline.

Dr Ebersbach has served as a consultant for Boehringer Ingelheim and Orion Corporation. Dr Ebersbach has received honoraria for presentations from Abbott Laboratories (now AbbVie, Inc); Boehringer Ingelheim; Desitin Pharma AB; GlaxoSmithKline; Lundbeck; Novartis; Orion Corporation; Teva Pharmaceutical Industries Ltd; Valeant Pharmaceuticals International, Inc; and Schwarz Pharma, Inc (UCB). Dr Ebersbach has also received grants for research from Deutsche Parkinson Gesellschaft (DPV) and Deutsche Forschungs-Gesellschaft (DFG).

Dr Urban has served on the advisory boards of Orion Corporation and Abbott Laboratories (now AbbVie, Inc) and has received honoraria from Orion Corporation; Lundbeck; Meda Pharmaceuticals Inc; Abbott Laboratories (now AbbVie, Inc); UCB Pharma, Inc; and Boehringer Ingelheim.

Dr Valldeoriola has served on the advisory boards of UCB Pharma, Inc and Abbott Laboratories (now AbbVie, Inc). Dr Valldeoriola has received honoraria for lectures and courses from Abbott Laboratories (now AbbVie, Inc); Boehringer Ingelheim; UCB Pharma, Inc; GlaxoSmithKline; Medtronic Europe; and Lundbeck.

Dr Antonini has served on the advisory boards of Abbott Laboratories (now AbbVie, Inc); Boehringer Ingelheim; Novartis; Lundbeck; UCB Pharma, Inc; Merck Serono; Chiesi; GlaxoSmithKline; GE Healthcare; and Valeant Pharmaceuticals International, Inc. Dr Antonini has received honoraria from Abbott Laboratories (now AbbVie, Inc); Boehringer Ingelheim; Novartis; Lundbeck; UCB Pharma, Inc; Merck Serono; Chiesi; GlaxoSmithKline; GE Healthcare; and Valeant Pharmaceuticals International, Inc.

Disclosures

Dr Müller participated on an advisory board of Abbott Laboratories (now AbbVie, Inc), which was performed to write this manuscript. Dr van Laar has received consulting and speaker fees from Abbott Laboratories (now AbbVie, Inc). Dr Cornblath has received consulting fees from Abbott Laboratories (now AbbVie, Inc). Dr Odin has received honoraria for lectures, consultancy for clinical study programs, and participation on advisory boards from Abbott Laboratories (now AbbVie, Inc) and has participated as principal investigator in clinical studies with levodopa/carbidopa intestinal gel. Dr Klostermann reports no financial disclosure/no conflict of interest. Dr Grandas and Dr Antonini have received honoraria from Abbott Laboratories (now AbbVie, Inc) for participating on advisory boards. Dr Ebersbach has received honoraria for presentations from Abbott Laboratories (now AbbVie, Inc). Dr Urban participated on an advisory board of Abbott Laboratories (now AbbVie, Inc) and has received honoraria from Abbott Laboratories (now AbbVie, Inc). Dr Valldeoriola has received honoraria for lectures and courses from and for participating on an advisory board for Abbott Laboratories (now AbbVie, Inc).

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