

Research Article



Intestinal Gel Levodopa + Carbidopa in Parkinson's Patients with Frequent and Prolonged Akinesia – An Economic Evaluation

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ABSTRACT

There is a small subgroup of patients with rare form of Parkinson's disease (PD) characterized by prolonged akinesia, which could not be controlled by the standard treatment. The infusion of Levodopa + Carbidopa intestinal gel, applied in the small intestine with a portable pump by a permanent tube via percutaneous endoscopic gastrostomy, is an alternative treatment of deep brain stimulation in advanced phase of PD associated with severe dyskinesia and motor fluctuations. The aim of the study was to evaluate the economic characteristics of combination pharmacotherapy Levodopa + Carbidopa applied as intestinal gel in patients with rare form of PD in Bulgaria. The study is done from the perspective of the Bulgarian health care system. Cost analysis and cost-effectiveness analysis were applied. The pharmacotherapy costs were calculated before and after applying of intestinal gel Levodopa + Carbidopa of 12 PD patients. The outcomes are measured by assessing improvements in Unified Parkinson's Disease Rating Scale (UPDRS). The incremental cost-effectiveness ratio (ICER) which shows additional monthly costs for every additional unit of improvement of patient's condition after treatment with intestinal gel Levodopa + Carbidopa is 1903.56 BGN per patient, per year. These costs are far below the recommended threshold of annual GDP per capita of Bulgaria. The intestinal gel Levodopa + Carbidopa is cost-effective for patients who are indicated for this therapy.

Keywords: Parkinson's disease, intestinal gel Levodopa + Carbidopa, pharmacoeconomics, medical devices.

INTRODUCTION

Parkinson's disease (PD) is a chronic progressive disease which is characterized neurochemically as a syndrome of striatum dopamine deficiency. The main symptoms tremor, akinesia, and rigidity of muscles significantly affect the quality of life of patients.¹

PD is a common disease spread among people from different ethnic and gender groups and it affects most often men and women in the age between 45 and 65 years old.¹ The prevalence is between 66 and 258 per 100 000 persons and because of that is one of the most common neurodegenerative diseases.² In USA between 50 000 and 60 000 new cases are diagnosed every year. Worldwide 4 to 6 million people are affected by PD.³

Pharmacotherapy is performed with central dopaminergic medicines (Amantadine, Bromocriptine, Entacapone, Levodopa, Levodopa + Benserazide, Levodopa + Carbidopa, Ropinirole, Pramipexole, Selegiline) and central M-cholinolytics (Biperiden, Trihexylphenidil).⁴ The therapy is supportive, controls the symptoms and aims to improve the patients' quality of life.⁵

Innovation in treatment is a combination of Levodopa and Carbidopa – intestinal gel introduced in the small intestine with a portable pump by a permanent tube via percutaneous endoscopic gastrostomy.^{6, 7} This way of application allows direct delivery of the active ingredients into the blood stream, accurate dosing, and faster recovery of patients. It is designated for very small group of patients suffering from prolonged period of akinesia which is considered as a rare condition and could not be

controlled by the standard treatment. Infusion of the gel is alternative of deep brain stimulation in advanced phase of PD associated with severe dyskinesia and motor fluctuations. Compared with conventional oral therapy with levodopa, intestinal gel provides stable plasma levels of Levodopa and thus there is significant average extension of 'on'-period associated with conditions without severe dyskinesia as well as improvement in scores in the context of Unified Parkinson's Disease Rating Scale (UPDRS) and statistically significant improvement in quality of life.⁸ Many investigations indicate the benefits of intestinal gel as delay in progression of the disease and decrease in consumed resources, stabilization and significant improvement in motor fluctuations and in quality of life, significant clinical recovery in quality of life and daily activities, reduction of the severity of dyskinesia.⁹⁻¹¹

This study evaluates the economic characteristics of combination pharmacotherapy Levodopa + Carbidopa applied as intestinal gel in patients with rare form of PD in Bulgaria.

MATERIALS AND METHODS

This is a retrospective observational study. All 12 Bulgarian patients with PD on therapy with intestinal gel Levodopa + Carbidopa were included. 10 of them are men and 2 – women. The medical history of every patient was traced, and pharmacotherapy was reviewed. The study was approved by the Medical Science Council at the Medical university of Sofia.



Cost analysis of pharmacotherapy

Individual monthly average costs for pharmacotherapy were calculated on the basis of fundamental requirements given by cost analysis^{12, 13}. The perspective of analysis was payers' and time horizon was from the beginning of therapy from the moment of diagnosis to the moment of starting the new therapy with intestinal gel. The average monthly costs for therapy with new drug were determined. The medicines prices were taken from the official database of the prescription medicines prices at the Ministry of health in 2012 at the exchange rate 1 euro = 1.95 Bulgarian leva (BGN).

Cost-effectiveness analysis

The health state of all 12 patients was assessed by Unified Parkinson's Disease Rating Scale (USPDR).^{14, 15} UPDRS is rating scale for examination the linear progression of PD. It is consisted from 3 parts studying the mentation, behavior and mood; activities of daily living; and motor examination

The USPDR was applied twice - in the beginning of treatment with Levodopa + Carbidopa intestinal gel at the moment of patients' recruitment and at the time of the study. The variance in individual assessment is measured. According to the scale the maximum points are 199 which reflect the worst (total) disability. The point of 0 reflects lack of disability.

The incremental cost-effectiveness ratio, the ratio of the change in costs to incremental benefits of a treatment, was calculated following the standard formula¹²:

ICER = $\Delta E / \Delta C$ = Differences in the USPDR before and after the therapy – Differences in pharmacotherapy cost

RESULTS AND DISCUSSION

Demographic characteristics of patients

All treated with levodopa plus carbidopa intestinal gel patients in the country are included in the study. They are with advanced Levodopa responsive Parkinson's disease, with severe motor fluctuations and hyper-/dyskinesia, who are passed to treatment with intestinal gel. The average age of patients is 60.8 years (SD=5.83) and it's varying between 72 and 45 years. The duration of the disease is between 22 and 10 years (Figure 1). There is significant prevalence of men as the ratio men: women equal 5:1.

Pharmacotherapy costs

Pharmacotherapy, before implementation of intestinal gel Levodopa + Carbidopa, includes medicines from following therapeutic groups: central dopaminergic and central M-cholinolytics. The preferred therapy is Levodopa + Benzeraside and Pramipexole – applied to 84.62% of all patients. At least patients are treated with Bromocriptine – 7.69%.

The long term dopaminergic therapy is a risk factor for manifestation of symptoms such as confusion, visual

hallucinations and psychotic reactions. Administration of typical neuroleptics leads to exacerbation of motor symptoms. Therefore atypical neuroleptics such as Clozapine are preferred.¹⁶ Also Mianserine is administrated to control the psychotic reactions.¹⁷ In the patient group object to this analysis only 1 patient (7.69%) was treated with Clozapine and 1 – with Mianserine for 1 and 2 years respectively. (Figure 2)

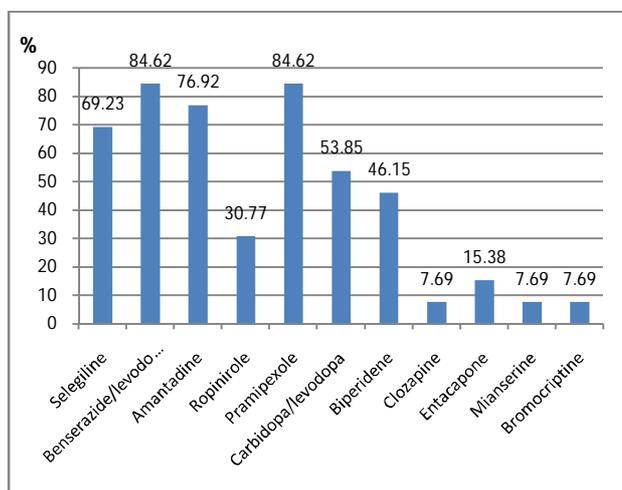
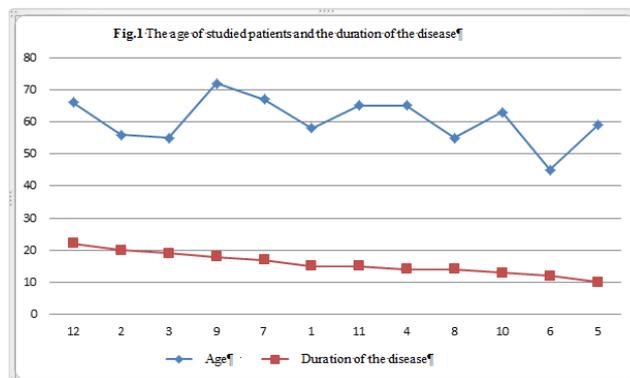


Figure 2: Distribution of patients according to type of previous pharmacotherapy

In all patients (100%) is reported administration of dopaminergic medicines during the whole therapy period. 46.15% of them are treated with M-cholinolytic in a certain period of treatment course.

There is significant difference in pharmacotherapy cost before and after the implementation of intestinal gel Levodopa + Carbidopa. The average monthly cost of the therapy with intestinal gel is 5655.91 BGN (SD=662.19) which is higher than pharmacotherapy cost for previous treatment equal to 143.49 BGN (SD=38.49). The total costs for this group of patients are 5.5% of total value for all PD patients in Bulgaria due to limited number of patients which are treated with intestinal gel. In 2012 National Health Insurance Fund (NHIF) reported that pharmacotherapy costs for treatment of Parkinson's disease is equal to 14 751 437.61 BGN.

Assessment of the therapy results

The assessment of the therapy results was conducted by Unified Parkinson's Disease Rating Scale (USPDR) before

and after therapy with the intestinal gel Levodopa + Carbidopa. The results indicate improved condition and symptoms after administration of new treatment. The highest points equal to 199 identify the worst condition in which the patient could be. Before infusion of Levodopa + Carbidopa intestinal gel the average scores were 57.45 (SD=15.39) and after the infusion was 22.67 (SD=13.11).

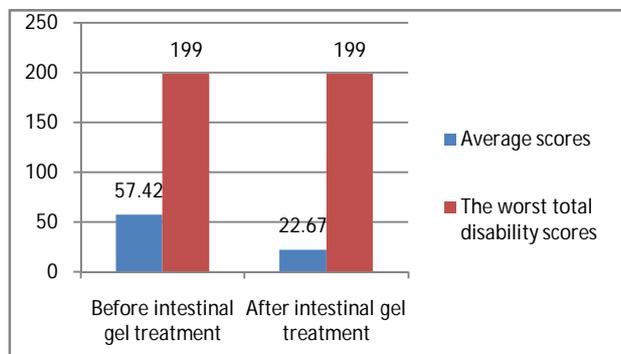


Figure 3: The reported scores according to UPDRS before and after intestinal gel treatment

Cost-effectiveness analysis

The implementation of systematic approach to compare the additional costs per additional outcomes between the two health alternatives (standard and new therapy with intestinal pump), in this case two pharmacotherapies, is a method for determine the value for additional benefits. The application of incremental analysis is based on the fact that the new therapy is more expensive but it is more effective, i.e. leads to significant improvement in the health status established by USPDR. The incremental ratio for the two alternatives – conventional therapy and innovative therapy is as follows.

$$ICER = \Delta C / \Delta E = (5655.91-143.49)/(57.42-22.67) = 158.63 \text{ BGN}$$

The value of ICER represents the additional monthly costs for every additional unit of improvement of the state of a patient treated with intestinal gel Levodopa + Carbidopa. The additional annual cost was 1903.56 BGN. These costs are far below the recommended threshold of annual GDP per capita of Bulgaria which is equal to 5000 euro.

CONCLUSION

The cost for pharmacotherapy with intestinal gel Levodopa + Carbidopa is significantly higher than the conventional therapy, but there is an improvement in the assessment of the health state – in motor examination, mentation and activities of daily living. Taking into account the limited number of patients with progressive form of Parkinson's disease using infusion therapy with intestinal gel, the impact of costs for health insurance system is not expected to be significant. The additional annual costs are far below the recommended threshold of annual GDP per capita in Bulgaria. Therefore the new medicinal product is cost-effective for the patients who are shown for this treatment.

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