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Tolcapone improves outcomes in patients with Parkinson disease treated by levodopa/carbidopa intestinal gel

A pilot study

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Abstract

Background: Patients with Parkinson disease (PD) treated with levodopa/carbidopa intestinal gel (LCIG) have higher prevalence of hyperhomocysteinemia and peripheral nerves damage.

Objective: The aim of our study was to test the effect of catechol-*O*-methyl transferase inhibitor tolcapone—as an add-on therapy to LCIG in patients with PD—on homocysteine (HCY) metabolism and nerve conduction study (NCS) parameters.

Methods: We evaluated NCS and serum B12, folic acid, and homocysteine in 16 patients with advanced PD on LCIG. Quality of life (QoL) was also assessed. Six subjects were treated with tolcapone add-on therapy (and LCIG dose reduction), 5 with B vitamin supplementation, and 5 without additional treatment.

Results: The level of HCY increased among patients without treatment (4.95 ± 12.54), and decreased in the vitamin (–17.73 ± 11.82) and tolcapone groups (–8.81 ± 8.36). Patients with tolcapone demonstrated improvement in polyneuropathic symptoms and signs compared with patients treated with vitamins or those without additional treatment (–0.83, d = 0.961). Although the most robust improvement in NCS parameters were observed with tolcapone, the findings were inconsistent to prove the effect of any intervention. Only tolcapone treatment was associated with improvement in QoL (d = 1.089).

Conclusion: Our study indicates potential of tolcapone add-on therapy in LCIG treated patients in control of homocysteine levels, and improvement of polyneuropathic symptoms, as well as QoL.

Abbreviations: 3OMD = 3-O-methyldopa, ANOVA = analysis of variance, COMT = catechol-O-methyl transferase, HCY = homocysteine, LCIG = levodopa/carbidopa intestinal gel, NCS = nerve conduction study, PD = Parkinson's disease, PDQ-39 = Parkinson's Disease Questionnaire, PN = peripheral neuropathy, QoL = quality of life, SD = standard deviation, SPC = summary of product characteristic.

Key Words: B12 vitamin, homocysteine, levodopa/carbidopa intestinal gel, peripheral neuropathy, quality of life, tolcapone

1. Introduction

Patients with Parkinson disease (PD) have higher prevalence of peripheral neuropathy (PN) compared with general population.[1] The presence of PN in patients with PD presents dominantly with sensory signs, which is also associated with gait difficulties and frequent falls and decreased quality of life (QoL).[2] The spectrum of etiologies leading to PN is generally wide, but late-onset large-fiber somatosensory axonal and demyelinating PN in PD is often connected with long-term levodopa exposure.[3] The most severe cases of acute PN were reported in patients treated by levodopa/carbidopa intestinal gel (LCIG).[4,5] Continual delivery of relatively high doses of levodopa might put these patients in higher risk for PN development. The results by Mancini et al[6] confirm that lower vitamin B12 and higher homocysteine (HCY) blood levels may be a crucial factor. Our previous research confirmed that catechol-O-methyl transferase (COMT) inhibition can successfully control levodopa-induced increased plasmatic level of HCY in patients with PD.[7]

The aim of our study was to test the effect of anti-Parkinsonian medication involved in homocysteine metabolism—COMT

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The datasets generated during and/or analyzed during the current study are publicly available.

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inhibitor *tolcapone*—as an add-on therapy to LCIG in modification of plasmatic level of B vitamins and HCY, and improvement of signs and symptoms of PN and QoL.

2. Methods

This was a prospective interventional study at the Second Department of Neurology, Derer University Hospital of Comenius University in Bratislava, Slovakia. Informed consents were obtained in accordance with the Declaration of Helsinki, and the local Ethics Committee approved the study protocol.

We enrolled consecutive patients meeting following criteria:

(1) patients with advanced PD diagnosed according to the Movement Disorders Society criteria,[8]
(2) treatment with stable dose of LCIG for at least 3 months,
(3) ability to complete quality of life questionnaire (assistance of caregiver was allowed).

Patients who met at least 1 exclusion criterion were not enrolled:

(1) use of COMT inhibitor at least 3 months prior the study enrollment,
(2) presence of any severe comorbidity leading to PN (diabetes, end-stage kidney disease, etc)
(3) Montreal cognitive assessment below 10 (severe dementia).[9]

We examined 16 consecutive patients fulfilling all criteria, all demographic and clinical data are shown in Table 1.

Patients were admitted to hospital in order to perform Visit 1. After signing informed consent, all patients in their best ON state underwent all necessary procedures in fixed order:

(1) The Parkinson Disease Questionnaire (PDQ-39),
(2) Montreal Cognitive Assessment (MoCA),
(3) PN questionnaire—for subjective sensory and motor symptoms of PN,
(4) Objective structured clinical neurological examination including procedures focusing on objective manifestations of PN at the level of lower limbs (second, objective part of PN questionnaire),
(5) Blood samples drawn at fasting condition in the morning between 7 and 10 AM from a peripheral vein and immediately processed and examined in the local laboratory.
(6) After all these procedures in our air-conditioned lab with standard temperature of 20°C, a blinded neurologist performed nerve conduction studies.

Details about methodology and normal value range are available in Supplementary materials, http://links.lww.com/MD/G889.

Participants were assigned into 3 separate groups:

(1) Patients with no previous COMT inhibitor intolerance, no history of liver disease and normal levels of liver enzymes entered the "tolcapone" group. Tasmar (tolcapone 100 mg) was taken according to the official SPC recommendation—100 mg 3 times per day at 6:00–12:00–18:00 hours with or without meal (we instructed patients to take the first dose before LCIG morning dose). Tolcapone was added to current therapy with corresponding reduction of LCIG dose to meet satisfactory motor response and patients' satisfaction. All the patient used maximum of 1 cassette (100 mL of LCIG) during day for 16 hours (6:00–22:00)—this was confirmed (and adjusted if necessary) during "Baseline" stay at the hospital. Two patients were excluded due to inability to achieve satisfactory and stable motor state, 1 patient was excluded because of temporary psychosis during tolcapone treatment.

The final group size was N = 6.

(2) The patients not eligible for tolcapone treatment entered "vitamins" group to provide them with necessary B12 and folate supplementation and homocysteine level reduction. The dosing followed official recommendations. Vitamin B12 was injected intramuscularly in dose of 1000 μg at following study timepoints: day 1, day 7, day 14 (once per week during the stay at the hospital), month 1, month 2, month 3, month 4, and month 5 (once per month). The dosing of folic acid was 10 mg orally once per day with meal.

The final group size was N = 5.

(3) Those not eligible for tolcapone, with additional contraindications for B12 and folate supplementation, entered "no treatment" group. Four patients were excluded from vitamins group because of contraindications (2 patients with warfarin and 2 patients with a cancer history). One patient was not willing to take frequent intramuscular injections.

The final group size was N = 5.

Flowchart of patients assigned into specific groups is available in Figure 1.

There was no statistically significant difference in age (P = .201), PD duration (P = .650), LCIG duration (P = .655), or LCIG dose (P = .250) among treatment groups—making these 3 groups relatively more comparable, regarding PD characteristics. The main difference was in comorbidities contraindicating individual patients for assignment to specific treatment group (liver disease excluding patients from tolcapone group, contraindication of B vitamins in the patients with any history of cancer, etc).

Liver function tests were performed every 2 weeks at the local laboratories for "tolcapone" group. All patients completed visit 2 after 6 months of stable treatment—with the same procedures as at the visit 1.

2.1. Statistical analysis

We performed statistical analysis of data in SPSS Statistics 21. ANOVA was used for group comparison. The level of variables was characterized by mean and median. We assessed the effect size of the intervention according to the Cohen *d*, based on the

Table 1

Demographic and clinical data of patients (N = 16)

	Mean	Median	SD	Min	Max
Age (yrs)	73.56	74.50	6.29	59.00	82.00
Female gender	0.38	0.00	0.50	0.00	1.00
MoCA	20.94	21.00	5.52	12.00	30.00
PD duration (yrs)	13.81	13.50	5.91	5.00	23.00
LCIG treatment duration (mo)	30.31	27.50	21.49	4.00	72.00
LCIG dose (mg of levodopa/d)	1401.31	1390.50	405.12	632.00	2000.00

LCIG = levodopa/carbidopa intestinal gel, MoCA = Montreal Cognitive Assessment, PD = Parkinson disease, SD = standard deviation.

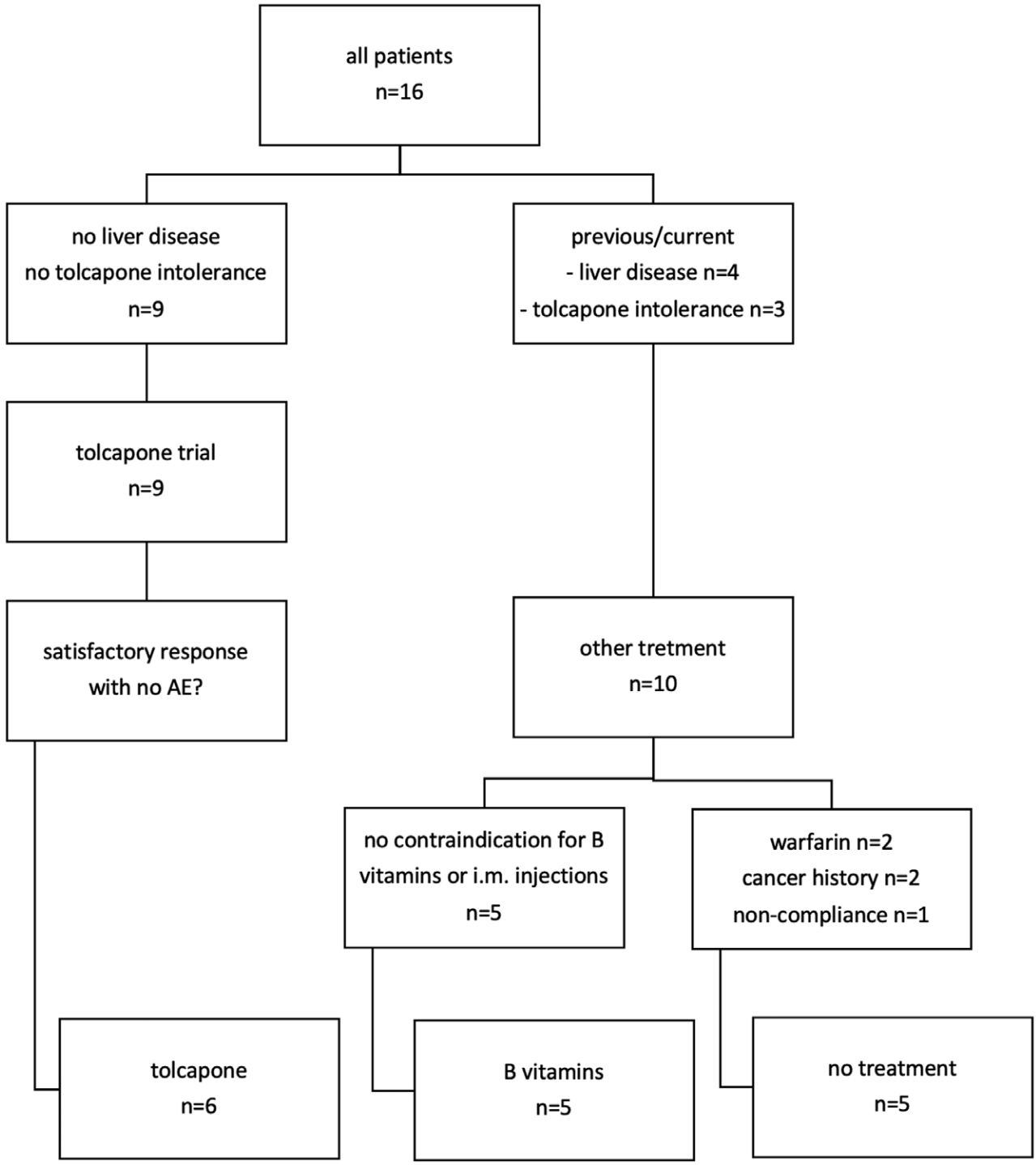

Figure 1. Flowchart of patients assigned into specific treatment groups.

following rules of interpretation—large (>0.8), very large (>1.2), huge (>2.0).[10,11] We considered $d > 0.80$ (large, very large, and huge effect size) as "significant." Data are displayed in tables and graphs (boxplot, line chart).

3. Results

On average, the level of HCY increased among patients with no treatment (4.95 ± 12.54) and decreased in vitamins group (–17.73 ± 11.82) and tolcapone group (–8.81 ± 8.36). According to the Cohen *d*, the effect size of difference was very large between no treatment and both treatment groups (d = 1.861 and d = 1.320, respectively) (Fig. 2).

The level of B12 decreased among patients with no treatment (–32.60 ± 32.95) and increased in vitamins group (79.20 ± 100.85) and tolcapone group (32.67 ± 45.03). The effect size of difference was very large between no treatment and both treatment groups (d = 1.490 and d = 1.627, respectively).

Active B12 increased robustly only in vitamins-supplementation group (17.70 ± 12.86).

Folic acid did not change significantly in any group.

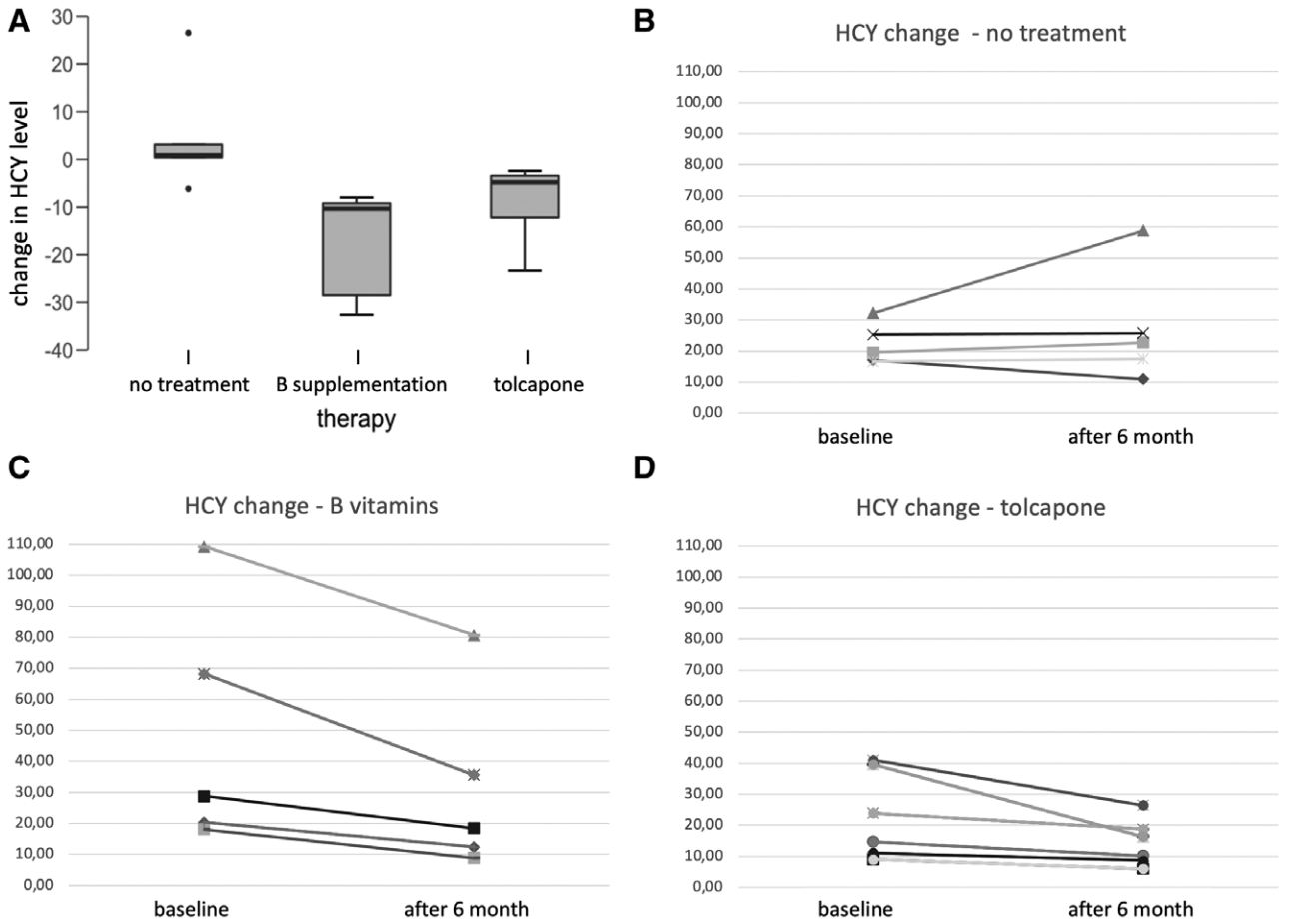

Figure 2. HCY plasmatic level change. (A) Boxplots showing average differences among therapeutical groups (0—no treatment, 1—B vitamins, 2—tolcapone), (B–D)—change between baseline visit (1) and after 6 months (2) in each patient in all therapeutical groups. HCY = homocysteine.

Total PDQ-39 score decreased only in tolcapone group (–12.17 ± 28.13, the effect size was large, d = 1.089), increased in no treatment group (11.40 ± 8.02) and B vitamins group (4.60 ± 8.62) (Fig. 3).

Average total PN score decreased only in tolcapone group (–0.833 ± 3.189, large size effect compared with no treatment, d = 0.961). Motor subjective subscore, motor, reflexes, pain perception, vibration perception, and total objective subscore decreased only in tolcapone group—all the data are available upon request.

The most robust improvement in nerve conduction studies parameters was observed in tolcapone group (especially improved motor conduction velocities); however, the findings were not enough consistent to prove the effect of any intervention (Fig. 4). All data are available in the Supplemental Digital Content, http://links.lww.com/MD/G889.

4. Discussion

Our pilot results suggest a favorable effect of tolcapone as an add-on therapy to LCIG in patients with advanced PD. These patients are treated with relatively high doses of pure levodopa/carbidopa. Metabolization of levodopa leads to increased levels of both 3-O-methyldopa (3OMD) and homocysteine (HCY), with concurrent consumption of B vitamins (Fig. 5).

It is proved that increased HCY leads to peripheral neuropathy (PN), reversible encephalopathy, and cognitive decline in patients with PD.[12–14] Elevated 3OMD seen in patients treated with levodopa is associated with both decreased brain uptake of levodopa and lower dopamine turnover rate. In addition, chronic accumulation of 3OMD might be connected with potential toxicity of long-term use of levodopa.[15] In 1 group of our patients, we confirmed that B vitamins supplementation led to decrease in HCY plasmatic levels.

In tolcapone group, also COMT inhibition leads to decrease in HCY levels, even without B vitamins supplementation. Moreover, except of laboratory parameters normalization, patients with tolcapone add-on therapy experienced also improvement in polyneuropathic signs and symptoms compared with patients treated with B vitamins or those without specific therapy. The most robust improvement in nerve conduction studies parameters was observed in tolcapone group, too. In addition, only patients with tolcapone reported improvement in QoL. Thus, inhibition of COMT seems to be superior to sole B vitamin supplementation. Adding tolcapone to LCIG allowed us to reduce the daily dose of levodopa without a negative impact on motor state or worsening of fluctuations (we adjusted and confirmed optimal pump parameters during the stay at the hospital). The effect of tolcapone on QoL in fluctuating patients with PD was documented in previous research, where the improvement were linked to the fluctuations reduction.[16,17] We report QoL improvement with tolcapone in patients treated by a continual dopaminergic therapy (with significantly less severe fluctuations), thus assuming that other benefits than reduction of fluctuations contribute to better QoL in LCIG patients on tolcapone. The effect on the levels of 3OMD might play an important role. Decrease in 3OMD production probably leads to better availability of levodopa in the brain. In addition, contrary to peripheral COMT inhibitor entacapone, tolcapone with its central effect enables a better turnover of levodopa to dopamine. To sum up, tolcapone might result in more efficient utilization of levodopa in LCIG with better overall motor state; and, together with improved symptoms of peripheral nerves damage, may lead to better quality of life in patients with advanced PD. A

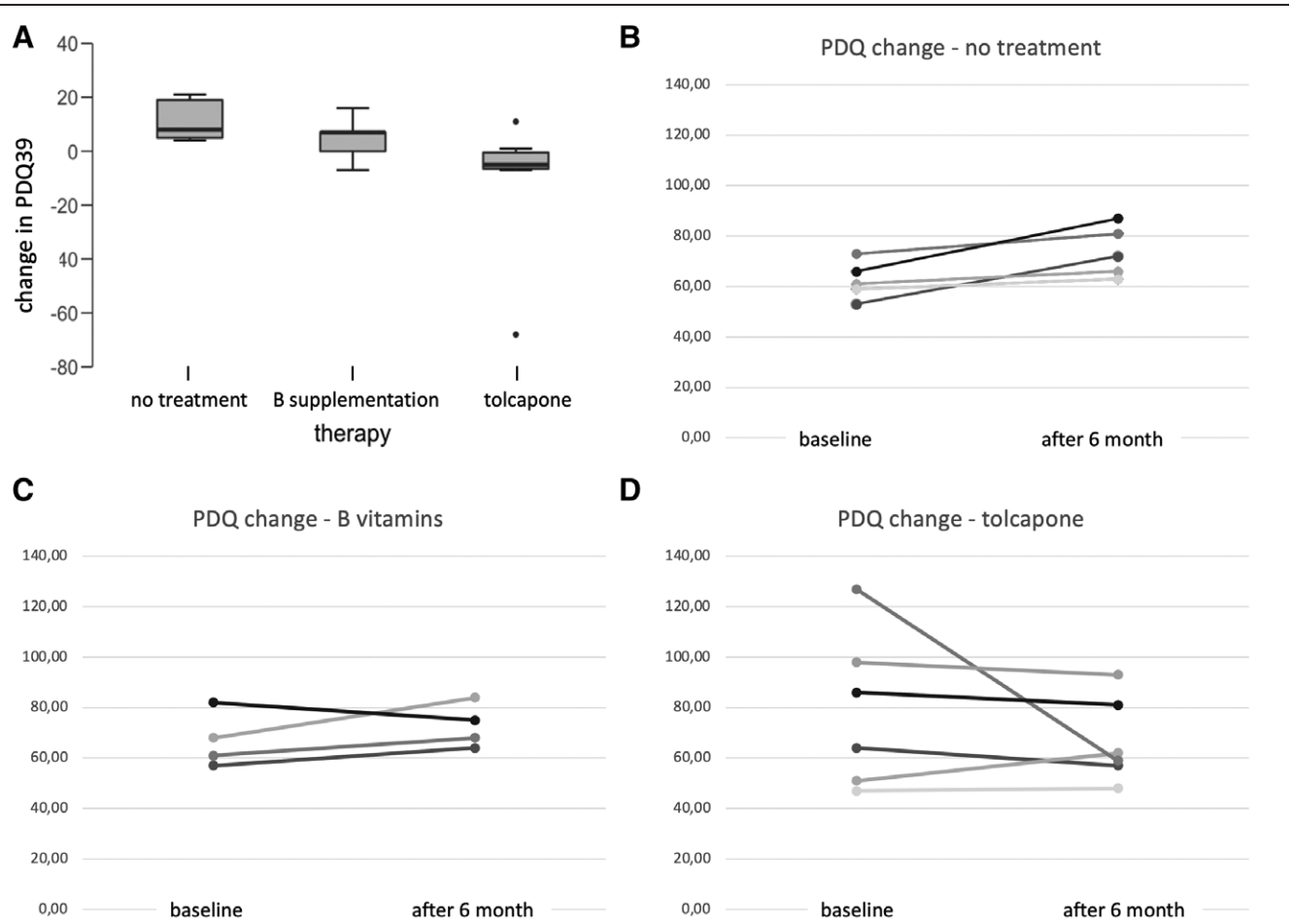

Figure 3. Change in quality of life according to PDQ-39 score. (A) Boxplots showing average differences among therapeutical groups (0—no treatment, 1—B vitamins, 2—tolcapone), (B–D)—change between baseline visit (1) and after 6 months (2) in each patient in all therapeutical groups.

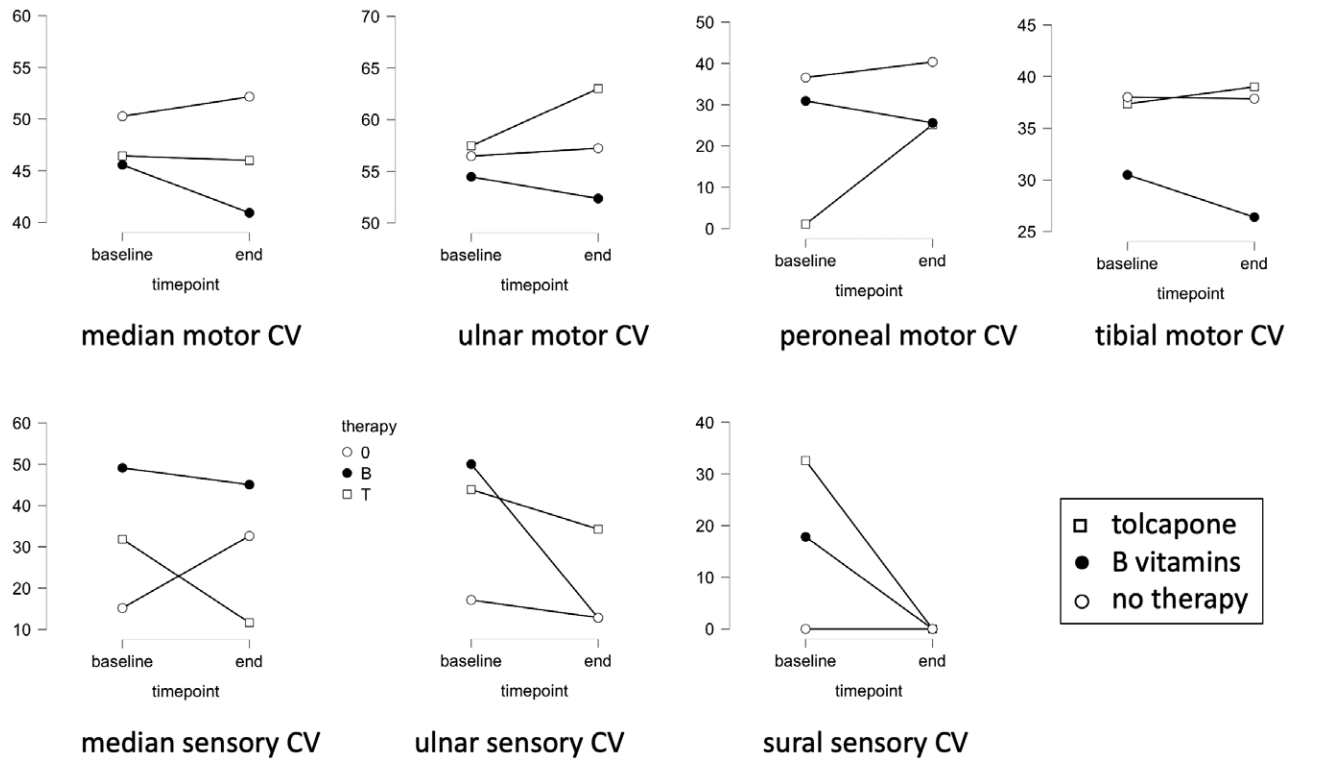

Figure 4. Changes in NCS parameters in all groups between baseline and end-of-study visit. CV = conduction velocity, NCS = nerve conduction study.

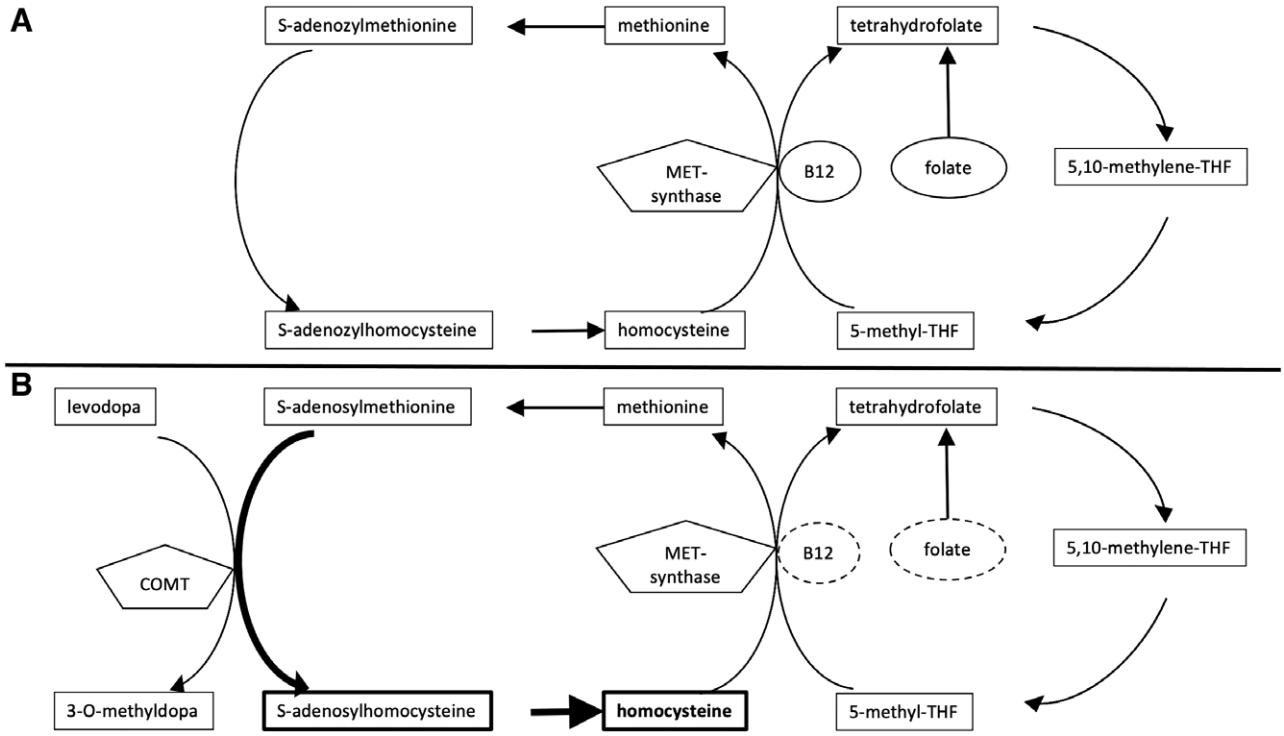

Figure 5. Mechanism of levodopa-induced homocysteine overproduction and excessive B vitamins consumption (A—normal state, B—levodopa intake). COMT = catechol-*O*-methyl transferase, MET = methionine, THF = tetrahydrofolate.

long-term effect of reduced exposition to high levels of 3OMD would be of great interest, and it requires further research.

Tolcapone has been connected with relatively high risk of toxicity. We did not detect impairment in liver function among our patients. One patient developed temporary psychosis, which resolved after tolcapone withdrawal, and there were no permanent consequences.

Limitations of our study include the relatively small number of patients. Assignment to treatment group was not randomized and the sample included 3 groups according to the indications or contraindications to specific therapies. Nevertheless, comparing these groups, we did not find any significant difference in age, PD duration or LCIG dose, making these 3 groups relatively more comparable.

In summary, our study highlights the favorable effect of add-on therapy with COMT inhibitor tolcapone in LCIG treated patients with advanced PD. It leads to normalization of homocysteine and B vitamins levels (and probably 3OMD, as well), improvement in polyneuropathic signs and increase in quality of life. Tolcapone therapy seems to be well-tolerated in patients without a known risk of any liver damage.

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