

# AMBULATORY UTILIZATION OF ANTI-PARKINSONIAN DRUGS IN ALBANIA DURING 2004-2014

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## ABSTRACT

**Aim** To analyze utilization of Anti-Parkinsonian drugs in Albania using the Anatomic Therapeutic Chemical Classification-Defined Daily Dose (ATC/DDD methodology), in comparison to the Parkinson's morbidity for the period 2004-2014. **Methods** The data were assembled from Health Insurance Institute (HII) and analyzed for the period 2004-2014. The consumption of drugs was expressed as some Defined Daily Dose (DDD) /1000 inhabitants/day. Also, for all the period under study 2004-2014, there also analyzed the data of import and domestic production of drugs, which represent the real consumption of drugs in the country. These data were subsequently involved in a comparative analysis of the utilization data according to the HII. **Results** The values of consumption of Anti-Parkinsonian drugs were .145-1.53 DDD/1000 inhabitants/day respectively in 2004-2014. The combination of levodopa with benserazide has the highest value of prescription 0.47-0.75 DDD/1000 inhabitants/day 2004-2014. On the other hand, the consumption of levodopa+carbidopa is 0.04-0.29 DDD/1000 inhabitants/day 2004-2014. This notable difference probably reflects the pressure and the marketing incentives used by the pharmaceutical companies. Furthermore, it turns out that the consumption of levodopa+benserazide based on HII data is superior to the use of this formulation based on Import data, which cannot be true. This finding probably reflects fictive prescriptions and the entry of drugs by contraband. It also results that a consistent part of Parkinson patients does not benefit from the reimbursement scheme (out-of-pocket expenditure). **Conclusions** There is only a small increase in the national consumption of Anti-Parkinsonian drugs during these years, but the values remain very low in comparison with other countries. It results that the use of antiparkinsonian drugs flows out of the scheme at the level of around 30%.

**KEYWORDS:** Drug utilization, DDD, Anti-Parkinsonian drugs

## Introduction

In idiopathic Parkinson's disease, the progressive degeneration of pigmented neurons in the substantia nigra leads to a deficiency of the neurotransmitter dopamine. The resulting neurochemical imbalance in the basal ganglia causes the characteristic signs and symptoms of the illness. Drug therapy does not prevent disease progression, but it improves most patients quality of life. About 5-10% of patients with Parkinson's disease respond poorly to treatment.

This progressive degenerative disorder of the nervous system affects movement. It develops slowly, starting in some cases with a poorly noticeable tremor in just one hand. The most well-known sign of Parkinson's disease is the tremor, but the disorder

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DOI:10.5455/ijsm.acs

First Received: July 07, 2016

Accepted: September 11, 2016

Manuscript Associate Editor: George Baitchev (BG)

Editor-in-Chief: Ivan Inkov (BG)

Reviewers: Stefka Mantarova (BG);

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also commonly causes stiffness or slowing of movement[1]. Economic status of a country (health care cost) is having a greater effect on a predicted increase in life expectancy of elderly patients with Parkinson disease. As the prevalence of Parkinson disease rises, the burden on the economic status of the family members increases[1].

The morbidity data referred from HII indicates that the number of Parkinson patients in Albania (expressed cases/1000 inhabitants) is 1.30-1.92 cases/1000 inhabitants, 2004-2014. Treatment for Parkinson's disease should be initiated under the supervision of a physician specializing in Parkinson's disease. Treatment is not usually started until symptoms cause significant disruption of daily activities.

Albania has the highest prevalence in Europe of people over the age of 60 suffering of Parkinson. Based on a study published by the Neurologist Society of Albania in April 2016[2], around 0.8 per thousand inhabitants in Albania are affected by the Parkinson disease. There are cases of persons of around 50 years old affected by Parkinson, an age which is unusually young for this type of disease.

The relative number of affected people in all age groups is much higher in Albania compared to other European countries. In general, males and females are equally affected, but there is a slight predominance of males in the number of affected people. According to the same study, the figures as of today are significantly higher also compared to the year 1995, the last year in which a similar study was conducted in the past in Albania[2]. Our guidelines according to HII indicate the formulations of levodopa (either with benserazide or with carbidopa) the first line for Parkinson's treatment accompanied with receptor agonists such as bromocriptine. In these guidelines is also included Amantadine usually as a supplement in the treatment scheme. The last anti-Parkinsonian drug involved in the scheme form HII is trihexyphenidyl which is indicated for the treatment of idiopathic Parkinson disease and drug-induced parkinsonism. Other Anti-Parkinsonian drugs such as newer dopamine receptor agonists, monoamine oxidase B inhibitors (MAOIs), catechol-o-methyl transferase inhibitors (COMTIs) are not included in our reimbursement scheme.

## Methods

### Objective

To evaluate the out-of-hospital Anti-Parkinsonian drugs use in Albania during the period 2004-2014.

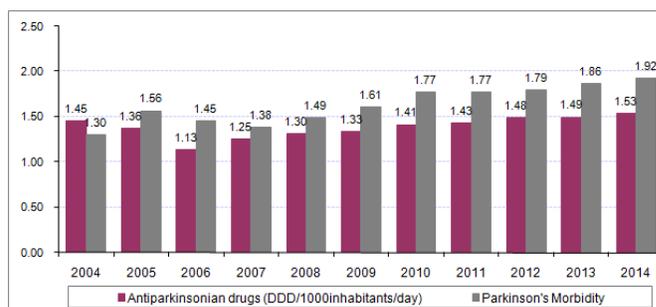
### Materials and Methods:

The data were obtained from the HII [3]. These data were collected and analyzed for all the period 2004-2014. In the were included, the total number quantities of drugs used from the prescriptions. The population data were obtained from the Institute of Statistics (INSTAT)[4]. The consumption of drugs was expressed as some Defined Daily Dose (DDD)/1000 inhabitants/day. All drugs were classified by groups of Anatomic Therapeutic Chemical Classification (ATC).

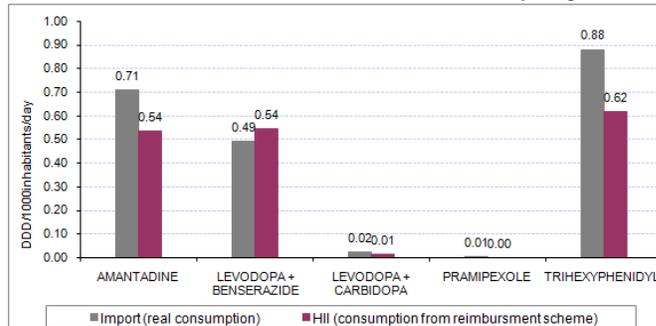
### Data on the levels of Parkinson morbidity

From the database of HII, we extracted the overall number of patients reported with this diagnose, for each year. Also, we calculated the respective levels of annual morbidity (based on the individual code-diagnoses) for 1000 inhabitants.

The total number of Parkinson patients reported from the HII database is shown in the table above:

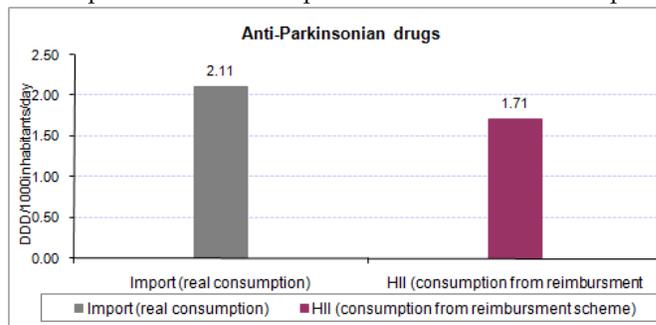


**Fig.1** Consumption of Anti-Parkinsonian drugs at the national level (DDD/1000 inhabitants/day) versus Parkinsonian morbidity (cases/1000 inhabitants); ( $p = 0,9877$ ; strength (with significance level  $\leq 0,05$ ) = 2,59%; correlation coefficient is not statistically significant).

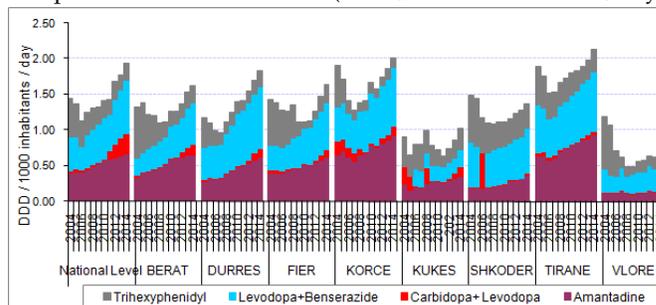


**Fig.2** Annual average value of consumption of drugs used for Parkinson disease: consumption based on import (real consumption) [\*] versus consumption based on HII.

[\*] The "Import" item includes the consumption based on import data as well as the consumption based on domestic production: this represents the actual consumption.



**Fig.3** Annual average value of consumption of drugs used for Parkinson disease in total: consumption based on import (real consumption) versus consumption based on HII (DDD/1000 inhabitants/day).



**Fig.4** Consumption of drugs used for Parkinson disease in different regions and at the national level (DDD/1000 inhabitants/day).

**Table 1** Total number of Parkinson patients reported from HII in each year of the study period.

Years	Number of Parkinson patients
2004	4,094
2005	4,890
2006	4,575
2007	4,351
2008	4,738
2009	5,129
2010	5,679
2011	5,743
2012	5,845
2013	5,921
2014	6,086

**Data on real consumption (import and domestic production).**

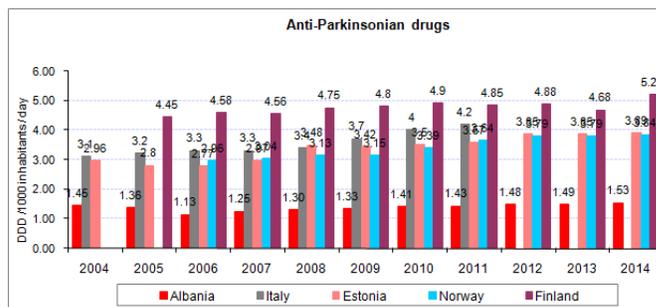
For all the period under study 2004-2011 there were collected and analyzed data from the import and domestic production of the drugs,[5] which represent the real consumption of drugs in the country. It was noted that the increase in use from one year to another was small, e.g. the consumption from 2011 to 2014 (i.e. four years) was increased by only 2.98%. Consequently, to obtain an updated study, there were chosen the data of import and domestic consumption only for the last three years, 2012, 2013, 2014, and those were included in a comparative analysis with the comparable consumption data according to HII. To minimize the effect of variations in use and stock inventory balances from one year to another, it was calculated and put into analysis the annual average value of the three chosen years (on one hand that of the import and domestic consumption, and on the contrary that of HII).

**Presentation of the results and statistical elaboration**

The database of HII was modified in Microsoft Office Excel 2007, whereas the statistical explanation of the obtained results was conducted with the statistical package StatsDirect (version 2.7.2.). A descriptive statistics was used to report all data on drugs consumption and the results obtained were displayed in tabular form as well as through the histogram method. Average annual values of consumption at the country level and for each district were used as a basis to generate the overviews and the graphics that illustrate the trends of consumption for each class of drugs during the 10-years period 2004-2014. The linear regression model was used to evaluate the trends of consumption of drugs at the time. A value of  $p \leq 0.05$  was considered as significant. To assess if there exists a correlation statistically significant between the level of consumption of drugs and the level of morbidity, it was applied the Spearman correlation (with a significance level of  $\leq 0.05$ ).

**Results**

The data were expressed as some defined daily doses per 1000 inhabitants/day (DDDs/1000 inhabitants/day). Drugs included in the reimbursement list are amantadine, carbidope+levodope,



**Fig. 5.** International comparisons of Anti-Parkinsonian drugs consumption. Norway [6,7], Estonia [8, 9], Finland [10,11], Italy [12,13,14], (DDD/1000 inhabitants/day).

levodope+benserazide, trihexyphenidyl. Dopamine receptor agonists are not included in the reimbursement scheme. Total consumption of this class (period 2004-2014) is 1,45 - 1,53 DDD/1000 inhabitants/day. Parkinsonian morbidity data indicate that there does not exist a correlation statistically significant between this disease and the trend of consumption of Anti-Parkinsonian drugs, ( $p = 0,0713$ ), (Figure 1).

The annual average value of drugs used for Parkinson disease and the annual average value of consumption of each alternative, as a consumption from import (actual use) versus the consumption reported by HII (DDD/ 1000 inhabitants/day), (2004-2011), are respectively presented in Figures 2 and 3.

**Discussion**

The Parkinson disease has been recognized as a distinct entity since the publication by James Parkinson of An Essay on the Shaking Palsy, in 1817 [15]. The first drug for the treatment of this disorder (alkaloid hyoscyamine) was recognized in 1870 [16]. Following, different synthetic substances with central anticholinergic action were introduced in the market and took priority in therapies until the end of '1950s when amantadine was identified as being useful in the treatment of this disease [14].

In 1960, there was introduced the principal drug for the treatment of this disease: the converting therapy of dopamine with levodopa, accompanied with peripheral inhibitors of its metabolism.

Afterward, the spectrum of anti-Parkinson alternatives extended: MAO-B inhibitors -selegiline (1993), COMT inhibitors -entacapone (2005), dopamine agonists: bromocriptine (1992), pergolide (1994), cabergoline (2000), ropinirole (2008) and pramipexole (2008) [17]. In Figure 1, there can be noted discrepancies and irregularities between the data of consumption of anti-parkinsonian drugs and Parkinson morbidity at the national level. More specifically, in 2004, the consumption of anti-parkinsonian drugs results higher compared to the number of Parkinson patients, whereas in subsequent years, this ratio is reversed, by indicating an increase in the number of patients that do not obtain the particular medication. On the other hand, even the variations of morbidity reported from year to year, do not link with the naturally expected increase of such disease.

We compared the data of consumption received from HII with the values of consumption deriving from imports (representing the real consumption) to understand how they link with each other. In Figure 2 describes three features:

- Only 70% of amantadine and trihexyphenidyl is consumed

within the scheme; the rest flows out of it;

- There is an extreme disproportion between the consumption of the two different formulations of levodopa (further discussed below);
- There are higher values of consumption based on HII than based on import for the formulation levodopa + benserazide, a fact that could difficultly be realistic and does probably reflect a non-effective application of the reimbursement scheme (fictive prescriptions); another reason that could explain this finding may also be the entry of drugs out of the public authorities control.

It results (Figure 3) that the consumption of anti-Parkinson drugs flows out of the scheme at a level of around 30%. The consumption of anti-Parkinson drugs is characterized by expressed differences between the regions in the country (Figure 4). In general, a standard feature for the majority of areas is the tendency for a slight decline in consumption, and afterward, an increase in recent years. The highest consumption values are marked in 2004 in Tirana and Korca, respectively 1,90 and 1,91 DDD/1000 inhabitants/day. The lowest consumption values appear in Vlora in 2010: 0,56 DDD/1000 inhabitants/day. Low consumption, almost twice as low as in other regions, is noted in Kukes. This fact probably reflects gap as regards the coverage of the drugs between urban and rural areas, which reflects the differences in income and formal employment (e.g. only 20% of the population in mountain areas is covered) [18].

The highest possible values of coverage by the scheme are found in Tirana and regions close to it, mainly urban areas, with a relatively high social economic standard. Whereas, more distant from Tirana (far regions, rural areas with low economic standard), the lower the coverage of consumption by the scheme and the access of the population to the scheme and reimbursement service.

There can be noted an expressed difference between the consumption of two different formulations of levodopa + decarboxylase inhibitor: levodopa + benserazide (0,47-0,59 DDD/1000 inhabitants/day, 2004-2010) and levodopa + carbidopa (0,04-0,01 DDD/1000 inhabitants/day, 2004-2010). In the pharmacological aspect, the levodopa + carbidopa, and levodopa + benserazide combinations are exchangeable with each other, with similarities in effectiveness and the profile of adverse effects, a fact which makes difficult to explain such difference. On the other hand, in the reimbursement list, the levodopa + benserazide combination exists as a single alternative, whereas the levodopa + carbidopa combination is found in several alternatives i.e. marketed by several pharmaceutical companies. The main reason remains to be the aggressive marketing campaigns made for the levodopa + benserazide combination.

Initially, in 2004, trihexyphenidyl (anticholinergic agent) was the anti-Parkinsonian alternative with the highest consumption values, gradually decreasing in subsequent years (2005-2010) against the increase in use of levodopa + benserazide. Trihexyphenidyl constitutes a necessary addition to the anti-Parkinson therapy, from a pharmacological aspect. Its indications are for the treatment of Parkinsonism and drug-induced extrapyramidal symptoms. So, this fall of consumption probably reflects an entirely inadequate adherence of the physicians to the guidelines. During this period (2004-2010), the Parkinson morbidity has increased in the context of the natural aging of the population in our country. In these circumstances, the general decrease in consumption and prescription of anti-Parkinson drugs can be explained, first, by the reduction of prescription

of the combined anti-Parkinson schemes to the same patient as a result of the release in the market of standard combined formulations, and second, with the lower usage of anticholinergic drugs and dopaminergic agonists (that are not included in the reimbursement scheme) not accompanied by an equilibrated increase of usage of levodopa.

### **International comparison of consumption.**

As compared with other European countries the level of consumption of Anti-Parkinson drugs in Albania is too small. (Figure 5). In other international comparisons of the two formulations of levodopa, differently, to Albania, it can be noted higher values of the consumption of levodopa + carbidopa. For example, in Australia, levodopa + carbidopa: 0,76-0,82 (1995-2009), levodopa + benserazide: 0,34-0,55 (1995-2009), levodopa + carbidopa + entacapone: 0,03-0,10 [19]. The formulation levodopa + carbidopa was the most widely used agent, followed by levodopa + benserazide, then benzotropine. Since 2005, [19] dispensed use of levodopa + carbidopa + entacapone has steadily increased in Australia, from 0.03 to 0.10 DDD/1000 population/day. In our country this triple formulation, it is not available in the pharmaceutical market. In Spain, levodopa + carbidopa constitutes the alternative with the highest value of prescription, followed by selegiline, pergolide, levodopa + benserazide, ropinirole, bromocriptine, and entacapone [20].

### **Conclusion**

There is only a small increase in the national consumption of Anti-Parkinsonian drugs during these years, but the values remain very low in comparison with other countries. A consistent part of anti-Parkinson drugs flows out of the reimbursement scheme. The highest possible values of coverage by the scheme are found in Tirana and regions close to it, mainly urban areas. Several times is noted an entirely inadequate adherence of the physicians to the pharmacological guidelines and a strong influence of the pharmaceutical companies over the medical prescriptions.

### **Authors' Statements**

#### *Competing Interests*

There were no financial support or relationships between the authors and any organization or professional bodies that could pose any conflict of interests.

### **References**

1. T.L.Pitcher, M. R. MacAskill, and T. J. Anderson, "Trends in Antiparkinsonian Medication Use in New Zealand: 1995-2011," *Parkinson's Disease*, vol. 2014, Article ID 379431, nine pages, 2014. doi:10.1155/2014/379431.
2. Neurologist Society of Albania; Ministry of Health, April 2016.
3. Health Insurance Institute; Ministry of Health.
4. Institute of Statistics; INSTAT Albania.
5. General Customs Directorate, Ministry of Finance, Albania.

6. Norwegian Institute of Public Health. Drug Consumption in Norway 2006-2010. Department of pharmacoepidemiology, Norwegian Institute of Public Health; <http://www.legemiddelforbruk.no>.
7. Estonian Statistics on Medicines 2006–2010. Ravimiamet State Agency of Medicines Copyright: Ravimiamet, 2010; ISSN 1736-5813.
8. Statistical Yearbook of the State Agency of medicines 2015, ISSN 2228-2300.
9. Finnish Statistics on Medicines 2007. National Agency for Medicines, Department of safety and drug information; ISSN 0786-2180.
10. Finnish Statistics on Medicines 2014. National Agency for Medicines, Department of safety and drug information; ISSN 0786-2180.
11. Gruppo di lavoro OsMed. L'uso dei farmaci in Italia. Rapporto nazionale anno 2007. Roma: Il Pensiero Scientifico Editore, giugno 2008.
12. Gruppo di lavoro OsMed. L'uso dei farmaci in Italia. Rapporto nazionale anno 2008. Roma: Il Pensiero Scientifico Editore, giugno 2009.
13. Gruppo di lavoro OsMed. L'uso dei farmaci in Italia. Rapporto Nazionale anno 2009. Roma: Il Pensiero Scientifico Editore, 2011.
14. Pierce JMS. Aspects of the history of Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, Special Supplement* 1989; 6-10.
15. Parkinson J. An essay on the shaking palsy, 1817. *J Neuropsychiatry Clin Neurosci* 2002; 14(2):223-236.
16. Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med* 2007; 356(1):29-38.
17. WB. Albania Health Sector Note. Report No. 32612-AL. Human Development Sector Unit; South East Europe country Unit; Europe and Central Asia Region; February 2006. Document of the World Bank.
18. Hollingworth SA, Rush A, Hall WD, Eadie MJ. Utilization of anti-Parkinson drugs in Australia: 1995–2009. *Pharmacoepidemiology and Drug Safety* 2011; 20: n/a. doi: 10.1002/pds.2114.
19. Grandas F, Kulisevsky J. Treatment of Parkinson's disease in Spain. *Mov Disord* 2003; 18(1):87-89.