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Significance of noncompliance when treating patients with epilepsy

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ABSTRACT

Introduction: The absence of patient's cooperation when it comes to his/her treatment (" noncompliance") is typical to chronic diseases and it is significant problem in medical practice. The term "compliance" means patient's capability of strictly adhering to the recommendations concerning the prescribed treatment. The noncompliance with drug regime is frequent case in patients with epilepsy, it is related to increased risk of epileptic seizures' occurrence and other undesired consequences, including increased costs in the healthcare area.

Objective: The objective of our research is assessing the interconnection between compliance with the treatment and social-demographic and clinical factors in patients with epilepsy.

Contingent and methods: The research covers 131 consecutively included patients with epilepsy of various social-demographic and clinical characteristics. We have utilized analysis of the medical documentation, anamnesis, study of the somatic and neurological status, self-assessment scales and statistical methods.

Results: We established statistically significant positive correlations between the number of patients with poor compliance and the absence of professional/educational occupation, frequency of epileptic seizures, number of the antiepileptic drugs taken during the present and past treatment, the simultaneous presence of poor control of epileptic seizures and adverse drug events being the reason behind the modification of the previous treatment.

Conclusion: Patient's poor compliance, the great frequency of seizures, the higher number of antiepileptic drugs and the adverse drug reactions have negative impact on the course of the epileptic disease. The improved compliance results in optimizing the antiepileptic treatment, improving patients' condition and significantly cutting down costs incurred in the healthcare area.

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1.   Introduction

The term "compliance" is patient's ability to strictly adhere to the recommendations concerning the prescribed treatment. The absence of compliance ("noncompliance") is typical to chronic diseases and it is significant problem in medical practice. The noncompliance with the drug regime is frequent case when it comes to patients with epilepsy and it is related to increased risk of epileptic seizures (ES) and other harmful consequences, including increased costs in the healthcare sector [1–4]. Despite the guidelines and recommendations, many patients do not take the antiepileptic drugs (AED) according to doctor's precise prescription. The per cent of poor compliance with the treatment of patients with epilepsy is high and it is observed within the limits from 20% to 80% [5–8].

The notion "noncompliance" includes error in the AED dose (intake of higher or lower quantity), erroneous interval between the individual doses, noncompliance with the treatment duration, intake of AED that were not prescribed by the doctor, noncompliance with the living regime. The compliance degree could be formulated as per cent of the drugs taken from the prescribed dose for particular time period [9]. The absence of validated assessment scales creates difficulties when it comes to defining the impact of the specific factors on patient's unsatisfactory compliance [10].

The adverse events (AE) and the absence of satisfactory control of ES are the main reason for modifying the antiepileptic treatment. On the other hand many seizures are being provoked directly by skipping AED. The noncompliance significantly deteriorates disease progression [11] and is directly related to poor therapeutic reaction, increased disease rate, emergency examinations and hospitalizations, as well as increased costs in the healthcare sector [2]. The non-assessment of poor compliance could result in unwanted modification of antiepileptic treatment by the doctor (modification of drugs and doses) and in many cases it is the reason behind the imprecise assessment of epilepsy as therapeutically resistant [12]. This is the reason behind running unnecessary expensive tests (for example, pre-surgical preparation), treatment with higher number and higher doses of AED, oftentimes with increase of toxic drug effects. That is why the adequate therapeutic approach requires detailed information about compliance from the patient and his/her relatives.

2.   Objective

The objective of our research is to assess the interconnection between compliance with treatment and the social-demographic and clinical factors in patients with epilepsy.

3.   Contingent and methods

The research covered 131 consecutively included patients with epilepsy of total 449 screened middle-aged, i.e. 40.13 ± 13.37-year-old, of whom 57 (43.5%) male and 74 (56.5%) female. The patients were treated and monitored in Multi-profile Hospital for Active Treatment in Neurology and Psychiatry "Saint

Naum" in Sofia. The research included patients that have had the disease for more than 1 year, without modifying the antiepileptic treatment in the last 3 months, without comorbid somatic, neurologic and psychiatric diseases that require additional treatment.

We utilized analysis of the medical documentation, anamnesis, study of the somatic and neurological status. We assessed the significance of the following factors: epilepsy type (in conformity with the International Classification of Epilepsies from 1989), number of taken AED during the present and past treatment, monthly frequency of ES, AE. We used interviewing questionnaire that included 4 points for assessing patient's compliance with the treatment in the last 3 months: 1) daily dose skipping; 2) modifying the AED dose; 3) noncompliance with the AED intake regime; 4) noncompliance with the recommended living regime (enough sleep, regular eating habits, no alcohol use). The answer provided to each question was assessed correspondingly with 1 (never); 2 (1–3 times monthly) and 3 (more often than 3 times monthly). With the possible questionnaire values from 4 to 12 points, patient's compliance was assessed as good with general value of 5 and more points, and as unsatisfactory with less than 5 points. The presence and frequency of AE were assessed with adapted and validated Bulgarian version of the Liverpool Adverse Event Profile (LAEP-BG), which contains 2 subscales: "neurologic and psychiatric side effects" and "non-neurological side effects" [13,14]. Disease's impact onto the health-related Quality of Life (QoL) of patients was researched with the Bulgarian version of the Quality of Life in Epilepsy Inventory – 89 (QOLIE-89 questionnaire), which consisted of seventeen subscales [15]. The higher scores indicated better QoL.

3.1.   Statistical methods

Descriptive statistics was used for calculating the demographic and clinical data, and the scores of psychometric questionnaires QOLIE-89 and LAEP-BG subscales. The continuous variables were presented as a mean value $\pm$ standard deviation (SD), while noncontinuous data were presented as percentages. Differences between scores of both patient groups (with poor and with good compliances) were calculated by nonparametric pair Student's t-tests. The chi-square tests and Fisher exact test were used for the categorical variables. The Spearman Rank Correlation was calculated to evaluate the relationships of some investigated parameters. The level of significance was chosen at $p < 0.05$. Statistical analysis was performed using the statistical package Statistica 8.0 for Windows (Stat Soft Inc., USA).

4.   Results

The participants in our research were with different seizure frequency: seizurefree patients (48.9% without seizures in the last 6 months) and the ones with varying resistance degree: 38.2% with up to 3 seizures monthly and 13.0% with 4 and more seizures monthly. On the grounds of the analysis of patient's compliance with the treatment we established that in 81.7% of the cases the patients rendered good cooperation during the therapeutic process. In order to define the relationship between the ES, AEs persistence and the need of treatment

modification, we analysed the reasons behind changing the previous therapy. In general for all research participants the most frequent reason behind modifying the treatment in the past was the simultaneous presence of AEs and poor control of ES (56.5%), followed by the single AEs presence (16.8%), and to the least degree the reason behind the change was only ES poor control (7.6%).

Table 1 presents patients' distribution in view of compliance degree (good and poor) and the social-demographic and clinical characteristics. We established the lack of dependency between the compliance degree and the social-demographic characteristics such as age, gender, family status, education. We observed the trend of patients' number with poor compliance increasing with the increase of disease duration and age (Table 1).

We established statistically significant dependency between the presence of good compliance and professional/academic occupation. We observed that 66% of the patients with professional/academic occupation manifest good compliance with the treatment, while 58% of the unemployed are with poor compliance (Table 1). We established statistically significant dependency between the compliance and the clinical characteristics: epilepsy type, ES monthly frequency, number of AED taken during the present and the past treatment, and the reasons behind the modification of the previous treatment (Table 1). Poor compliance was observed in 54% of the patients with cryptogenic epilepsy, and in 45% of the patients with symptomatic epilepsy and in only 1% of those with idiopathic epilepsy. In view of seizure frequency statistically significant difference between the patients with good and poor compliance in the group without ES and the one with more than 4 ES monthly, and good compliance was observed in 56% of the patients without seizures and in only 9% of the patients with more than 4 seizures monthly (Table 1). It was established that the number of AED taken during the previous and present antiepileptic treatment is the reason behind the poor compliance (Table 1). The patients with monotherapy show significantly good compliance compared to the ones that intake higher AED number. The most prominent difference was between the two researched patient groups (with good and with poor compliance) with monotherapy and with intake of 3 and more AED, while in the case of those treated with 2 AED the difference was insignificant. We established significant effect of poor compliance with the AE treatment related to the manifestation of Neurologic and psychiatric symptoms, assessed with the LAEP-BG questionnaire. While the values of the subscale Neurologic and psychiatric AE increase, patients' number with poor compliance increases as well (Table 1).

Data analysis depending on the number of AED taken during the present AET shows moderate positive correlation between the number of taken AED and seizures' frequency (Spearman Rank Correlation $r_s = 0.34$, $p < 0.05$) and between the number of AED taken and compliance ($r_s = 0.26$, $p < 0.05$). Depending on the number of AED taken during the previous antiepileptic treatment we established strong correlation between the number of AED taken during the previous treatment and the reasons behind modifying the treatment ($r_s = 0.69$, $p < 0.05$), as well as the number of AED taken during the present treatment ($r_s = 0.63$; $p < 0.001$).

After analysing the QoL of patients with epilepsy depending on the compliance degree we established that the patients with good compliance show higher average assessments in the majority of QOLIE-89 questionnaire subscales, which are more pronounced for the subscales "medication effects", "health discouragement", "seizure worry", "role limitations: emotional" and "physical function" (Fig. 1). We did not establish any statistically significant differences between the groups with good and poor compliance for the subscales "social support", "language", "attention/concentration" and "overall QoL".

5. Discussion

In literature we have found a total of three factor types that impact patient's compliance with antiepileptic treatment: 1) patent-related, for example own decision, based on assessing treatment's effectiveness, expected teratogenicity in women, memory violations, no understanding, accidental omission or stigmatization; 2) drug-related, for example price, AEs (adverse cosmetic effects of drugs, their impact on sexual life, cognitive functions), number of prescribed AED, distribution of daily doses and 3) disease-related, for example the ES type, disease gravity and duration [16].

This is the first systematic research in Bulgaria for assessing compliance depending on the social-demographic and clinical characteristics in the general population of patients with epilepsy. The significance of compliance is important because of the chronic course of the disease, the continuous treatment, the deteriorated QoL and patients' adaptation. Patient's compliance with antiepileptic treatment could be hardly measured with precision. The aimed interview with the patient could show higher assessment of compliance than the objective one, but this is the simplest, most convenient and cheap method. The relative share of the participants in our research with poor compliance is low (18.3%), and it is lower compared to other research works [17–21], which is probably related to the versatile social-demographic and clinical characteristics of our patients. Our results approximate the lower limit of the data summarized by Tomson, according to which around 1/5 to 2/3 of the patients with epilepsy show noncompliance [22]. Our results on the professional occupation being the most significant social-demographic factor when it comes to compliance degree from social point of view is related to the more difficult professional realization of patients with epilepsy, the possibility of finding job, as well as the successful performance of professional and educational obligations [23], and reflects the present circumstances in the country with high degree of general unemployment. We established that the intake of less than the prescribed AED quantity is related to increased ES frequency in the research participants which was established in many more research works [19,24–26]. According to Cramer 45% of the patients who have skipped the AED intake reported ES [17]. In the case of our patients that take higher AED number we established deteriorated compliance. Usually these are cases of higher anticonvulsants doses, with more complicated treatment scheme and more profound AEs. The better compliance of patients with monotherapy is easy to explain

Table 1 – Social-demographic and clinical characteristics – comparison between patients with good and poor compliance.			
Variables	Good compliance	Poor compliance	Statistic test and significance
Aetiology of epilepsy			
Genetic epilepsy	24%	1%	χ^2 (2,131) = 38.4, $p < 0.05$
Structural-methabolic epilepsy	46%	45%	
Unknown epilepsy	30%	54%	
Total	100%	100%	
Seizure frequency per month			
Seizure-free	56%	17%	χ^2(2,131) = 46.7, $p < 0.001$
1–3 seizures	35%	54%	
≥4 seizures	9%	29%	
Total	100%	100%	
AED number in past AET			
Without previous treatment	22%	8%	χ^2(2,131) = 34.4, $p < 0.05$
1 AED	30%	29%	
>1 AED	48%	63%	
Total	100%	100%	
AED number in present AET			
Monotherapy	53%	25%	χ^2(2,131) = 28.8, $p < 0.05$
2	30%	33%	
>3	17%	42%	
Total	100%	100%	
Reasons behind modifying the previous treatment			
Without previous treatment	21%	8%	χ^2 (3,131) = 51.2, $p < 0.05$
Poor control of ES	9%	1%	
AEs	21%	1%	
AEs + poor control of ES	49%	90%	
Total	100%	100%	
LAEP-BG (total score)			
Neurol. and psych. side effects	31.9 ± 8.04	39.2 ± 8.35	Unpaired t-test $t = 0.98$, df = 129: $p < 0.05$
Non-neurological side effects	9.5 ± 3.2	9.2 ± 3.2	Unpaired t-test $t = 0.14$, df = 129: NS
Age (years)	39.25 ± 13.2	44.1 ± 13.8	Unpaired t-test $t = 0.37$, df = 129: NS
Duration of epilepsy	15.43 ± 9.28	16.42 ± 10.35	Unpaired t-test $t = 0.17$, df = 129: NS
Sex			
Male	45%	38%	Fisher exact test: NS
Female	55%	62%	
Total	100%	100%	
Marital status			
Living alone	40%	31%	Fisher exact test: NS
Living with family	60%	69%	
Total	100%	100%	
Education level			
Primary education	10%	17%	χ^2(2,131) = 27.9, $p < 0.05$
Intermediate school	50%	58%	
University degree	40%	25%	
Total	100%	100%	
Employment status			
Employed/student	66%	42%	Fisher exact test: <0.05
Unemployed	34%	58%	
Total	100%	100%	
Note: Data are presented as mean ± SD or number of patients (%), NS – no significance, statistical significance $p < 0.05$.			

because of the easier drug regime, the more favourable course of the disease, probably the better forecast and the higher expectations of full seizures' control correspondingly. This thesis was supported by numerous authors [13,27–30]. The established positive correlation between the number of AED taken and the noncompliance demonstrates the critical role of compliance when it comes to making adequate decisions and fully realized antiepileptic treatment. Baulac outlines the
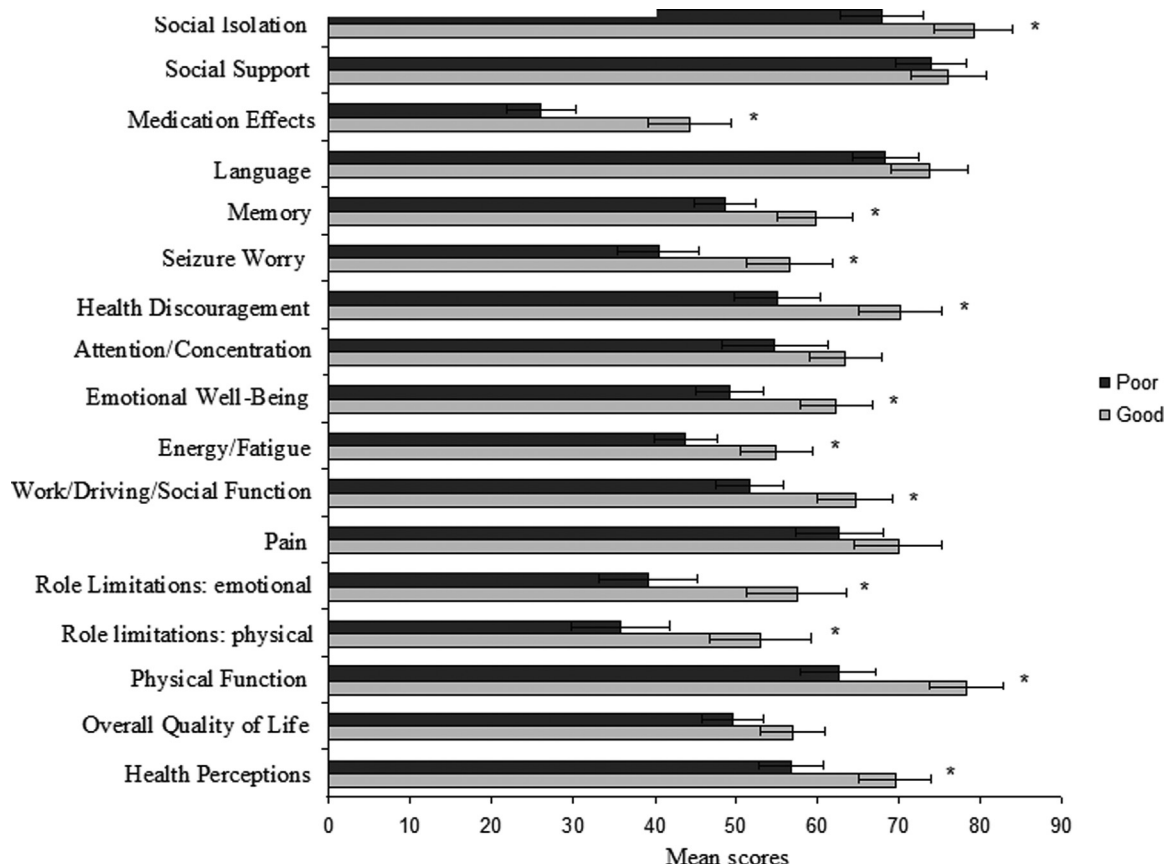
Fig. 1 – Mean scores of QOLIE subscales – comparison between patients with good and poor compliance. * statistical significance *p* < 0.05.

improved effectiveness of the comprehensive therapy and in particular of compliance when proceeding from combined treatment to monotherapy [31], and Matsuura assesses patient's general satisfaction when polytherapy is being reduced [32]. The present research work reports the interrelation between the most prominent AE and the deteriorated patient's compliance. The worries related to the manifestation and persistence of AE oftentimes provide the occasion for suspending the drug intake. In view of the general score of LAEP–BG – 47.75 (SD ± 7.82) in our patients, the assessment that contributes the most is the one of ''neurologic and psychiatric adverse effects'' subscale – 32.82 (SD ± 7.86), showing the great significance of neurotoxic effects when taking AED. The majority of the patients, especially the ones treated with higher number and doses of AED are with deteriorated concentration and memory, which has negative impact on compliance [28,33,34]. Most of our participants with great disease duration are with poor compliance, which is probably related to age and discouragement because of treatment effectiveness [5].

On the grounds of the results of patients with previous antiepileptic treatment we established great significance of the simultaneous presence of AEs and ES being the reason behind the unsuccessful antiepileptic treatment, deteriorated compliance and modified therapy in the past. In the case of persisting ES we apply higher AED doses, and polytherapy is more frequent with more profound AEs, the subjective feeling of absence of wellbeing in these cases is stronger and it deteriorates patients' QoL. In most cases the impact of the adverse drug effects in patient's everyday life is significantly more profound than the presence of ES [29]. When making the decision to change the antiepileptic treatment we should accurately assess compliance. In the case of 34.6% of our participants with 1–3 ES monthly and 9.3% the ones with ≥4 ES are with better compliance, and to these patients the best clinical solution is changing the dose or the drug. In 54.2% of patients with 1–3 ES monthly and 29.1% of those with ≥ 4 ES with established poor compliance, and in these cases it is suitable to improve compliance before changing the treatment. This belief is supported by the data of the previous research works about the higher number and doses of AED in the case of patients with poor compliance, as well as the more frequent therapy change [4]. The optimization of drug regime (therapeutic plan and/or two-time dose of AED), the more frequent contact and improved communication with patients, training of the patient and his/her relatives could significantly improve the compliance degree [20,35].

The notion QoL includes the subjective sensation of well-being and satisfaction with life and it depends on clinical, demographic and social-economic factors. In the researched

group of patients with good compliance we established higher correlation with better QoL and higher values of the QOLIE-89 questionnaire, especially in the areas that reflect drugs' effects, the discouragement in view of health, the worries concerning the seizures, the physical functions and emotional limitations. The adverse drug effects and ES have negative impact on the compliance degree and QoL. The participants with better compliance have more optimistic attitude towards their health, they have higher QoL, better emotional status and better physical functioning, which supports what was established during the previous research works [20,25,36].

The poor compliance not only has negative impact on disease progression, but it increases treatment costs [2,11]. After reviewing the medical registers of 10 892 patients with epilepsy in USA, Davis established that the deteriorated compliance was related to 11% hospitalization increase and 47% emergency examinations increase hence we have significant healthcare price increase [37].

We could conclude that treatment success greatly depends on the compliance degree, i.e. patient's capability to strictly adhere to the drug regime for certain period of time. The treatment that is not fully realized results in more frequent seizures, adverse effects of AED and increased disease rate [2]. The noncompliance that remains unnoticed by the doctor results in frequent change of the AED type, frequent increase of the daily dose and the number of AED taken and the AEs acceleration correspondingly. The responsibility for compliance with the drug regime is comprehensive and should be shared by the healthcare specialists, the healthcare system and the patients [11].

Conflict of interest

None declared.

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