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Antipsychotic Drugs Consumption in Primary Health Care in Albania During the 2004 - 2016 Period

Laerta Kakariqi¹, Gentian Vyshka²

¹Section of Pharmacology, Biomedical and Experimental Department, Faculty of Medicine, University of Medicine in Tirana, Albania, ²Biomedical and Experimental Department, Faculty of Medicine, University of Medicine in Tirana, Albania

Abstract - The era of new antipsychotics that started with Clozapine and the ever growing number of newly patented drugs have strongly influenced the pattern of drug use and consumption among psychiatric patients. Authors present a study aiming to assess exclusively the out-of-hospital antipsychotic drug consumption within Albania, during a period covering thirteen years [2004-2016]. Data were obtained from official sources [Health Insurance Institute] that registers and eventually reimburses all prescriptions in this field. Some outflows from the officially reimbursement scheme has been as well reported, due to circulating (but not yet registered) new drugs. A significant trend towards the decrease of consumption of old, typical antipsychotics is seen; in favour of new and modern drugs whose side effects profile is obviously a better one. Also, Albania has a lower figure of overall out-of-hospital antipsychotic usage when compared with other countries. Under-diagnosing and under-treatment might be some of the factors leading to such a fact, together with accessibility of psychiatric care and society stigma that still deeply impregnate the today Albanian society.

Keywords: antipsychotics, out-of-hospital care, psychosis, morbidity, atypical antipsychotics

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Introduction

Antipsychotics represent a variegated family of active principles, aiming to reduce positive symptoms of a psychosis (among other hallucinations, agitation and combativeness) as well as negative ones (such as social isolation

and emotional flatness). Humanity has ever since its written history exists, attempted to influence thought and behaviour, but ancient medicine had at hand exclusively plant by-products (opiates, cannabis) that generally produced sedation and induced sleep, without modulating the extorted perspective / perception of life, such as encountered during psychosis.

The chance discovery of chlorpromazine in 1951 and the wide usage of this drug

Correspondence to:
Gentian Vyshka, MD, PhD
Section of Pharmacology, Biomedical and Experimental
Department, Faculty of Medicine, University of Medicine
in Tirana, Albania
E-mail: gvyshka@gmail.com

thereafter in a diversity of psychic disorders opened the door of an ever growing pharmaceutical research, that gave birth to a new generation of antipsychotics with larger efficacy, and less side effects [1,2]. The psychiatrists obviously started shifting their therapeutics from typical to the so-called atypical, new and modern antipsychotics in a trend that seems universal [3].

Studying the trend and characteristics of antipsychotic usage in a population will have to consider several aspects of drug availability, access to psychiatric care and generally speaking, the overall public health situation. Denial of psychiatric issues, related to an overinflated ideology, have been common to totalitarian regimes [4]. However, history differs largely enough to render impossible any comparison in between usage of antipsychotics during certain time frames; not only antipsychotics are available only since a few decennia, but the consumption is influenced from many factors, such as population ageing [5,6].

The present study aims at describing the pattern of antipsychotic consumption in Albania, in an outpatient population and for a period covering thirteen years; similar studies performed in neighbouring countries will facilitate comparisons and possibly the creation of a larger, regional perspective [7,8].

Materials and methods

The study aimed to assess the out-of-hospital antipsychotic drugs use in Albania during the period 2004-2016. The data were obtained from the Health Insurance Institute, (HII) [9]. All data were collected for the period 2004-2016 and analysed. The analysis included the total number of prescriptions made and quantities of drugs used.

The data about the population were obtained from the Institute of Statistics (IN-STAT) [10]. The data about the consumption of drugs were expressed as a number of Defined Daily Dose (DDD_s)/1000 inhabitants/day. All drugs were classified by groups of Anatomic Therapeutic Chemical Classification (ATC).

Data on real consumption (import and domestic production)

For all the period under study 2004-2016 there were collected and analysed data from the import and domestic production of the drugs, which represent the real consumption of drugs in the country [11]. It was noted that the increase in consumption from one year to another was small, e.g. the consumption from 2013 to 2016 (i.e. 3 years) was increased by only 1.68%. Consequently, in order to obtain an updated study, the data of import and domestic consumption were chosen only for the last three years, 2014-2016, and those were involved in a comparative analysis with the equivalent consumption data according to HII. In order to minimize the effect of variations between consumption and stock inventory balances from one year to another, it was calculated and put to analysis the annual average value of the three chosen years (on one hand that of the import and domestic consumption, and on the other hand that of HII).

Presentation of the results and statistical elaboration

The statistical elaboration of the obtained results was conducted with the statistical package StatsDirect (version 2.7.2.). A descriptive statistic was used to report all data on drugs consumption and the results ob-

tained 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 2004-2016. The linear regression model was used to evaluate the trends of consumption of drugs relative to the time. A value of $p \leq 0.05$ was considered significant.

In order to assess if there exists a correlation statistically significant between the level of consumption of drugs and the level of morbidity, the Spearman correlation was applied (with a significance level of ≤ 0.05).

Results

The data were expressed as a number of defined daily doses per 1000 inhabitants/day (DDD/1000). The consumption of antipsy-

chotic drugs were 2.19-3.49 DDD/1000 inhabitants/day respectively during the period 2004-2016. The most prescribed are the atypical antipsychotics with values of 0.59-1.79 DDD/1000 inhabitants/day (2004-2016). The new generation drugs included are risperidone, clozapine, and olanzapine. Meanwhile the typical antipsychotics consumption was 1.60-1.70 DDD/1000 inhabitants/day.

Psychosis morbidity data indicate that there exists a correlation statistically significant between number of cases of the disease and DDD/1000 inhabitants/day of antipsychotics [$p = 0,0014$] (Figure 1). For the Atypical Antipsychotics: $p=0,0005$; strength (with significance level $\leq 0,05$) = 97,43%; correlation coefficient statistically significant; for the Typical antipsychotics: $p=0,9815$; strength (with significance level $\leq 0,05$) = 2,63%; correlation coefficient is not statistically significant.

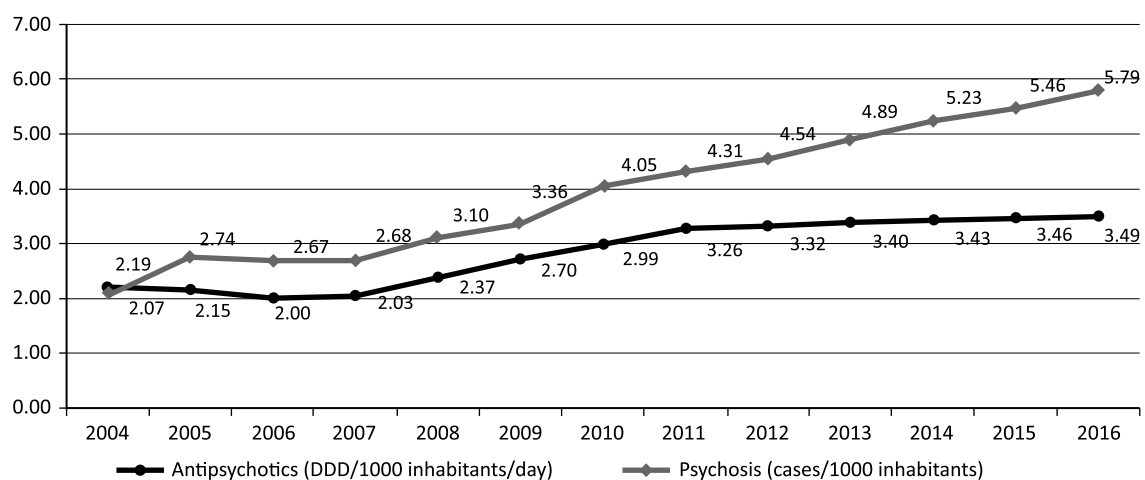


Figure 1. Consumption of Antipsychotics at national level (DDD/1000 inhabitants/day) versus Psychosis morbidity (cases/1000 inhabitants).

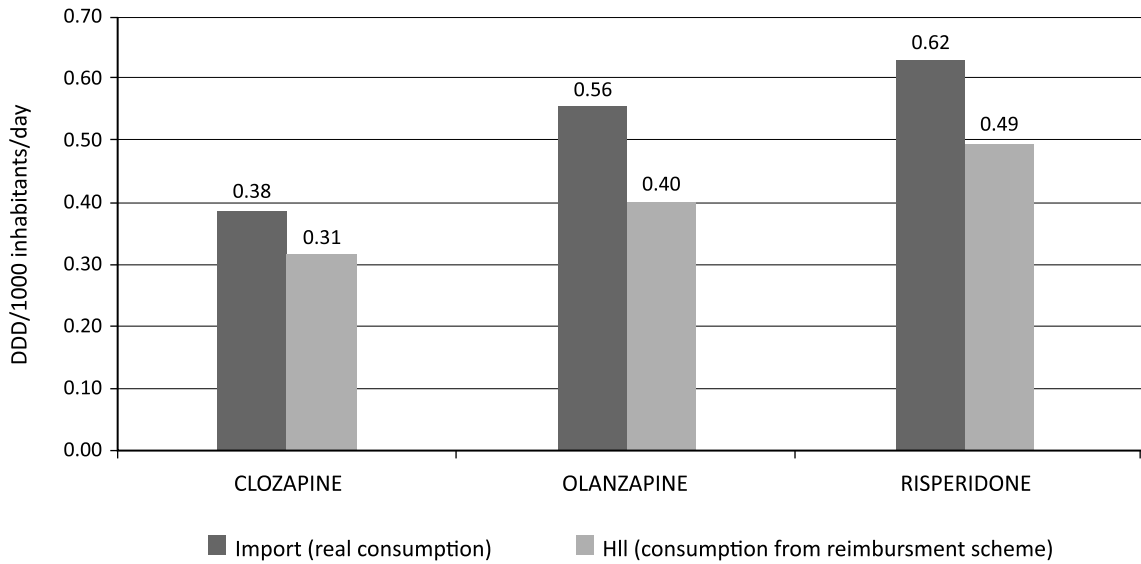


Figure 2. Annual average value of consumption of Atypical Antipsychotics: consumption based on import (real consumption) [*] versus consumption based on HII.

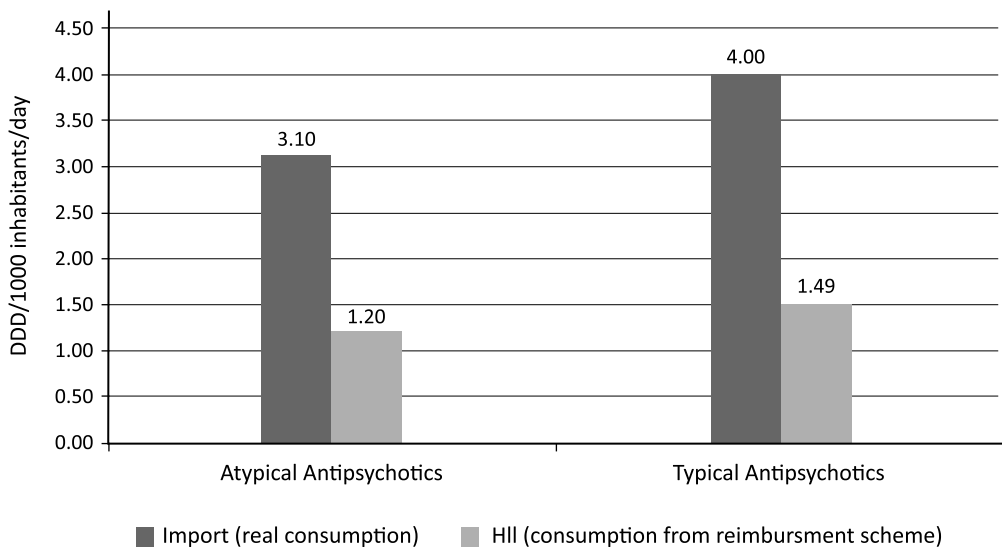


Figure 3. Annual average value of consumption of Typical and Atypical Antipsychotics: consumption based on import (real consumption) versus consumption based on HII.

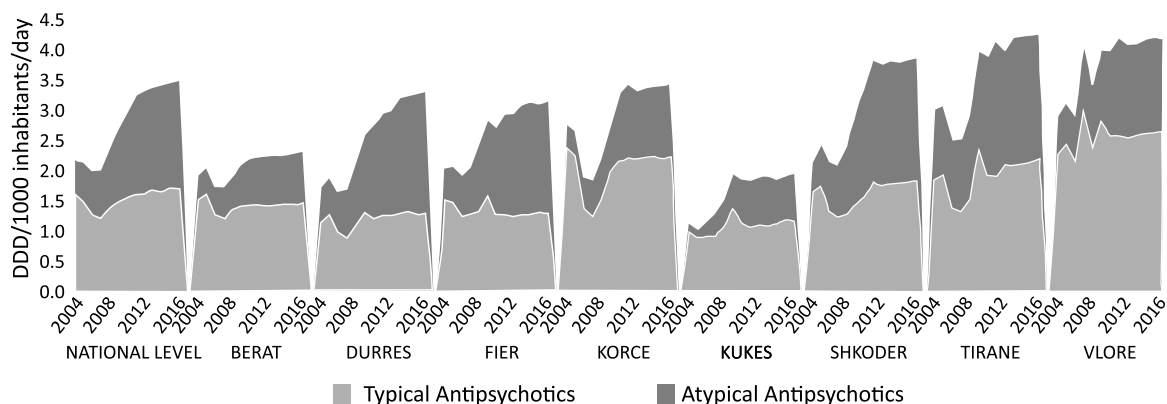


Figure 4. Consumption of typical and atypical antipsychotics in different regions and at the national level (DDD/1000 inhabitants/day). At a national level ($p = 0,0004$; strength (with significance level $\leq 0,05$) = 98,7%; correlation coefficient is statistically significant).

Figure 2 represents the comparison import-HII in the consumption of some atypical antipsychotics. Around 20-30% of the consumption flows out of the scheme. For clozapine ($p = 0,1097$; strength (with significance level $\leq 0,05$) = 35,05%; correlation coefficient is not statistically significant). For olanzapine: $p = 0,0421$; strength (with significance level $\leq 0,05$) = 53,6%; correlation coefficient is statistically significant. For risperidone: $p = 0,1618$; strength (with significance level $\leq 0,05$) = 27,62%; correlation coefficient is not statistically significant. The “Import” item includes the consumption based on import data as well as the consumption based on domestic production: this represents the factual consumption.

Figure 3 represents the comparison in the consumption of typical and atypical Antipsychotics. The consumption is based on import (real consumption) versus consumption based on HII. There is an evident difference

between imports – HII, leading to the conclusion that only 40% of the consumption of antipsychotics is covered by the scheme. For the Atypical Antipsychotics ($p = 0,1097$; strength (with significance level $\leq 0,05$) = 35,05%; correlation coefficient is not statistically significant). for the Typical antipsychotics: $p=0,9724$; strength (with significance level $\leq 0,05$) = 2,65%; correlation coefficient is not statistically significant). The “Import” item includes the consumption based on import data as well as the consumption based on domestic production: this represents the factual consumption.

Figure 4 represents the consumption of typical and atypical antipsychotics in different regions and at the national level (DDD/1000 inhabitants/day).

Figure 5 represents the international comparison in the consumption of antipsychotic drugs class (DDD/1000 inhabitants/day).

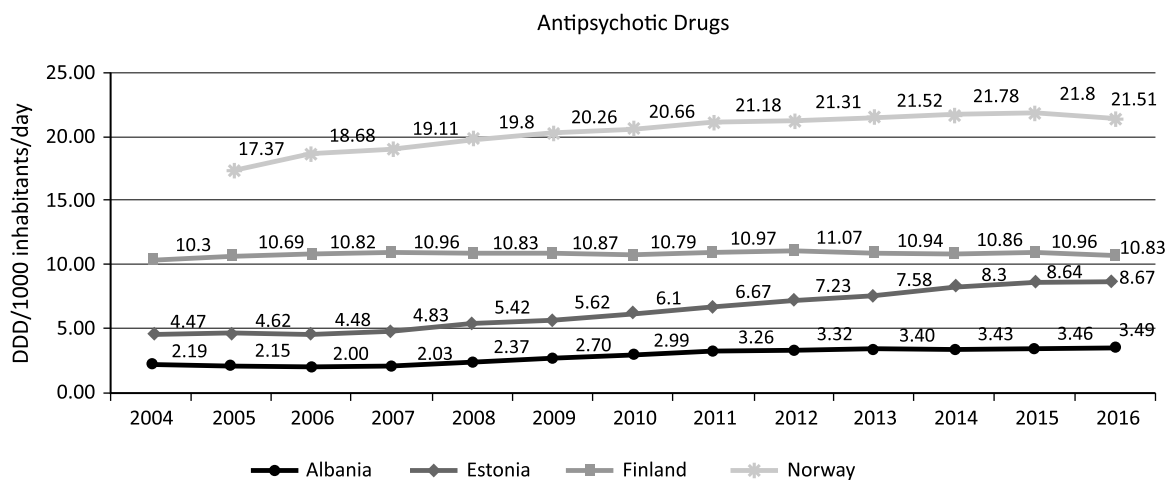


Figure 5. International comparison in the consumption of anti-psychotic drugs class (DDD/1000 inhabitants/day): Albania, Estonia [12-14], Norway [15-17], Finland [18-20].

Discussion

Figure 1 shows clearly that the morbidity and consumption of antipsychotics have the same increasing trend, but from 2005 and onwards it is evident that a non-minor fraction of the psychotic patients are not treated within the scheme. The non-compliance in the relationship morbidity – treatment under the scheme becomes again evident.

Attempting to obtain a deeper understanding of what has really happened and taking into consideration the specifics of the new generation of antipsychotic drugs – that are expensive ones – we included in the analysis the import data (which represent the real consumption), by comparing the average annual value of consumption of antipsychotic drugs from imports with the equivalent value reported by the HII.

Figure 2 presents the comparison import-HII in the consumption of some atypical antipsychotics, which factually are the only ones included in the reimbursement scheme. We note that around 20-30% of the consumption flows out of the scheme. Meanwhile, in the domestic pharmaceutical market circulate other new antipsychotics, consumed out of the scheme, such as piperazine, quetiapine, sulphiride.

A possible reason of this flow out of the scheme may be the fact that the scheme does not sufficiently cover the indispensable alternatives of treatment of psychotic disorders. Another noticeable fact is that, according to HII's protocol, the maintenance dose for olanzapine is recommended at 5 mg/day, whereas the international therapeutic guidelines recommend daily maintenance dose of 5 to 20 mg in one taking or split between a

few meals. HII recommends maintenance dose for risperidone of 3 mg/day, whereas the international therapeutic guidelines recommend a daily maintenance dose of 3 to 5 mg [21]. Hence, it can be clearly noted the propensity to a therapeutic treatment with diminished doses, which can result deficient.

On the other hand, based on HII's protocol, the prescription of the new generation of antipsychotics (atypical) should be limited only to cases of schizophrenia resistant to classic antipsychotics. In these circumstances, obtaining these drugs through the scheme becomes difficult. In Figure 3, the difference imports-HII is even more evident, concluding that only 40% of the consumption of antipsychotics is covered by the scheme.

With the launch in the market of the new generation of antipsychotics (atypical) in the mid 90's, this new group has widely substituted antipsychotics of the first generation (classic) as a chosen therapy for disorders of psychotic nature [22]. These drugs are characterized by a higher security profile and their broad use has reduced significantly the need for hospitalization of psychotic patients [23].

The consumption of antipsychotic drugs is subject to changes and refractions from year to year in nearly all regions (Figure 4), a result not consistent with the natural increasing trend of psychotic morbidity. The minimum consumption is noted in Kukës throughout all years under study. High values of consumption for this class are noted in Tiranë, Vlorë, Korçë since in 2004. In 2006, there is a reduction of consumption for all regions, and subsequently a gradual increase. The fact that this occurrence in 2006 is reflected in the majority of classes, it can be related to the increase of restrictions in prescription determined by HII.

Vlora region draws particular attention due to the high consumption values (it is the region with the maximum consumption values for the class in years 2007 and 2009). This occurrence may be explained with the presence in this region of a psychotic service center with a long experience. It needs to be emphasized though that this is the only class of drugs that achieves high consumption values in Vlora, a region that as outlined above, is characterized by a low consumption of all other therapeutic classes.

At the national level, the consumption of antipsychotic drugs undergoes a discrete increase of 36.94% (from 2.19 to 3.49 DDD/1000 inhabitants/day during the period 2004-2016), which is lower than the increase that would be expected based on the data on psychotic morbidity during the same period which show an increase of 96.05%, almost the double (from 2.07 to 5.79 cases/1000 inhabitants).

In the list for this class dominate typical antipsychotics as compared to atypical antipsychotics (the new generation), including clozapine, olanzapine and risperidone. It can be noted a non-consistency in the trend of consumption of these two antipsychotic generations: there is only a small increase in the consumption of typical (old) antipsychotics of 6.01% (from 1.60 to 1.70 DDD/1000 inhabitants/day, 2004-2016) while there is an evident increase of the consumption of the new generation from 0.59 to 1.79 DDD/1000 inhabitants/day, 2004-2016).

This movement in consumption towards atypical antipsychotics is clearly reflected also in the prescription trends (DDD%) for each antipsychotic alternative.

A decrease can be noted, in certain cases even drastic, in the prescription of old anti-

psychotics. As such, the prescription of haloperidol falls from 22.43% to 14.11% during the period 2004-2016. Furthermore, thioridazine, fluphenazine, chlorpromazine have been prescribed 2-3 times less during this period. On the other hand, there is a burst of prescriptions of the new generation: e.g. the prescription of olanzapine increased from 4.07% to 18.10%; of clozapine from 7.20% to 11.77%.

This polarization in the consumption of antipsychotics is a phenomenon observed in many countries. During the last decade, the therapeutic treatment of schizophrenia and psychotic syndromes has been subject to changes with the launch in the market of atypical antipsychotics (generation II). In different international therapeutic guidelines, the new antipsychotics are considered as the first therapeutic choice in the treatment of schizophrenia, taking into account that these drugs offer a more favorable security profile as compared to old antipsychotics [24,25].

Several studies have reported that the use of the new generation is accompanied with a notable reduction in the appearance of extrapyramidal side effects, although on the hand, there is an increasing concern related with side effects in the metabolic sphere, including diabetes, dyslipidemia and obesity [26,27].

Other studies demonstrate that atypical antipsychotics have higher efficacy in the prevention of re-occurrence of psychotic crisis, very low risk of extrapyramidal effects and superior adherence of patients to the therapy. However, the debate on the cost-efficacy ratio of these drugs in ongoing one [28,29]. From this perspective, regardless of their high direct cost, these drugs offer a more favorable long term cost-efficacy ratio, since they reduce significantly the suffering that

this pathology causes to the individual, his family, the society, as well as the economic cost related to the hospitalization of patients.

While sketching international comparisons (Figure 5), a common feature for all countries is the movement in prescription and consumption towards the new generation, accompanied by a decrease in consumption of classic antipsychotics. Regarding the values of such consumption, we may again conclude that in Albania, these drugs are consumed a few times less as compared to the majority of other countries, leaving room to assume that there is maybe an under-diagnosis and under-treatment of psychotic disorders in our country.

Many factors might influence this fact; with the main finding that suggest a much lower consumption of antipsychotics in comparisons with other countries. Authors have performed comparisons with northern European countries and found significant changes; although the trend of consumption has increased recently, figures are still below average values. This might be true even when comparisons are made within neighboring countries. Worth mentioning as well is the impressive decrease in the consumption of old-generation antipsychotics in favor of the atypical ones. The ever-changing drug market the availability of some new principles that are used off-label or unregistered, and the flow of surrogate medications out from the reimbursement scheme represent some of the limitations of the findings disclosed in the present study. The demographic changes might have also their say in the overall consumption data, as long as newly approved drug indications will enlarge the scope of use of antipsychotics in an ageing population, especially for people with dementia [30].

Conclusions

Different particularities in the overall out-of-hospital antipsychotics consumption inside Albania are found during the period of study (2004-2016). Of interest would be the extension of this study among in-patient consumers, i.e. inside hospital facilities, where until recently the pharmacological treatment

was mostly based on old, typical antipsychotics.

Acknowledgements

None.

Conflicts of interest

None to declare.

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Potrošnja antipsihotika u primarnoj zdravstvenoj zaštiti u Albaniji od 2004. do 2016. godine

Sažetak - Razdoblje novih antipsihotika koje je započelo s klozapinom i sve većim brojem novopatentiranih lijekova snažno je utjecalo na obrazac uporabe i korištenja lijekova u psihijatrijskih pacijenata. Istraživači predstavljaju istraživanje čiji je cilj procijeniti isključivo izvanbolničku potrošnju antipsihotika u Albaniji u razdoblju od trinaest godina (2004-2016). Podaci su dobiveni iz službenih izvora (Zavoda za zdravstveno osiguranje) koji registriraju i u konačnici pokrivaju trošak svih propisanih lijekove u ovome području. Objavljeni su i određeni odljevi iz sustava službene nadoknade troškova, a zbog korištenja novih (no ne i registriranih) lijekova. Primijećen je značajan trend smanjenja potrošnje starih, tipičnih antipsihotika; u korist novijih i modernijih lijekova čiji je profil nuspojava očigledno bolji. U usporedbi s drugim državama, Albanija ima niže brojke ukupnog izvanbolničkog korištenja antipsihotika. Nedovoljno dijagnosticiranje i liječenje mogli bi biti neki od čimbenika koji objašnjavaju takvo stanje, zajedno s pristupačnošću psihijatrijske skrbi i društvenom stigmom koja je i danas duboko ukorijenjena u albansko društvo.

Ključne riječi: antipsihotici, vanbolnička njega, psihoza, morbiditet, atipični antipsihotici

