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Original Article

Predictors of Non-Adherence to Medications in Hypertensive Patients

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Abstract

Background: Elevated blood pressure (BP) is one of the leading causes for developing major cardiovascular events and still represents a major public health challenge worldwide. We aimed to provide data on predictors of poor adherence to medication in hypertensive patients in Serbia.

Methods: Observational, analytical study was undertaken at a group of 388 patients who refilled their medications in the Pharmacy Institution, "Apoteka Kragujevac", Kragujevac, Serbia between Jan and Mar 2019. Afterward, we conducted a case-control study to evaluate the influence of the variables associated with the adherence. We used a self-developed questionnaire and SF-36 to assess the influence of the quality of life on medication adherence.

Results: Results revealed four independent predictors of non-adherence: increased number of medications, living in a city, forgetfulness of the dosing regimen and low energy. The odds of non-adherence were the highest among the participants living in the city and the low energy was the only factor inversely associated with the level of non-adherence.

Conclusion: Many factors were associated with the non-adherence to medication. Further studies are needed to find the most appropriate protocol to promote adherence. The four risk factors (increased number of medications, living in a city, forgetfulness of the dosing regimen and low energy) are associated with non-adherence in adult hypertensive patients.

Keywords: Adherence; Hypertension; Risk factors; Questionnaire

Introduction

Elevated blood pressure (BP) is one of the leading causes for developing major cardiovascular events and still represents a major public health challenge worldwide (1). The global prevalence of high BP is 31.1% (2) and that the total number of persons

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with hypertension in 2025 will be around 1.56 billion (3). The number of these patience in Central and Eastern Europe is over 150 million with the progressively more frequent onset among people with 60 yr old and older (4) and with the increasing incidence in low-to-middle-income countries (2) such as Republic of Serbia. Nevertheless, although the effectiveness of antihypertensive treatment options is well established, the target levels of BP achieve only 40 to 50% of patients (5).

One of the major factors associated with uncontrolled BP is weak adherence towards the antihypertensive medications (4). Consequently, nearly 75% of the hypertensive patients do not achieve optimal control of the BP and therapeutical target (6). Adherence may be defined as the extent to which person's behavior regarding the daily taking of medications, corresponds with agreed recommendations from a health care provider (7). This may be a huge challenge when the medication is used as a long-term treatment rather than short-term, symptom relief option, such in chronic disease-primarily or secondary hypertension (8).

From the patient's perspective, non-adherence may be divided into two categories: intentional and non-intentional (9). Intentional non-adherence patients do not accept diagnosis and/or proposed treatment, or these patients are not able to purchase medication due to the low income. Non-intentional non-adherent patients may simply forget to take medication, or this type of non-adherence may be associated with patient's emotional state, beliefs and concerns about illness and medications (10). Previous reports underlined various factors associated with both types of non-adherence: demographic characteristics of patients - age, education, marital status, socioeconomic conditions and patient being unable to purchase the medications (11, 12), depression, insomnia, cognitive disorders (11), presence of comorbidities (13), complicated treatment options – dosage regimen, number of medications, changes in treatment (14), patient's knowledge about hypertension and relevant medication (13), multiple daily doses, adverse drug effects (15) and others. All known factors can be divided into five main domains: socioeconomic, healthcare related, disease related, therapy related and patient related (16).

We hypothesized that many factors related with patients could be a strong predictor of adherence or non-adherence in hypertensive patients. Improving of early recognizing and prediction of all risk factors, should be important facts in management of hypertensive patients.

We aimed to evaluate the possible factors associated with poor adherence to medication in patients with hypertension.

Methods

Ethical concerns

This study was done in accordance with Good Clinical Practice and Declaration of Helsinki. In addition, protocol of study was approved by the local Ethical committee of the Clinical Centre Kragujevac, Serbia, number 01/18-4834 (obtained 13 Dec 2018). From all participants was obtained filled written and informed consent to participation in study.

Study design

This research was designed as a cross-sectional analytical, observational study to investigate potential predictors of poor adherence towards antihypertensive treatment. The study was conducted at the State Pharmacy Institution "Apoteka Kragujevac" in Kragujevac, Serbia, between Jan and Mar 2019.

Participants of study

Participants for this study were consecutively included in the investigation as a convenience sample. Inclusion criteria were that participants must be older than 18 yr with a confirmed diagnosis of hypertension, male or female and under regular treatment with at least one medication for a minimum of 12 months before including in study. Patients younger than 18 yr, with the language issues, low motivation, severe cognitive disorders and serious concomitant diseases (carcinoma, severe chronic obstructive pulmonary disease (COPD), severe heart failure according to the New York

Heart Association (NYHA) III and IV, were not included in the study.

We enrolled 338 patients, divided into cases (n=88) as a non-adherent group and controls (n=250), as a group adherent regarding the treatment of hypertension. The non-invasive method was used to assess the adherence - how many times the patient missed to refill monthly prescribed medications in the last 12 months according to the pharmacy dataset. The control group was defined as the group adherent to antihypertensive medications at the level of ≥ 80%. This group of patients didn't take their monthly medication once or twice while poor adherence was defined as adherence at the level of < 80%, where patients missed to refill their monthly medications more than two times, consecutive or not. A similar approach was described previously (9, 11).

Socio-demographic Instrument

We generated the questionnaire with the assets about the socio-demographic characteristics of patients (age, gender, level of education, material status, residence area etc.), their beliefs towards the medications they use (effect of medication, burden of taking the drug, issues with purchasing a medication or with monthly refill, current blood pressure control etc.).

Short Form Health Survey Questionnaire (SF-36)

To evaluate the quality of life we used standardized Short Form Health Survey Questionnaire (SF-36), a general health multidimensional survey with 36 questions. It measures health related quality of life organized into eight domains: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health. Each domain was recoded accordingly and has a maximum value of 100. Higher scores indicate better quality of life. We calculated the average values in all domains. All participants fulfilled the Serbian version of SF-36 validated and used to asses quality of life of patients suffering of various diseases (17, 18).

Sample size

A total sample size for his study was calculated using G-power software. Starting points were study power of 0.95, α error of 0.5 and effect size at the level of 0.56, determined based on the results of previous research (15), where the observed number of medications in groups was mean (SD) - 1.7 (0.8) and 1.3 (0.6). Based on these parameters, using t-test family and a-priori two tails analysis, with 1:2 allocation ratio between the groups, we calculated the minimum of 62 patients in the case group and 124 in control group. We managed to include 88 cases and 250 controls in this research. In choosing control, we followed the next principle: The control group should be representative of the source population from which cases are derived in the more than 2:1 allocation, which this means that there were more than twice as many patient-subjects observed in study as those receiving the standard or placebo.

Statistical analysis

All of the continuous variables were described as means ± SD, while categorical variables were described as frequencies (percentages). The differences between groups were assessed by parametric Student's *t* test for continuous variables following normal distribution, and by its non-parametric alternative Mann-Whitney test for the data not following normal distribution. We used the Chi-square test to calculate the differences between categorical variables and Fisher's test of real likelihood for low frequencies. To determine potential predictor of non-adherence we used univariate and multivariate binary logistic regression and values of crude and adjusted odds ratios with corresponding confidence interval of 95%. All of the analysis were performed using statistical program SPSS ver. 23 (IBM Corp., Armonk, NY, USA). The *P* -value less than 0.05 was considered as statistically significant.

Results

The basic demographic characteristics of the included participants are presented in Table 1.

Table 1: Baseline characteristics in both groups

Variables	*Cases (n=88)*	*Controls (n=250)*	*Test value*	*Significance of null hypothesis*
Age (mean ± SD)	65.6 ± 11.6	65.03 ± 10.96	Z = - 0.239	*P*=0.81
Gender M/F	28 / 60 (31.8%/68.2%)	124 / 126 (49.6%/50.4%)	χ^2 = 8.316	*P*=0.004
Level of education			χ^2 = 0.579	*P*=0.901
Elementary	20 (23.3%)	50 (20.7%)		
High school	40 (46.5%)	118 (48.8%)		
Higher school	10 (11.6%)	24 (9.9%)		
Faculty	16 (18.6%)	50 (20.7%)		
Marital status			χ^2 = 0.877	*P*=0.833
Single	4 (4.5%)	14 (5.8%)		
Widower / widow	18 (20.5%)	46 (16.5%)		
Divorced	10 (11.4%)	26 (10.7%)		
Married	56 (63.3%)	162 (66.9%)		
Residence area - rural/city	24/62 (27.9%/72.1%)	120/118 (50.4%/49.6%)	χ^2 = 12.968	*P* <0.001
Employment			χ^2 = 3.6	*P*=0.308
Employed	30 (34.9%)	76 (31.7%)		
Unemployed	10 (11.6%)	24 (10%)		
Farmer	4 (4.7%)	28 (11.7%)		
Retired	42 (48.8%)	112 (46.7%)		
Material status			χ^2 = 1.207	*P*=0.751
Low	12 (13.6%)	26 (10.7%)		
Middle	44 (50%)	128 (52.5%)		
Good	30 (34.1%)	80 (32.8%)		
Very good	2 (2.3%)	10 (4.1%)		

Results are presented as frequency in percent or mean plus standard deviation. Statistical significance was confirmed by Mann-Whitney or Chi square test, depending the type of variables, with the statistical threshold of 0.05

Variables of interest included into the analysis were: number of medications, stopped using any medication in the last 6 months, dosing regimen, using medication in the last 7 d, effect of medication, burden of taking the drug, issues with remembering the dosing regimen, purchasing and monthly renewal of medication, time of diagnosis, current HTA control compared to last year, family history of HTA, regular self-control of blood pressure and whether the participant received information from healthcare practitioner. We did not observe the statistical significant differences in assessing information gathering, self-control of the blood pressure, time of diagnosis and the termination of using some of medications in the last 6 months. All other variables are shown to be significantly different between the groups (Table 2).

Table 2: Potential predictors of nonadherence in study population

Variables	*Cases (n=88)*	*Controls (n=250)*	*Test value*	*Significance of null hypothesis*
Number of medications			$\chi^2 = 17.194$	*P*=0.002
1	22 (25%)	102 (40.8%)		
2	30 (34.3%)	96 (38.4%)		
3	22 (25%)	34 (13.6%)		
4	14 (15.9%)	16 (6.4%)		
6	0 (0%)	2 (0.8%)		
Stopped using any medication in last 6 months Y/N	12/76 (13.6%/86.4%)	40/210 (16%/84%)	$\chi^2 = 0.279$	*P*=0.597
Dosing regimen			$\chi^2 = 10.100$	*P*=0.005
Every day	82 (93.2%)	246 (99.2%)		
As needed	6 (6.8%)	2 (0.8%)		
Using medication in the last 7 d Y/N	86 (97.7%) 2 (2.3%)	250 (100%)	$\chi^2 = 5.670$	*P*=0.017
Effect of medication			$\chi^2 = 6.238$	*P*=0.044
Moderate	8 (9.1%)	24 (9.7%)		
Well	70 (79.5%)	214 (86.3%)		
I don't know	10 (11.4%)	10(4%)		
Burden of taking the drug			$\chi^2 = 20.650$	*P*<0.001
No burden	46 (53.5%)	164 (75.2%)		
Little	34 (39.5%)	52 (23.9%)		
A lot	4 (4.7%)	0 (0%)		
I don't know	2 (2.3%)	2 (0.9%)		
Issues with remembering the dosing regimen			$\chi^2 = 18.685$	*P*<0.001
No	58 (65.9%)	198 (86.8%)		
A little	24 (27.3%)	26 (11.4%)		
A lot	6 (6.8%)	4 (1.8%)		
Issues with purchasing a medication			$\chi^2 = 20.714$	*P*<0.001
No	66 (75%)	184 (80.7%)		
A little	20 (22.7%)	16 (7%)		
A lot	2 (2.3%)	28 (12.3%)		
Issues with monthly renewal of medication			$\chi^2 = 9.256$	*P*=0.010
No	68 (77.3%)	186 (80.9%)		
A little	20 (22.7%)	30 (13%)		
A lot	0 (0%)	14 (6.1%)		
Time of diagnosis <5 / >5 years	24/64 (27.3%/72.7%)	92/148 (38.3%/61.7%)	$\chi^2 = 3.446$	*P*=0.063
Current HTA control compared to last year			$\chi^2 = 19.042$	*P*=0.001
Better	38 (43.2%)	124 (51.2%)		
The same	32 (36.4%)	98 (40.5%)		
Worsen	8 (9.1%)	2 (0.8%)		
I don't know	6 (6.8%)	6 (2.5%)		
I don't control regularly	4 (4.5%)	12 (5%)		
Family history of HTA Y/N	74/14 (84.1%/15.9%)	168/74 (69.4%/30.6%)	$\chi^2 = 7.101$	*P*=0.008
Regular self-control of TA Y/N	72/16 (81.8%/18.2%)	218/26 (89.3%/10.7%)	$\chi^2 = 3.315$	*P*=0.069
Information from healthcare practitioner Y/N	70/18 (79.5%/20.5%)	200/44 (82%/18%)	$\chi^2 = 0.250$	*P*=0.617

Results are presented as frequency in percent or mean plus standard deviation. Statistical significance was confirmed by Mann-Whitney or Chi square test, depending the type of variables, with the statistical threshold of 0.05.

Quality of life among study population

To assess the health-related quality of life and to determine potential differences between non-adherent and adherent group we used SF-36 as a tool. It contains 36 questions divided into eight domains. The average values of two domains - energy/fatigue and pain were statistically different between observed groups. The minimum score was 42.6 in the case group for the domain - Role limitations due to physical health, while maximum value was 67.1 and was observed in the control group for the domain - Social functioning. All other results are presented in Table 3.

Table 3: SF – 36 score divided into domains in study population

Variables (mean ± SD)	*Cases (n=88)*	*Controls (n=250)*	*Test value*	*Significance of null hypothesis*
Physical functioning	54.3 ± 33.4	65.2 ± 27.4	Z = -1.726	*P*=0.084
Role limitations due to physical health	42.6 ± 43.5	50.8 ± 43.3	Z = -0.369	*P*=0.712
Role limitations due to emotional problems	50.8 ± 45.2	58.2 ± 43.8	Z = -0.314	*P*=0.754
Energy/fatigue	48.7 ± 22.6	57.5 ± 17.9	Z = -2.272	***P*=0.023**
Emotional well-being	63.9 ± 19.1	65.5 ± 16.9	Z = -0.536	*P*=0.592
Social functioning	62.2 ± 23.9	67.1 ± 22.4	Z = -1.234	*P*=0.217
Pain	58.4 ± 21.3	65.9 ± 23.6	Z = -1.990	***P*=0.047**
General health	46.5 ± 22.1	53.5 ± 18.6	Z = -1.929	*P*=0.054

Results are presented as mean plus standard deviation. Statistical significance was confirmed by Mann-Whitney with the statistical threshold 0.05.

All of values of aforementioned variables were used to analyze the potential predictors of non-adherence. We performed univariate binary logistic regression and revealed ten factors that may be associated with the level of adherence: gender, residence area, number of medications, burden of taking the drug, issues with remembering the dosing regimen, Family history of high bold pressure and physical functioning, energy/fatigue and general health as a domains of the health related quality of life evaluated trough the SF-36 questionnaire. Other values of univariate regression are shown in Table 4.

Table 4: Univariate logistic regression – possible predictors of nonadherence

Variables	*Odds Ratio (95% CI)*	*P-value*
Age (mean ± SD)	1.006 (0.984-1.029)	0.591
Gender M/F	2.109 (1.263-3.521)	0.004
Level of education	0.953 (0.747-1.215)	0.696
Marital status	0.950 (0.738-1.222)	0.690
Residence area - rural/city	2.627 (1.538-4.487)	<0.001
Employment	0.968 (0.806-1.162)	0.727
Material status	0.900 (0.638-1.269)	0.547
Number of medications	1.522 (1.196-1.936)	0.001
Stopped using any medication in last 6 months	1.206 (0.601-2.421)	0.598
Dosing regimen	9.000 (1.782-45.464)	0.008
Using medication in last 7 d	0.985 (0.979-1.005)	0.863
Effect of medication	1.700 (0.894-3.232)	0.106
Burden of taking the drug	2.287 (1.481-3.530)	<0.001

Issues with remembering the dosing regimen	2.698 (1.661-4.381)	<0.001
Issues with purchasing a medication	0.895 (0.600-1.337)	0.589
Issues with monthly renewal of medication	0.911 (0.563-1.474)	0.704
Time of diagnosis <5 / >5 years	1.658 (0.969-2.835)	0.065
Current HTA control compared to last year	1.236 (0.987-1.548)	0.065
Family history of HTA	0.430 (0.228-0.809)	0.009
Regular self-control of TA	1.863 (0.946-3.668)	0.072
Information from healthcare practitioner Y/N	1.169 (0.634-2.156)	0.617
Physical functioning	0.991 (0.983-0.999)	0.024
Role limitations due to physical health	0.999 (993-1.004)	0.625
Role limitations due to emotional problems	0.999 (0.993-1.004)	0.652
Energy/fatigue	0.982 (0.969-0.994)	0.004
Emotional well-being	0.996 (0.982-1.010)	0.580
Social functioning	0.993 (0.982-1.003)	0.184
Pain	0.990 (0.979-1.001)	0.064
General health	0.986 (0.974-0.998)	0.027

After performing a multivariate binary logistic regression (*Forward Stepwise - Likelihood Ratio*), four independent predictors of non-adherence were determined, with the maximum value of odds ratio of 3.713 for the variable residence area (Table 5).

Table 5: Multivariate logistic regression – predictors of nonadherence

Variables	***Odds Ratio (95% CI)***	***P-value***
Number of medications	1.618 (1.214-2.156)	0.001
Residence area - rural/city	3.713 (1.977-6.972)	<0.001
Issues with remembering the dosing regimen	1.821 (1.004-3.302)	0.048
Energy/fatigue	0.981 (0.966-0.996)	0.015

Discussion

The scope of this research was to determine potential risk factors for non-adherence to antihypertensive treatment. We confirmed four independent predictors of non-adherence - number of medications, residence area - rural/city, issues with remembering the dosing regimen and energy/fatigue. We observed almost 2-fold increase in odds of non-adherence with each additional medication. In our analysis, we had patients taking 1 to 6 medications concomitantly (we did not have patients taking five drugs).

The main difference was founded between patients who taking the 3 and 4 drugs (Table 2). This finding supports the hypothesis that polypharmacy is a potential risk factor for non-adherence as described in previous studies (3). Unlike our indirectly method for the assessment of non-adherence, the authors of aforementioned research confirmed this association by using biochemical analysis of blood and urine as a direct method for non-adherence evaluation. A retrospective cohort research, conducted on over the 5000 participants, also confirmed the influence of polypharmacy on non-adherence. The risk of non-adherence to the treatment was 5.22 times higher in the group of patients taking 3 or more medications (19), similar to the number of medications (3 and 4) taken by the group of patients that showed main differences in our results (Table 2). Although, some authors suggested the level of adherence to the medication would be the same, regardless of whether the patient is taking one, two, or three drugs (20) or reported improved adherence as number of medications increased (21), our results may be considered as a strong evidence of the influence of the number of medications on non-adherence.

The second independent predictor of non-adherence in our study was the residence area. We revealed that the living in the city has 3.713 times higher risk for non-adherence than having the residence in the rural area. The prevalence of the participants living in the city was 72.1% in case group and 49.6% in the control group (Table 2). The association between residence and adherence to medication is controversial. Patients who lived in urban area have two times (22,23) or even six times (24) more chances to adhere to their antihypertensive medication in relation to those lived in rural areas while others.

Our analysis showed that the forgetfulness of the dosing regimen is associated with the poor adherence with an almost two times higher risk (Table 5). Participants reported to have issues remembering the dosing regimen were groups with the most significant difference observed – (Table 2) with the standardized residuals values of 2.7 and 1.9 (data not shown).

While assessing the health related quality of life (HRQoL) of the patients with hypertension and the possibility of the association with the level of adherence, we revealed only Energy/fatigue domain of the SF-36 with the significant influence (Table 3). Energy/fatigue is the protective factor decreasing the poor adherence for 19% (OR=0.981, CI = 0.966-0.996), meaning the more energy patients have, the less non-adherence will be present. However, there is a dilemma whether adherence firstly affects the QoL or vice versa. Poor adherence negatively affects HRQoL, which further decreases adherence level, as we showed, which again decreases HRQoL scores.

We generated the questionnaire to assess adherence. Although this method has disadvantages such as recalling for bias and eliciting only socially acceptable answers, yet simple and economic tool can provide insight regarding potential reasons for poor adherence.

Conclusion

The four risk factors (increased number of medications, living in a city, forgetfulness of the dosing regimen and low energy) are associated with non-adherence in adult hypertensive patients. Patient education at GP office as well in the pharmacy, use of different reminders such as mobile phone apps or a daily checklist could be useful addressing forgetfulness and the increased number of medications, while lifestyle modification may increase adherence especially among patients living in the city area. Future studies are needed to explore all available approaches and choose the most appropriate one to increase adherence level and improve overall HRQoL of the patients with hypertension.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflicts of interest

The authors declare that there is no conflict of interests.

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