RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2024, DOI: 10.5603/pjnns.100132

ISSN: 0028-3843, e-ISSN: 1897-4260

# Acute polyneuropathy: a serious complication of levodopa/carbidopa intestinal gel treatment for Parkinson's Disease

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## ABSTRACT

**Aim of study.** To determine whether a high dose of levodopa-carbidopa intestinal gel (LCIG), expressed as levodopa equivalent daily dose (LE daily dose), is a risk factor for acute polyneuropathy in patients treated with LCIG.

**Clinical rationale for study.** Treatment with LCIG is an effective device-assisted therapy in the advanced stages of Parkinson's Disease (PD). Polyneuropathy is a well-known complication of PD treatment. Patients treated with oral levodopa usually suffer from sub-clinical or mild chronic sensory polyneuropathy. However, severe acute polyneuropathy occurs in patients treated with LCIG, which is causally related to the treatment and leads to its immediate discontinuation. The etiology is not yet clear, but some patients with acute polyneuropathy have been given high doses of LCIG.

**Material and methods.** A retrospective multicentre study of patients treated with LCIG was performed. Patients with acute polyneuropathy were subjected to a detailed analysis including statistical processing.

**Results.** Of 183 patients treated with LCIG in seven centres, six patients (five females, median age 63 years) developed acute polyneuropathy with LCIG discontinuation. The median (interquartile range) initial and final LE daily dose in patients with and without acute polyneuropathy was 3,015 (2,695–3,184) and 1,898 (1,484–2,167) mg, respectively. The final LE daily dose of 2,605 mg cut-off had 83% sensitivity and 93% specificity for the prediction of acute polyneuropathy.

**Conclusions and clinical implications.** The risk of acute polyneuropathy in LCIG-treated patients was associated with a daily LE dose of greater than 2,605 mg or with more than a 62% increase in the daily LE dose during LCIG treatment.

**Keywords:** acute polyneuropathy, Parkinson's Disease, levodopa/carbidopa intestinal gel, levodopa equivalent daily dose

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Received: 05.04.2024 Accepted: 19.08.2024 Early publication date: 20.11.2024

## Introduction

Treatment with levodopa/carbidopa intestinal gel (LCIG) is an effective device-assisted therapy in the advanced stages of Parkinson's Disease (PD).

Polyneuropathy is a well-known complication of PD treatment. Patients treated with oral levodopa usually suffer from sub-clinical or mild chronic sensory polyneuropathy associated with elevated homocysteine levels and cobalamin or folate deficiency [1]. The prevalence of polyneuropathy is higher in patients with LCIG (up to 75%), and polyneuropathy is divided into chronic, subacute, and acute cases. Acute polyneuropathy in LCIG can occur especially during the first two years of LCIG treatment, and its prevalence is up to 11% [2, 3]. Some patients have experienced a rapid progression of severe acute polyneuropathy, leading to discontinuation of the LCIG treatment [3–5]. The etiology is not completely understood, but it seems certain that this is an acute and serious complication of LCIG treatment and that the condition improves or stabilizes after treatment is stopped. Some research has suggested that this could result from the high doses of LCIG [3, 6]. Other causes of acute polyneuropathy have been repeatedly ruled out.

## Clinical rationale for study

Acute polyneuropathy is a serious and disabling complication of LCIG treatment. In this retrospective study, we focused on the association between the development of acute polyneuropathy and the dose of LCIG (expressed by levodopa equivalent (LE) daily dose [7]). If a statistically significant correlation were to be demonstrated, the results would be important for setting rules when starting LCIG treatment to minimize the risk of developing acute polyneuropathy.

## Material and methods

Specialists from seven movement disorders centres in the Czech Republic and Slovakia were invited to complete a multicentre retrospective survey of all patients treated with LCIG therapy. All patients met the clinical criteria for advanced Parkinson's Disease [8]. The survey included basic demographic information including sex, age, clinical data, the incidence of polyneuropathy, the LE daily dose immediately before starting LCIG therapy (the initial LE daily dose), and the dose after three months on LCIG or before LCIG discontinuation due to acute polyneuropathy (the final LE daily dose).

In all patients with polyneuropathy, we were interested in its clinical manifestation and management: symptomatic therapy, LCIG dose reduction, or discontinuation. The diagnosis of polyneuropathy was based on a clinical examination and electrophysiological studies. Special attention was paid to cases of acute severe polyneuropathy which led to the discontinuation of LCIG. Acute polyneuropathy was defined as the development of polyneuropathic symptoms from within a few days to maximally a few weeks, leading to a rapid deterioration of the condition. Polyneuropathic symptoms were defined as dysesthesia/paraesthesia, hypesthesia, pain, or weakness in the extremities beginning in a typical distribution distally in the lower extremities and spreading proximally to the upper extremities. A clinical diagnosis was made according to the clinical criteria of polyneuropathy [9]. In these patients, more detailed information was further requested: clinical symptoms, concomitant diseases, and medication, electrophysiological studies, information about cobalamin or folate substitution, plasma levels of cobalamin and folate, lumbar puncture results, the interval between LCIG titration and polyneuropathy onset, the clinical outcome after LCIG withdrawal, and the actual LE daily dose at the time of polyneuropathy diagnosis.

When appropriate, continuous data was expressed as median and interquartile range (IQR). Differences in the primary outcomes between sexes were compared using the Fisher exact test. For univariate and multivariate prediction models, logistic regression was used, and the odds ratio was computed. The differences between the centres were subject to the Kruskal-Wallis test. P-values of less than 0.05 were considered statistically significant. Analyses were conducted using the R statistical package version 4.0.3.

## Results

A total of 183 patients in the advanced stage of PD (80 females and 103 males, median age 69 (IQR 63–74)) years treated with LCIG were reported. Clinically relevant polyneuropathy occurred in 27 (15%) patients (10 *de novo* and 17 pre-existing cases), the majority of whom had mild chronic axonal polyneuropathy.

However, six of the 183 patients (3.3%), 5/6 women, median age 63 (IQR 57–68) years, developed acute severe polyneuropathy, which led to an immediate discontinuation of LCIG treatment. All patients with acute polyneuropathy met the clinical criteria for advanced stage Parkinson's Disease, and no red flags indicating another cause of Parkinson's syndrome were observed. Two patients developed acute polyneuropathy as a *de novo* polyneuropathy, and one patient had mild axonal polyneuropathy before LCIG initiation. In the remaining three patients, no electrophysiological studies were performed before LCIG treatment, but the patients did not have any pre-existing subjective or clinical signs of polyneuropathy. Polyneuropathic symptoms arose and worsened within a matter of days. Patients 1 and 2 suffered from paresthesia and dysesthesia, and patient 6 from dysesthesia only. Other patients developed flaccid paraparesis that progressed to tetraparesis. Patients 1, 2, 3, and 5 experienced a loss of dyskinesias and a gradual deterioration of Parkinsonian symptoms despite LCIG dose escalation. All patients with acute polyneuropathy were on LCIG monotherapy.

**Table 1.** Characteristics of six patients with acute polyneuropathy and LCIG discontinuation

| Patient No. | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Sex | F | F | F | F | F | M |
| Age [years] | 66 | 56 | 68 | 60 | 69 | 54 |
| PD duration [years] | 16 | 13 | 6 | 16 | 5 | 14 |
| Initial LE daily dose [mg] | 2,238.75 | 1,950 | 1,845 | 2,671 | 1,363.25 | 923 |
| Final LE daily dose [mg] | 3,139 | 2,890 | 3,199 | 4,033 | 2,630 | 1,825 |
| LCIG duration [days] | 132 | 121 | 346 | 27 | 227 | 223 |
| Cobalamin plasma level [normal 191–663 ng/L] | 221 | 191 | 921 | 209 | 177 | 325.3 |
| Folate plasma level [normal 3.1–17.5 ug/L] | 5 | 2.2 | 3.1 | 6.4 | 1.7 | 3.74 |
| The main clinical symptoms of polyneuropathy | Paresthesia, dysesthesia | Paresthesia, pain, dysesthesia | Paraparesis, fatigue | Paresthesia | Paraparesis | Dysesthesia |
| Initial electrophysiological studies | Normal | NK | NK | Axon Sens | Normal | NK |
| Final electrophysiological studies | Axon Dem Sens Mot | Axon Sens | Axon Dem Sens Mot | Axon Dem Sens Mot | Axon Sens Mot | Axon Sens |
| Outcome | Improved | Improved | Improved | Stabilized | Stabilized | NK |
| Initial BMI | 16.7 | NK | 25.5 | 25 | 26.2 | NK |
| Final BMI | 17.7 | NK | 23.6 | 25 | NK | NK |

Age (years): age at the time of polyneuropathy onset; PD duration (years): duration of Parkinson's Disease; Initial LE daily dose (mg): LE daily dose before initiation of LCIG treatment; final LE daily dose (mg): LE daily dose at discontinuation of LCIG treatment due to acute polyneuropathy; LCIG duration (days): duration of LCIG treatment; Cobalamin plasma level after acute polyneuropathy onset; Folate plasma level after acute polyneuropathy onset; Initial electrophysiological studies: electromyography before LCIG treatment; Final electrophysiological studies: electromyography after acute polyneuropathy onset; Polyneuropathy specification (Axon = axonal, Dem = demyelinated, Mot = motor, Sens = sensory); Outcome after LCIG discontinuation (improved/stabilized/worsened); initial BMI (BMI before LCIG treatment); final BMI (BMI after polyneuropathy onset). M — male; F — female; NK — not known; BMI — body mass index

No significant weight changes were observed in patients with acute polyneuropathy during LCIG treatment. None of these patients took a cobalamin and folate substitution before the onset of symptoms. Cobalamin levels were low in patients 2 and 5 and high in patient 3. Folate depletion was shown in patients 2, 3, and 5. The other patients had these parameters within the normal range. However, after the development of polyneuropathy, a B-vitamin substitution was initiated. Acute polyneuropathy began 1-11 months after LCIG initiation. LCIG discontinuation and B-vitamin substitution led to stabilization or improvement of the polyneuropathy symptoms in five patients, while the outcome of patient 6 remains unknown. For more details, see Table 1.

Other causes of polyneuropathy were also considered. A basic screening was performed, where normocytic anemia was detected in patients 2 and 4. Patients 2, 3, and 4 also underwent a lumbar puncture, where the number of elements and protein levels were normal, and the serological examination did not show any pathological findings. Patients 1, 2, and 6 had no comorbidities and received dopaminergic treatment only. Patient 3 suffered from hypothyroidism for a long time but reacted well to substitution therapy. Patients 4 and 5 suffered from depressive syndrome and were chronically treated with selective serotonin reuptake inhibitors (SSRI).

The median initial LE daily dose in patients without acute polyneuropathy was 1,350 (IQR 1,118–1,713) mg, which did not differ across the centres ($p = 0.97$). The median final LE daily dose in patients without acute polyneuropathy was 1,543 (IQR 1,200–2,045) mg (Tab. 2). Nevertheless, the final LE daily dose significantly differed among the centres ($p < 0.01$). The LE daily doses were mostly increasing [median 14% (IQR -8–47%)], (Fig. 1).

The median LE daily dose of patients with acute polyneuropathy increased from an initial 1,898 (IQR 1,484–2,167) mg to a final 3,015 (IQR 2,695–3,184) mg, $p < 0.01$. Compared to patients without severe polyneuropathy, a higher dose change percentage was reported in acute polyneuropathy patients (median of 62% increase, IQR 49–88%, $p = 0.05$). In contrast to the LE daily doses, univariate analysis did not show that female sex *per se* was a predictor of acute polyneuropathy ($p = 0.09$).

A multivariate logistic regression model (Model 1 considering sex and the final LE daily dose) confirmed that acute polyneuropathy was predicted by female sex (OR = 17.4006, 95% CI: 1.3601–222.6088, $p = 0.0281$) together with final LE daily dose (OR = 1.0028, 95% CI: 1.0012–1.0044, $p = 0.0006$). A different model (Model 2 considering sex, initial LE daily dose, and dose change) showed that female sex (OR = 21.3809, 95%

**Table 2.** Epidemiological data of patients treated with LCIG with and without development of acute polyneuropathy

| | Patients with acute polyneuropathy (n = 6) | Patients without acute polyneuropathy (n = 177) | P-value |
|---|---|---|---|
| Male/female | 1/5 | 102/75 | 0.09 |
| Median age [years] (Interquartile range IQR) | 63 (57–67.5) | 69 (63–74) | 0.07 |
| Median initial LE daily dose [mg] (IQR) | 1,898 (1,484–2,167) | 1,350 (1,118–1,713) | 0.08 |
| Median final LE daily dose [mg] (IQR) | 3,015 (2,695–3,184) | 1,543 (1,200–2,045) | < 0.01 |
| Median LE daily dose change [%] (IQR) | 62 (49–88) | 14 (–8–47) | 0.05 |

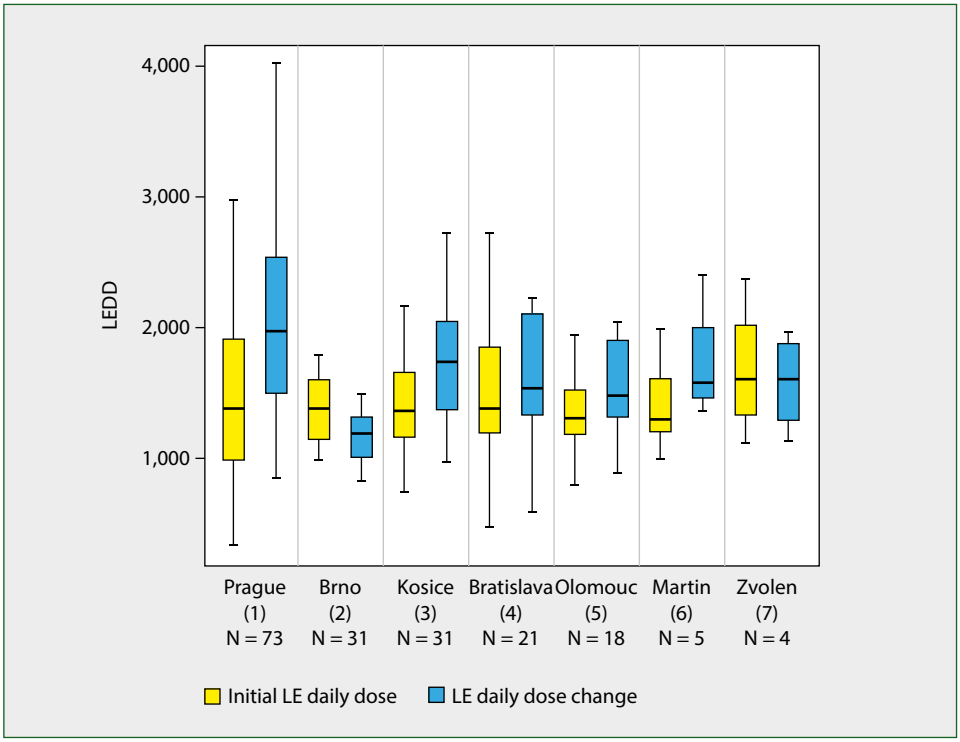


**Figure 1.** Comparison of initial LE daily dose and final LE daily dose among seven centres in the Czech Republic and Slovakia

CI: 1.2638–361.7058, p = 0.0338) together with initial LE daily dose (OR = 1.0032, 95% CI: 1.0012–1.0052, p = 0.0020) and dose change (OR = 1.0245, 95% CI: 1.0072–1.0420, p = 0.0052) also predicted acute polyneuropathy.

ROC (receiver operating characteristic) analysis (Fig. 2) showed high sensitivity and specificity for the LE daily dose as a predictor of acute polyneuropathy. The final LE daily dose was more strongly associated (area under ROC curve (AUC) 92%, threshold 2,605 mg, sensitivity 83% and specificity 93%) with the risk of acute polyneuropathy than the initial LE daily dose (AUC 70%, threshold 1,823 mg, sensitivity 67% and specificity 80%) or dose change (AUC 83%, threshold 40%, sensitivity 100% and specificity 71%).

## Discussion

Our study aimed to report a retrospective evaluation of the development of polyneuropathy in patients treated with LCIG.

The total prevalence of polyneuropathy, regardless of origin and progression rate, was 15% for all LCIG patients from the seven Czech and Slovak centres, which roughly corresponds to the incidence of polyneuropathy estimated in previous studies [2, 5, 10]. The cause, duration, and association with LCIG treatment in all forms of polyneuropathy were difficult to determine. Subjective symptoms can be minimal in many patients, and electromyography is not yet a routine examination in all patients treated with LCIG.

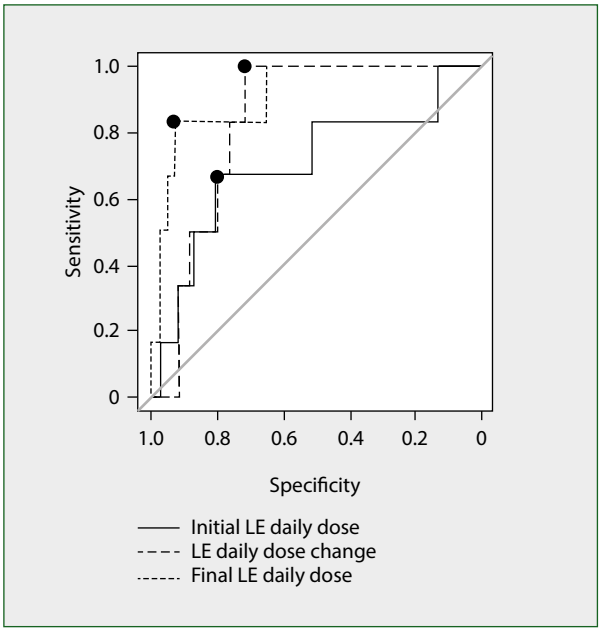


**Figure 2.** ROC analysis: sensitivity and specificity of factors associated with acute polyneuropathy. Depicted points indicate the level of sensitivity and specificity of each factor: initial LE daily dose (sensitivity 67% and specificity 80%); dose change (sensitivity 100% and specificity 71%); and final LE daily dose (sensitivity 83% and specificity 93%)

We focused on patients with acute polyneuropathy because this form is severe, often disabling, and repeatedly linked directly to the initiation of LCIG. It led to the immediate discontinuation of LCIG. The prevalence of acute polyneuropathy with the need for LCIG discontinuation in our group was relatively low (3.3%) and mostly linked to the female sex.

A causal relationship between the development of acute polyneuropathy and LCIG therapy appears to be unquestionable [3, 11–13] despite isolated objections [14]. The stabilization or even improvement of acute polyneuropathy after LCIG discontinuation, which we observed in our group of patients, also confirms a causal connection [4, 5, 12, 15]. A high LE daily dose as a risk factor for the development of acute polyneuropathy has been previously suspected; however, no detailed statistical analyses of patient cohorts were available [3–5, 12]. Therefore, we performed a comparison between patients with and without acute polyneuropathy.

The initial LE daily dose was not statistically different between patients with and without acute polyneuropathy. However, the final LE daily dose was significantly higher in the group of patients with acute polyneuropathy than in patients without. Also, the LE daily dose change was significantly higher in patients with acute polyneuropathy.

In addition, we demonstrated that a final LE daily dose over the threshold of 2,605 mg was a high-risk factor for acute polyneuropathy development in patients treated with LCIG. Since all patients with acute polyneuropathy were on LCIG monotherapy, the LE daily dose is equivalent to the LCIG dose. This result prompts a reconsideration of the appropriateness of such high doses.

We found only one safety study [10] in LCIG patients using doses higher than 2,000 mg, which reported more patients with acute polyneuropathy compared to patients with lower doses. However, no statistical analysis was performed. Thus, a dose of LCIG corresponding to the equivalent of 2,605 mg was considered the upper safe limit of LCIG treatment for the development of acute polyneuropathy in our study.

Two main mechanisms are probably involved in the development of acute polyneuropathy in LCIG patients: (i) intrinsic predisposition and (ii) the 'adverse' effects of high doses of LCIG on the jejunal membrane or directly on the peripheral nerves in predisposed patients. Predisposition could be a genetic factor, such as a low-activity catechol–O–methyltransferase (COMT) genotype, which is associated with a greater risk of polyneuropathy in PD patients [16]. Acquired predispositions include dysimmune or post-infective factors affecting the peripheral nerves. The 'adverse' effect could be direct damage caused by levodopa/carbidopa and/or gel to the peripheral nerves or the jejunal wall.

Adverse effects of levodopa/carbidopa *per se* are less likely because patients treated with oral levodopa/carbidopa may also suffer from polyneuropathy, but most commonly suffer from chronic axonal polyneuropathy at a mild to moderate intensity which is associated with higher levels of homocysteine and methylmalonate [1]. Acute polyneuropathy associated with oral levodopa/carbidopa has not been described in the literature but can develop accidentally due to another cause.

The gel in LCIG is composed of methylcellulose and water. For various reasons, methylcellulose is commonly used as a cheap and safe food additive. However, in studies using animal models, an association of methylcellulose administration with a change in microbiota and a higher incidence of inflammatory bowel disease has been described [17]. Prospective studies with a jejunal membrane biopsy in patients with acute polyneuropathy are needed. In contrast, no study has yet demonstrated methylcellulose's direct toxic effect on the peripheral nerves.

Considering malabsorption, we looked for cachexia development in patients with acute polyneuropathy. According to the BMI, only patient 1 showed evidence of cachexia, and, in contrast, there was a slight weight gain after the initiation of LCIG. Other available data (see Table 1) showed normal BMI values in half of the patients. Cachexia was not detected even in the patient who developed acute polyneuropathy after 11 months of treatment. Thus, we did not demonstrate a clear association between low weight and the development of acute polyneuropathy.

The insufficient effectiveness of LCIG treatment with the necessity to further increase doses and the loss of dyskinesias (even with higher dosing) could support the theory of damage to the jejunal wall when levodopa is not properly absorbed. Low levels of cobalamin and/or folate in some patients can also indicate some malabsorption. Unfortunately, no previous

studies have discussed the need for dose escalation and the presence or absence of dyskinesia in patients with subsequent acute polyneuropathies.

Five of our six patients with acute polyneuropathy were menopausal women. However, female sex alone is not a predictor of acute polyneuropathy, as it requires additional factors the final LE daily dose or the initial LE daily dose together with dose change. Several reports mention the preponderance of female sex in LCIG patients with acute polyneuropathy [4, 12], although statistical analyses are lacking. The reason for this is unknown, but dysimmune or endocrine mechanisms should be considered.

We are aware that the retrospective nature of this study and the small number of patients with acute polyneuropathy represent limitations. Fortunately for patients, acute polyneuropathy is a rare complication of LCIG treatment and therefore the number of patients with this diagnosis is not high.

Nevertheless, we still consider it important to publish these results even given these limitations, because they can help improve understanding of the risk factors, and by extension the causes, of acute polyneuropathy.

## Clinical implications/future directions

Our retrospective study found that patients with acute polyneuropathy received significantly higher LCIG doses than those without. We identified a threshold of 2,605 mg or a substantial dose increase (median 62%) as strong predictors for developing this condition. Additionally, we observed that the absence of dyskinesias and worsening akinesia, despite increasing LCIG doses, were warning signs for potential acute polyneuropathy. Considering these factors at the start of LCIG treatment can help minimize the risk of this complication.

## Article information

**Acknowledgements:** *The authors would like to thank Prof. Stepan Havranek MD, PhD, for providing feedback throughout this project.*

**Funding sources and conflicts of interest:** *This work was supported by The National Institute for Neurological Research (Programme EXCELES, ID Project No. LX22NPO5107) - Funded by the European Union – Next Generation EU; Charles University: Cooperation Programme in Neuroscience; General University Hospital in Prague project MH CZ-DRO-VFN64165 for PH, JR, JK, and RJ and by the Slovak Grant and Development Agency under contract APVV-22-0279, and by the EU Renewal and Resilience Plan entitled Large projects for excellent researchers under grant No. 09I03-03-V03-00007 for VH and MS.*

The authors declare no conflict of interest relevant to this work.

**Financial disclosures for previous 12 months:** *PH: received honoraria from Abbvie, Medis Pharma, Stada; JR: received honoraria from Abbvie; VČ: none; JK: none; MB: received honoraria from Abbvie, Ipsen, Medtronic, Medis Pharma; IR: none; VH: none; MS: received honoraria from Abbvie, Medtronic, Krka, Desitin, Takeda, International Parkinson and Movement Disorder Society, Stada, and received consultancies from Abbvie, Biogen, Stada, Medtronic; KG: none; MM: none; PV: none; MK: none; PK: received consultancies from Merz, Everpharma, Novartis; MG: none; EK: none; JN: none; RJ: none.*

## References

1. Toth C, Breithaupt K, Ge S, et al. Levodopa, methylmalonic acid, and neuropathy in idiopathic Parkinson disease. Annals of neurology. 2010; 68(1): 28–36, doi: 10.1002/ana.22021.
2. Artusi CA, Balestrino R, Imbalzano G, et al. Beyond 10 years of levodopa intestinal infusion experience: Analysis of mortality and its predictors, Parkinsonism Relat Disord. 2020(76): 98–103, doi: 10.1016/j.parkreldis.2019.10.004, indexed in Pubmed: 31610986.
3. Loens S, Chorbadzhieva E, Kleimann A, et al. Effects of levodopa/carbidopa intestinal gel versus oral levodopa/carbidopa on B vitamin levels and neuropathy. Brain Behav . 2017; 7(5): e00698, doi: 10.1002/brb3.698, indexed in Pubmed: 28523235.
4. Galazky I, Schoof J, Stallforth S. Guillain-Barre/CIDP-like neuropathy in two parkinsonian patients following intestinal levodopa/carbidopa treatment. Parkinsonism Relat Disord. 2014; 20(1): 125–7.
5. Merola A, Zibetti, M, Romagnolo MA, et al. Peripheral neuropathy associated with levodopa-carbidopa intestinal infusion: a long-term prospective assessment. Eur J Neurol. 2016; 23(3): 501–9, doi: 10.1111/ene.12846, indexed in Pubmed: 26498913.
6. Klostermann F, Jugel C, Muller T. Malnutritional neuropathy under intestinal levodopa infusion. J Neural Transm (Vienna). 2012; 119(3): 369–72, doi: 10.1007/s00702-011-0689-3, indexed in Pubmed: 21786115.
7. Tomlinson C, Stowe R, Patel S, et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Movement Disorders. 2010; 25(15): 2649–2653, doi: 10.1002/mds.23429.
8. Stoker TB, Greenland JC. Parkinson's Disease: Pathogenesis and Clinical Aspects [Internet]. Brisbane. 1018(AU): 2018, doi: 10.15586/codonpublications.parkinsonsdisease.2018, indexed in Pubmed: 30702835.
9. Mirian A, Aljohani Z, Grushka D, et al. Diagnosis and management of patients with polyneuropathy. Canadian Medical Association Journal. 2023; 195(6): E227–E233, doi: 10.1503/cmaj.220936.
10. Zadikoff C, Poewe W, Boyd JT, et al. Safety of levodopa-carbidopa intestinal gel treatment in patients with advanced Parkinson's Disease receiving ≥2000 mg Daily Dose of Levodopa. Parkinsons Dis. 2020: 9716317, doi: 10.1155/2020/9716317, indexed in Pubmed: 32104560.
11. Piekarski R, Roszmann A, Dulski J, et al. Acute/subacutae demyelinating polyneuropathy in Parkinson's Disease patients on levodopa-carbidopa intestinal gel therapy: systematic review with new case report. Neurologia i Neurochirurgia Polska. 2023; 57(2): 169–176, doi: 10.5603/pjnns.a2023.0001.
12. A. Uncini, R. Eleopra, M. Onofrj, Polyneuropathy associated with duodenal infusion of levodopa in Parkinson's disease: features, pathogenesis and management, J Neurol Neurosurg Psychiatry. 2015; 86(5): 490–5.

13. Piekarski R, Roszmann A, Dulski J, et al. Response to 'Before blaming levodopa/carbidopa intestinal gel for demyelinating polyneuropathy, all differential aetiologies must be ruled out'. Neurologia i Neurochirurgia Polska. 2023; 57(4): 403–404, doi: 10.5603/pjnns.a2023.0045.
14. Finsterer J. Before blaming levodopa/carbidopa intestinal gel for demyelinating polyneuropathy, all differential aetiologies must be ruled out. Neurologia i Neurochirurgia Polska. 2023; 57(4): 401–402, doi: 10.5603/pjnns.a2023.0043.
15. Lehnerer SM, Fietzek UM, Messner M, et al. Subacute peripheral neuropathy under duodopa therapy without cobalamin deficiency and despite supplementation. J Neural Transm (Vienna). 2014; 121(10): 1269–72, doi: 10.1007/s00702-014-1204-4, indexed in Pubmed: 24710647.
16. Andréasson M, Brodin L, Laffita-Mesa J, et al. Correlations between methionine cycle metabolism, comt genotype, and polyneuropathy in L-Dopa treated Parkinson's Disease: A Preliminary Cross-Sectional Study. Journal of Parkinson's Disease. 2017; 7(4): 619–628, doi: 10.3233/jpd-171127.
17. Martino JV, Van Limbergen J, Cahill LE. The role of carrageenan and carboxymethylcellulose in the development of intestinal inflammation. Front Pediatr. 2017; 5: 96, doi: 10.3389/fped.2017.00096, indexed in Pubmed: 28507982.