

Therapeutic Combinations in Psychiatric Disorders, a Descriptive-Retrospective Study in Korçë, Albania

Linda Matua*, Maria Koroveshi

Department of Pharmacy, Faculty of Medicine, University of Medicine Tirana, Albania

Abstract

Background: Only few studies have reported results on drug prescribing for psychiatric disorders in Albania.

Aim: The aim of this study is to evaluate the therapeutic combinations of the drugs most commonly used to treat psychiatric disorders, as well as to evaluate their safety and tolerability by comparing them to monotherapy.

Methods: This is a retrospective descriptive study that included patients who have received treatment from 2016 to 2021 for a psychiatric disorder at two different health centres in the city of Korçë, Albania. The data collected from the medical databases of patients in three neighbourhoods were analysed. Patients were categorized into groups: by age (age group 0-30

years; 31-60 years; over 60 years), by method of treatment (monotherapy and polytherapy), by the type of therapeutic combination administered, and by visits to specialists.

Results: Out of 83 patients from three different neighbourhoods who received treatment for a psychiatric disorder, 46 of them (55.4 %) were male. The most common diagnosis was psychotic disorder. The most commonly used drugs were antipsychotics, followed by antidepressants, mood stabilizers and anxiolytics. Only 18 (21.7%) of the patients had received only one psychotropic drug as monotherapy, while the majority, 65 (78.3 %) had been treated with two or more psychotropic drugs for longer than 3 months. The most common combinations were:

risperidone with fluvoxamine, olanzapine with fluvoxamine, risperidone with carbamazepine and risperidone with chlordiazepoxide. Patients treated with polytherapy complained significantly more ($p = 0.0085$) about side effects compared to patients receiving monotherapy, respectively, 10.8 % vs 5.6 % of arrhythmia, 9.2% vs 5.6 % of constipation, 13.9 % vs 11.1 of visual disturbances and 16.9% vs 11.1 of sleep disorders. Also, it was found that 25.0 % of patients who were treated with two antipsychotic drugs, received a treatment with an anticholinergic due to the extrapyramidal effects shown. In contrast, among patients treated with monotherapy, this figure resulted 11.1%. Overall, 25 patients (30.1 %) have had a check-up at the cardiologist, 16 (19.3 %) at the ophthalmologist and 8 (9.6 %) at the endocrinologist.

Conclusion: After analysing the data for these patients in retrospect, it is strongly implied that the administration of two or more psychotropic drugs simultaneously to the same patient is a risk factor for increased side effects. It was observed that the treatment with more than one antipsychotic drug is associated with increased chances of appearance of extrapyramidal effects.

Keywords: Psychiatric disorder, psychotropic drugs, polytherapy, monotherapy.

INTRODUCTION

There are several situations in psychiatric clinical practice where the medical staff considers that the administration of a single medication is not effective. The treatment of specific symptoms, the treatment of two distinct diseases in the same patient or of the side effects produced by a primary drug are some of the reasons for prescribing two or more psychiatric drugs. Polypharmacy has been an approach that doctors have been using in difficult circumstances for a long time. However, its suitability began to be studied very late. This therapeutic option is accompanied by limited data of the safety and efficacy of psychotropic drugs used in combination ().

A number of high-quality trials and systematic reviews have shown that collaborative care is more effective than standard care for depression and anxiety, is cost-effective when compared with usual care, and has positive effects in terms of case detection, treatment offer, clinical outcomes and patient satisfaction ().

There is evidence that patient-centered communication impacts positively on patient outcomes such as recovery and emotional health. For example, people with personality disorder often require multiagency input because of their multiple needs and attachment styles ().

A significant trend towards the decrease of consumption of old, typical antipsychotics is seen; in favor 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 (4). However, the prevalence of potentially inappropriate prescriptions of psychotropic drugs is comparable to other studies in Europe (5). New drugs and formulations have been introduced recently for the treatment of nervous system disorders such as anticholinergics (donepezil, rivastigmine, ipidacrine) (6).

The purpose of this study was to evaluate the therapeutic combinations of the most frequently used drugs to treat psychiatric disorders, as well as to evaluate the safety and tolerability of different combinations. We aimed to conduct a statistical evaluation of the demographic data of the patients included in this study: on the prevalence of some psychiatric disorders by sex and by age, on the most commonly used drugs, and on the therapeutic combinations most commonly used for the management of some psychiatric disorders.

We aimed to identify and statistically evaluate the adverse effects displayed in patients who have been treated or are continuing treatment with more than one psychotropic drug.

Another objective of our study was the evaluation of follow-up visits to the psychiatrist and other specialist doctors by the patients included in the study.

We also intended to compare the conclusions drawn from this study regarding the safety of different therapeutic combinations used in the treatment of some psychiatric disorders with the conclusions of other similar studies previously

conducted in different countries in Europe and worldwide.

MATERIAL AND METHODS

According to demographic data, in 2021 the city of Korçë had 155,613 inhabitants. In the district of Korçë, there are 19 Health Centers and 15 of them belong to rural areas. The different neighborhoods of the city are grouped in 4 regions, so there are 4 Health Centers.

In this study we included 8051 inhabitants from three different neighborhoods of the city, respectively number 7, 10 and 18. The medical records of patients who have received treatment for psychiatric disorders over a period of 5 years (January 2016 – January 2021), as well as the register of referrals to the psychiatrist were consulted. The data were obtained from two different Health Centers in order to increase the degree of randomization in cooperation with the medical staff of these centers.

Study design is descriptive retrospective with analytical component. The inclusion criteria were: patients with a diagnosis of psychotic disorders, affective disorders, anxiety disorders, personality disorders, and patients treated by the family doctor for a psychiatric disorder. Among the exclusion criteria were: patients diagnosed with eating disorders, obsessive-compulsive disorders, post-traumatic stress disorders, and patients being treated privately.

For the purposes of the study, patients were categorized by age into three main groups:

patients aged 0-30 years, 31-60 years, and more than 60 years.

Another categorization was done by gender.

Patients were classified according to the diagnosis for which they were treated.

Also, for the main purpose of the study, depending on the treatment, patients were divided into two groups: group I included all patients who have been treated with monotherapy alone, which have received only one type of psychotropic drug throughout the time period included in the study; group II included patients who have been treated with polytherapy, that have received two or more psychotropic drugs simultaneously for a period of at least three months. Patients in this group were categorized into 3 subgroups:

- First subgroup included patients who have been treated with only 2 psychotropic drugs for a period of at least 3 months.
- Second subgroup included patients who have been treated with 3 psychotropic drugs for a period of at least 3 months.
- Third subgroup included patients who have been treated with more than 3 psychotropic drugs for a period of at least 3 months.

Based on the complaints of patients referred to the family doctor, patients who showed side effects during treatment during the studied period were identified.

Based on the objectives, another classification of patients was made according to the type of therapeutic combination administered.

Depending on the examinations performed at the

specialist doctors, a categorization was made for:

- Patients who have undergone a check-up with a specialist during the study period.
- Patients who did not have a check-up by a specialist during the study period.

The time interval of periodic check-ups at the psychiatrist was assessed.

The statistical analysis was performed by comparing the sizes using Student's test (T test). A value of p less than 0.05 was considered statistically significant.

RESULTS

After consulting medical records of patients who have received pharmacological treatment during five years (2016 – 2021) for one of the psychiatric disorders included in the inclusion criteria, a total of 83 patients were identified (10.3%). Of these 83 patients, 46 were male (55.4 %).

The distribution of patients by age groups was as follows:

- Age group 0-30 years = 5 patients (6.0%)
- Age group 30-60 years = 43 patients (51.8%)
- Age group > 60 years = 35 patients (42.2 %)

The distribution of patients by type of pathology is shown in Figure 1.

Most prescribed medications

The most frequent psychotropic drugs prescribed in the medical files turned out to be: antipsychotics prescribed to 56 patients (67.5 %); antidepressants prescribed to 49 patients (59.0%); anxiolytics prescribed to 42 patients (50, 6%) and mood stabilizers in 30 patients (36.1%)

Types of therapies

Of all patients, just 18 of them (21.7 %) were treated only with monotherapy (have received only 1 psychotropic drug) and 65 of them (78.3%)

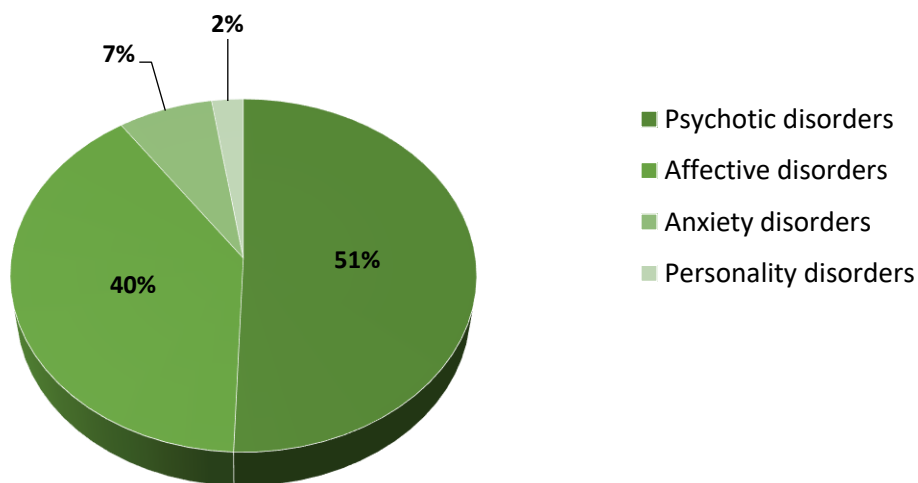


Figure 1. Distribution of psychiatric pathologies among patients included in the study.

were treated with polytherapy (have received more than 2 concomitant psychotropic drugs, for a period of more than 3 months). Of these patients, 28 were treated with dual combination (33.7% of patients), 27 were treated with triple combination (32.5%) and 10 remaining (12.0%) were treated with more than 3 psychotropic drugs for a period of at least 3 months.

the combination of haloperidol with olanzapine present in 5 patients, the combination of clozapine with haloperidol in 3 patients, olanzapine with clozapine in 2 patients, levomepromazine in 2 patients, olanzapine with risperidone in 2 patients and clozapine with risperidone in 1 patient.

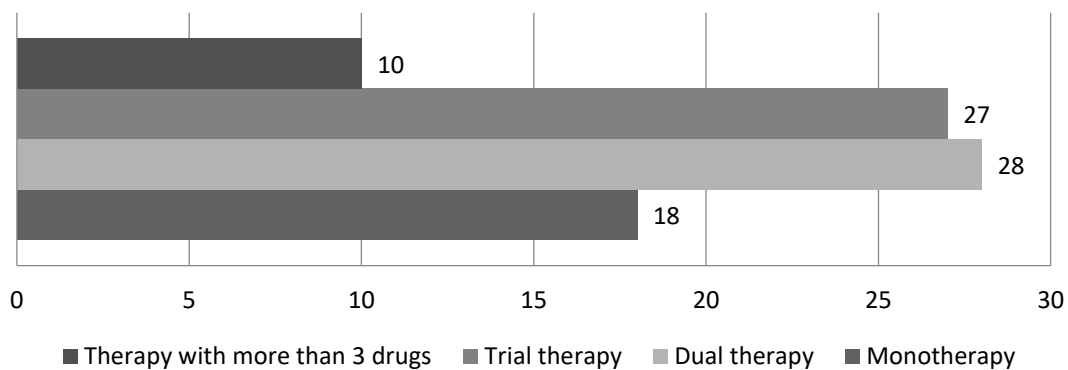


Figure 2. Distribution of types of therapy among patients included in the study.

Combinations of antipsychotics

Among the antipsychotics, the most used resulted to be risperidone, given to 32 patients. It was followed by olanzapine and haloperidol, which were taken by 23 patients each, clozapine taken by 10 patients, levomepromazine by 8 patients, fluphenazine by 2 patients, thioridazine and quetiapine by 1 patient.

Of all patients who received antipsychotic treatment, 22 received combination treatment with two antipsychotics, for a period of at least 3 months.

The most common combination was that between haloperidol and risperidone reported in 8 patients,

Comparison of the side effects of polytherapy and monotherapy

To assess the incidence of extrapyramidal effects in patients treated with 2 antipsychotics compared with patients treated with only 1 antipsychotic, data on additional treatments that patients may receive for the treatment of these effects were analyzed. From the patients treated with monotherapy, 4 of them were treated with an anticholinergic drug (trihexyphenidyl). Out of 20 patients treated with polytherapy, 5 of them receive this medication. When we calculate the percentage, it turns out that 11.11% of patients treated with an antipsychotic drug and 25% of

patients receiving 2 antipsychotics, were also treated with 1 anticholinergic drug.

Combinations of antidepressants

Of all the patients treated with antidepressants, none of them received more than one antidepressant drug at the same time for more than three months. The most commonly used antidepressant was fluvoxamine, given to 34 patients. It was followed by fluoxetine in 17 patients, amitriptyline in 9 patients, clomipramine in 8 patients, escitalopram in 5 patients, paroxetine and maprotiline in 1 patient. A total of 64 combinations between an antipsychotic drug and an antidepressant were used in 83 patients.

In 13 patients who were initially treated with clozapine or risperidone, and during the study period an antidepressant such as fluvoxamine or fluoxetine was added to the treatment, while only in 2 of them the dose of the antipsychotic was changed (reduced).

Combinations of mood stabilizers

The most common mood stabilizer was valproic acid, prescribed to 17 patients. Then it was followed by carbamazepine given to 16 patients, lithium given to 3 patients and lamotrigine given to 2 patients.

Of the 30 patients treated with mood stabilizers, 2 of them received lithium-valproic acid combination and 3 patients received valproic acid-carbamazepine combination. Of the 3 patients receiving valproic acid-carbamazepine

combination, no dose of carbamazepine was changed.

The combination clozapine-carbamazepine was given in none of the patients. No patient was given lithium concomitantly with any antidepressant. Four patients received valproic acid in combination with an antidepressant: 3 with fluvoxamine, and 1 with escitalopram. 17 patients received carbamazepine in combination with an antidepressant: 8 with fluvoxamine, 5 with clomipramine, 3 with fluoxetine and 1 with amitriptyline. No dose adjustment was made in any of the patients treated with carbamazepine after the antidepressant was added. Only 1 patient received lamotrigine in combination with fluvoxamine.

Combinations of benzodiazepines

The most commonly prescribed benzodiazepine was chlordiazepoxide, prescribed in 23 patients. It was followed by lorazepam and diazepam, given to 17 patients each, alprazolam and clonazepam given to 6 patients each, and lormetazepam given to 3 patients.

None of the patients was given 2 benzodiazepines at the same time. It was observed that out of 42 patients who received benzodiazepines, combined or in monotherapy, 30 of them continued to take them for a period longer than 3 months.

Combinations of risperidone with benzodiazepines were present in 22 patients, where the combination with chlordiazepoxide, given in 10 patients predominated. Combinations

of haloperidol were prescribed in 10 patients, olanzapine in 8 patients, clozapine in 3 patients and levomepromazine in 2 patients.

No combination of lithium with benzodiazepines was identified. Valproic acid combinations were 7, while carbamazepine 14.

Most common side effects

From the comparison by Student's test (T test) for the presence or absence of side effects in patients with polytherapy and monotherapy, it resulted $p = 0.0085$ (less than 0.05) which means that the comparison is statistically significant.

Follow-up visits to the specialists

Out of 83 patients treated for a psychiatric disorder at the family doctor, 25 of them had a check-up at the cardiologist within the included period of the study. 16 patients had a check-up at the ophthalmologist and 8 patients had a check-up at the endocrinologist.

Periodic examinations to the psychiatrist

Periodic visits to the psychiatrist were registered in 3-month, 6-month and 1-year periods. The frequency of intervals between check-ups performed by patients is given in the table 1 below.

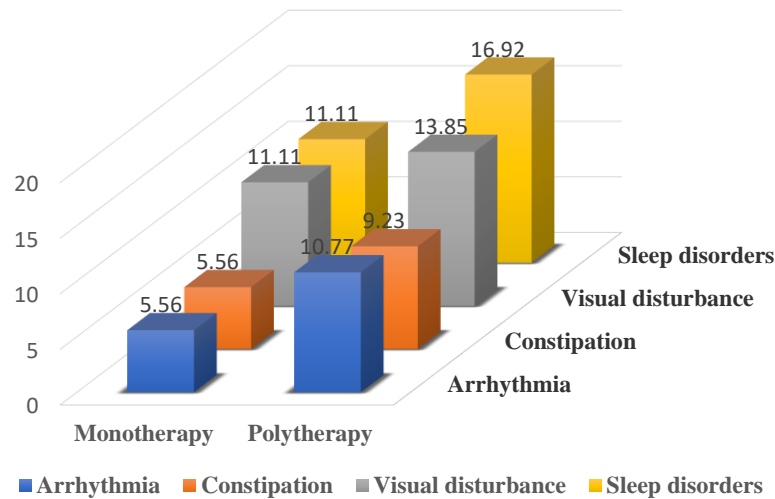


Figure 3. Frequency of side effects in patients with monotherapy and polytherapy.

Table 1. Frequency of intervals between check-ups to the psychiatrist.

<i>Period between controls</i>	<i>Frequency</i>
3 months	67%
6 months	21%
1 year	12%
	Total: 100%

1-year recommendations to the specialist doctor, to the extent of 82% belonged to the age group older than 60 years old.

DISCUSSION

Of the 83 patients included in our study, the incidence of side effects was higher in patients treated with polytherapy than in those who received monotherapy. In a systematic review by Gallego et al it was observed that the use of polytherapy (7) led to an increase in side effects such as: cardiovascular disorders (QT segment lengthening), weight gain, increased sedation and drowsiness, hyperprolactinemia etc. This study report included several parallel studies conducted in several psychiatric hospitals in the US and Denmark and at the Psychiatric University in Belgium. All were aimed at identifying side effects in patients treated with polytherapy compared to those treated with monotherapy. Similarly, in our study it was found that the incidence of side effects such as: arrhythmia, constipation, vision disorders or sleep disorders was higher in patients treated with polytherapy compared to those treated with monotherapy.

A study conducted in the USA (8) evaluated the effects of using multiple therapies with antipsychotics in hospitalized patients, where the focus was placed especially on the incidence of various side effects. It was observed that 30% of patients treated with polytherapy showed extrapyramidal effects, mainly dyskinesia, bradykinesia and akathisia. Whereas in patients treated with only one drug, 24.3 % of them showed these effects. In our study, 25.0 % of patients treated with 2 antipsychotics received treatment with an anticholinergic drug. Of the patients treated with only one drug, only 11.11 % of them received this treatment.

According to the Findings from Global Burden of Disease, 2017 in the United States of America, where it was included the entire global population, about 792 million (10.7 %) of the world's population suffered from a mental disorder, 9.3 % of men and 11.9 % of women. The most common was anxiety disorder that affected 3.8 % of the population. (9) In our study it was found that 10.3 % of the study population suffered from a psychiatric disorder. Of these, the most common diagnosis was psychotic disorder in 50.6 % of patients suffering from psychiatric

illness. This is because anxiety disorders are a pathology that often goes untreated. In terms of distribution by gender it was observed that the majority were male (55.4 %) compared to females (44.6 %).

The Agency for Healthcare Research and Quality (AHRQ) compiles data on the use and cost of health services, including prescription medications. These were the most prescribed psychiatric medications for 2020. (10) The most used drug was sertraline, followed by escitalopram, bupropion, fluoxetine, trazodone, venlafaxine etc whereas from antipsychotic class most frequent prescribed drugs were quetiapine and aripiprazole. In our study, the most used drug is fluvoxamine, followed by risperidone, chlorthalidone, olanzapine, haloperidol and so on. Some drugs such as aripiprazole or bupropion were not prescribed at all and some others such as escitalopram were given very little, compared to the data of AHRQ. The reason for this is thought to be the fact that these drugs are not included in the reimbursement scheme, as well as their high cost. (11)

A multinational study (12) was conducted in several Eastern European countries, including: Croatia, Romania, Serbia, Macedonia and Albania. According to that study regarding treatment schemes of patients admitted to psychiatric hospitals in these countries, it was concluded that only 6.8 % of patients admitted to these hospitals were treated with only one psychotropic drug, 26.5 % received 2 psychotropic drugs, whereas 42.1 % were treated

with 3 drugs and 22.1 % with more than 3 drugs. In comparison, in our study 21.7 % of patients receiving treatment for psychiatric disorders were treated with monotherapy, 33.7 % were treated with 2 drugs, 32.5 % with 3 drugs and 12.0 % with more than 3 drugs. There is a similar observed pattern of prescription among the studies related to psychiatric medications.

Despite the small sample of patients included in our study, which in fact reflect the extent of prescribing psychiatric drugs in a city in Albania, we provide valuable and important data on therapeutic combinations of drugs in psychiatric disorders and their related side effects.

CONCLUSIONS

Based on the obtained results we conclude that polytherapy in psychiatry poses an increased risk for side effects compared to monotherapy. Further studies in other cities of Albania are necessary to comprehensively evaluate the associated side effects of combination therapies in psychiatric disorders and generalize recommendations on a national level.

Acknowledgements: None declared.

Conflict of Interest Statement: The authors declare that they have no conflict of interest.

REFERENCES

1. Kukreja S, Kalra G, Shah N, Shrivastava A. Polypharmacy in psychiatry: a review. *Mens Sana Monog* 2013;11(1):82-99.
2. Saraiva S, Bachmann M, Andrade M, Liria A. Bridging the mental health treatment gap: effects of a collaborative care intervention (matrix support) in the detection and treatment of mental disorders in a Brazilian city. *Family Medicine and Community Health. BMJ* 2020;8(4):e000263.
3. Patel D, Konstantinidou H. Prescribing in personality disorder: patients' perspectives on their encounters with GPs and psychiatrists. *Fam Med Community Health* 2020;8(4):e000458.
4. Kakariqi, L. i Vyshka, G. (2020). Antipsychotic Drugs Consumption in Primary Health Care in Albania During the 2004-2016 Period. *Archives of Psychiatry Research*, 56 (2), 169-180. <https://doi.org/10.20471/dec.2020.56.02.05>.
5. Harasani K, Xhafaj D, Begolli A, Olvera-Porcel MC. Prevalence of potentially inappropriate prescriptions in primary care and correlates with mild cognitive impairment. *Pharm Pract (Granada)* 2020;18(3):2017.
6. Vyshka G, Kakariqi L. Ipidacrine and Cholinergic Pharmacotherapy: Are we Getting Closer to the Miracle Drug? *AJMHS Vol* 52, 2020.
7. Gallego JA, Nielsen J, De Hert M, Kane JM, Correll CU. Safety and tolerability of antipsychotic polypharmacy. *Expert Opin Drug Saf* 2012;11(4):527-42.
8. Centorrino F, Goren JL, Hennen J, Salvatore P, Kelleher JP, Baldessarini RJ. Multiple versus single antipsychotic agents for hospitalized psychiatric patients: case-control study of risks versus benefits. *Am J Psychiatry* 2004;161(4):700-6.
9. Institute for Health Metrics and Evaluation (IHME). Findings from the Global Burden of Disease Study 2017. Seattle, WA: IHME, 2018.
10. Agency for Healthcare Research and Quality (AHRQ) Data compilation of 25 most prescribed psychotropic drugs in 2020. Source (Psychcentral news website <https://psychcentral.com/blog/top-25-psychiatric-medications-for-2020>)
11. Lista e barnave të Rimbursuara 2019 https://www.fsdksh.com.al/images/2020/LBR2019_Indexuar_03022020/2019_indeksuar_tregu_hapur.pdf
12. Jordanova V, Maric NP, Alikaj V, Bajcs M, Cavic T, Iosub D et al. Prescribing practices in psychiatric hospitals in Eastern Europe. *Eur Psychiatry* 2011;26(7):414-418.