RISK FACTORS FOR NONCOMPLIANCE WITH ANTIPSYCHOTIC MEDICATION IN LONG-TERM TREATED CHRONIC SCHIZOPHRENIA PATIENTS

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SUMMARY

Background: The attitudes of schizophrenic patients toward medications directly impact the treatment compliance. Although noncompliance represents a serious concern in long-term schizophrenia treatment, a detailed information on the factors that impair compliance is still limited. The present study aims to assess the factors related to noncompliance with antipsychotics agents, in long-term treated chronic paranoid schizophrenia patients.

Subjects and methods: Two groups of such patients (total number n=162) were analyzed and compared: 1). patients with symptomatic remission on haloperidol (n=32), clozapine (n=40) or olanzapine (n=45), and 2). drug resistant patients (n=45). The mean duration of the disease was 19.3 years.

Results: Altogether, in our patient sample, a better drug attitude was found in the olanzapine and clozapine groups. Our findings have also revealed that worse attitude toward antipsychotics correlated with an earlier onset of schizophrenia, younger patient age, shorter duration of the disease, higher burden of symptoms, treatment with a typical antipsychotics, and higher severity of akathisia.

Conclusion: Our results suggest that detecting factors that influence the patient's attitude toward medications might be helpful for designing targeted educational strategies in chronic schizophrenia patients (particularly those with the high risk of noncompliance), and further trials are warranted to explore this topic.

Key words: *schizophrenia - compliance - drug attitude - antipsychotics - long-term treatment*

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INTRODUCTION

Lack of compliance to therapeutic agents is one of most important problems of contemporary medicine. In psychiatry, the crisis of compliance is one of the hot spots in every discussion on the decreasing treatment effectiveness during recurrent schizophrenia episodes, and in the development of drug resistance. For example, the results of our recent telemedicine study, showed that the compliance rate, among schizophrenic patients with symptomatic remission, in the first month of the treatment was 44.6%, and had been decreasing over the subsequent 6 months (Krzystanek et al. 2015).

Schizophrenia is a chronic, progressive disease, and if its treatment is not continued, the schizophrenic process maintains in progress, resulting in chronic symptoms and reduction of brain volume (Vita et al. 2015). Diminishing number of neurons, together with declining number of receptors, decrease the possibilities of favorable treatment outcomes. Altogether, the good prognosis in schizophrenia is augmented by an adequate therapeutic compliance, in every single patient (Vita et al. 2015).

The basic component of compliance is an attitude of each patient toward taking the medication. This attitude represents a combination of different factors, such as the patient's knowledge, education, judgement or prejudice, society stereotypes, stigma, philosophy of life, culture, age, gender, income level, duration of schizophrenia, etc. (Kuroda et al. 2008). For instance, patients from different cultures may be characterized by various levels of drug acceptance, schizophrenia insight, and stigma (Mohamed et al. 2014).

One of the possibilities to improve the medication compliance is to explore the patient's attitudes, and possible reasons for noncompliance. This may lead to designing some helpful and better targeted management strategies, suitable for clinical practice. Therefore, the primary goal of our study was to identify factors associated with the medication acceptance (as an important part of the patient's attitude), in long-term treated chronic paranoid schizophrenia patients. For this reason, we first, evaluated mental state of patients with symptomatic remission, treated with a classical antipsychotics – haloperidol, or one of the atypical antipsychotics – olanzapine or clozapine; second, assessed the same parameters, in the subgroup of patients without remission, who were treatment resistant, and third, explored the patients' attitudes toward the antipsychotic treatment with three different agents (haloperidol, clozapine, and olanzapine). Subsequently, we compared these attitudes

between the patients with symptomatic remission (SR) (on these three antipsychotics), and the ones, who were resistant to antipsychotic medications (RES).

SUBJECTS AND METHODS

Patients

A total of 162 schizophrenic patients were included into the study. The mean age of patients was 46.1 years, the average onset of the disease was at the age of 27.4 years, and the mean duration of the disease was 19.3 years. The symptomatic remission patients (SR) were recruited from outpatient clinics, and the treatment resistant patients (RES) were residents of social houses in the area of Silesia (Poland).

The study was approved by the Ethical Committee of the Medical School of Silesia in Katowice. All patients signed their written, voluntary informed consent.

The basic study sample characteristics are given in Table 1.

The study patients were diagnosed with paranoid schizophrenia (according to ICD-10 criteria) and treated in monotherapy with haloperidol (HAL, n=32), clozapine (CLO, n=40) or olanzapine (OLZ, n=45) for at least 6 months.

In our study, the patients included into the subgroup with symptomatic remission (SR) of schizophrenia met the following inclusion criteria (Andreasen et al. 2005, van Os et al. 2006): they had Positive and Negative Syndrome Scale (PANSS) score of three or less, simultaneously on all eight items: delusions (P1), unusual thought content (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), passive/apathetic social withdrawal (N4), lack of spontaneity and flow of conversation (N6), and their symptom severity criteria had been achieved for the minimum period of 6 months.

The patients included into the subgroup that was resistant to the treatment (RES, n=45) did not have any substantial remission in the history of their disease, and they were treated (upon the duration of the study) with more than one antipsychotic drug, including the first generation long acting injectable antipsychotics. The main exclusion criteria were: schizophrenia-like symptoms of organic origin, psychoactive substance abuse and concomitant mental disturbances.

Procedures

Clinical status of patients was assessed by using the following clinical scales: Drug Attitude Inventory (DAI-10), Positive and Negative Syndrome Scale (PANSS), Negative Symptom Assessment Scale (NSA-16), Simpson-Angus Extrapyramidal Symptoms Scale (SAS) and Barnes Akathisia Rating Scale (BARS).

Statistical analysis

Due to lack of normal distribution the non-parametric Kruskal-Wallis test was used. To show more detailed differences between groups post hoc analysis was performed. Two tests were used: the more rigoristic HSD Tukey test and liberal NIR test.
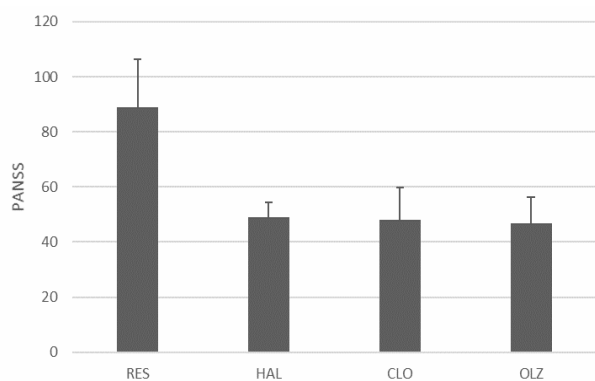
RESULTS

Main results

The highest intensity of schizophrenia symptoms in PANSS was present in treatment resistant schizophrenia patients (Figure 1). Pearson's correlation test showed that the PANSS results correlated with NSA-16 score (R=0.76, p=0.001) in the RES group of patients with shorter schizophrenia duration (R=-0.84, p=0.0001), and with NSA-16 results in the haloperidol group (R=0.63, p=0.0001), clozapine group (R=0.85, p=0.001) and olanzapine group (R=0.56, p=0.0001).

Table 1. Characteristics of the study subgroups

Patient's characteristic	Symptomatic remission (SR) patients Antipsychotic (n – number of patients in the group)			Treatment resistant (RES) patients (n=45)
	Haloperidol (n=32)	Clozapine (n=40)	Olanzapine (n=45)	
Gender				
females	15	15	21	29
males	17	25	24	25
Age[*]				
years (± SD[**])	52.3 (±9.6)	43.5 (±7.1)	41 (±12)	22-65
min-max[***]	37-65	34-53	22-61	22-65
Age of schizophrenia onset[*]				
years (± SD)	31 (±8.5)	25.9 (±8.2)	26.9 (±6.1)	27.4 (±7.9)
min-max	22-38	18-41	20-39	18-45
Duration of the disease[*]				
years (± SD)	20.6 (±11.9)	19.6 (±6.4)	16 (±7.9)	23.1 (±11.5)
min-max	6-40	6-29	1-31	4-50
Hospitalisations[*]	15.6	6.3	4.5	11.7

[*]arithmetic mean; [**]standard deviation; [***]minimum and maximum values

Results expressed as arithmetic means with standard deviation (SD); Kruskal-Wallis test: $H_{3.162}=94.9$, p=0.0001, $\eta^2_P=0.7$; RES - treatment resistant patients (n=45); HAL – patients on haloperidol (n=32); CLO – patients on clozapine (n=40); OLZ – patients on olanzapine (n=45)

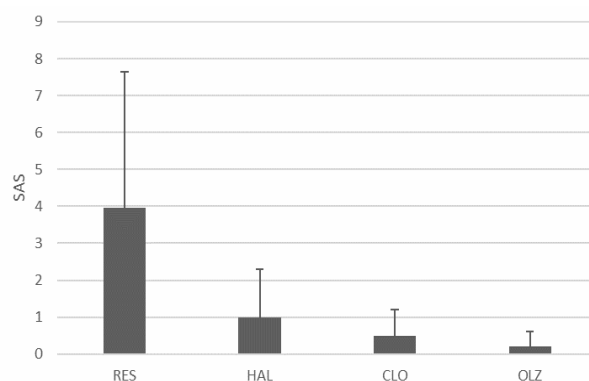**Figure 1.** Global PANSS results in schizophrenia patients
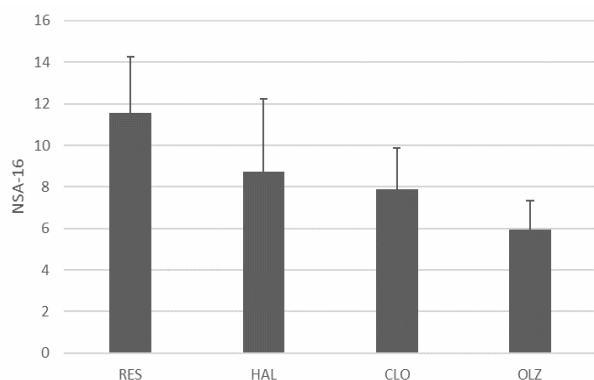
Results expressed as arithmetic means with standard deviation (SD); Kruskal-Wallis test: $H_{3.162}=52.6$, p=0.00001, $\eta^2_P=0.36$; RES – treatment resistant patients (n=45), HAL – patients on haloperidol (n=32); CLO – patients on clozapine (n=40); OLZ – patients on olanzapine (n=45)

Figure 3. SAS results in schizophrenia patients

Results expressed as arithmetic means with standard deviation (SD); Kruskal-Wallis test: $H_{3.162}=84.7$, p=0.00001, $\eta^2_P=0.53$; RES – treatment resistant patients (n=45); HAL – patients on haloperidol (n=32): CLO – patients on clozapine (n=40); OLZ – patients on olanzapine (n=45).

Figure 2. NSA-16 scale results in schizophrenia patients

Results expressed as arithmetic means with standard deviation (SD); Kruskal-Wallis test: $H_{3.162}=21.4$, p=0.0001, $\eta^2_P=0.05$; RES – treatment resistant patients (n=45); HAL – patients on haloperidol (n=32); CLO – patients on clozapine (n=40); OLZ – patients on olanzapine (n=45)

Figure 4. BARS results in schizophrenia patients

The highest intensity of negative symptoms was shown in RES group, and the lowest in olanzapine group (Figure 2). All the results were significantly different (p<0.05 in Kruskal-Wallis (H) test and in the post-hoc analysis – HSD Tukey and NIR tests).
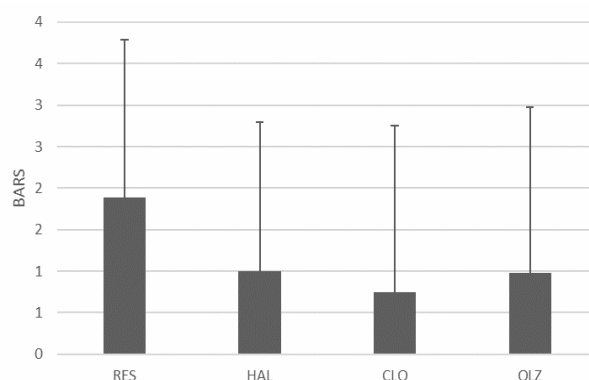
In RES group, higher NSA-16 result correlated with global PANSS result (R=0.76, p=0.0001), longer duration of the disease (R=0.39, p=0.009) and SAS score (R=0.34, p=0.02). In the haloperidol group the intensity of negative symptoms correlated with global PANSS score (R=0.63, p=0.0001), duration of the disease (R=-0.84, p=0.0001) and SAS result (R=0.55, p=0.001). In clozapine group, higher NSA-16 result correlated with schizophrenia duration (R=-0.43, p=0.005) and with BARS score (R=0.77, p=0.0001).

Intensity of extrapyramidal symptoms and akathisia were mild in all the study subgroups. The results are shown in Figures 3 and 4.
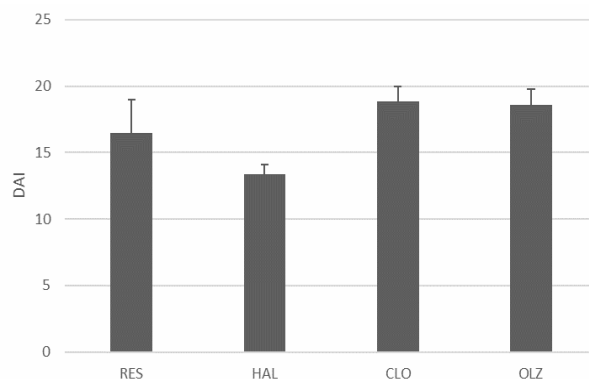

Results expressed as arithmetic means with standard deviation (SD). Kruskal-Wallis test: $H_{3.162}=86.3$, p=0.00001, $\eta^2_P=0.64$; RES – treatment resistant patients (n=45), HAL – patients on haloperidol (n=32); CLO – patients on clozapine (n=40); OLZ – patients on olanzapine (n=45)

Figure 5. DAI results in schizophrenia patients

Factors associated with compliance and non-compliance to medications

Patients' drug attitude differed in the analyzed subgroups, as presented in Figure 5. The worst attitude was expressed by the patients treated with haloperidol (this was even worse than in those, who were resistant to treatment). In the post-hoc analysis, the DAI results between groups were statistically different in all the study groups, except from the subjects, treated with olanzapine or clozapine (HSD Tukey test p=0.8, NIR test p=0.4).

The analysis of correlations in the haloperidol group showed that the worse drug attitude relates to the earlier schizophrenia onset (R=0.64, p=0.0001), younger patient's age (R=0.63, p=0.001) and higher score on PANSS (R=-0.49, p=0.004) and on BARS (R=-0.6, p=0.0001). In the RES group, higher results in DAI scores correlated with earlier schizophrenia onset (R=0.4, p=0.008). In clozapine patients, the worse attitude toward the antipsychotic was connected with shorter duration of the disease (R=-0.6, p=0.0001) and lower BARS score (R=-0.67, p=0.0001).

DISCUSSION

Main findings

In the present study, we report that in the patients with long-term treated chronic schizophrenia there was no difference in the severity of symptoms, between the patients in symptomatic remission (SR), regardless of the antipsychotic medication use (classical versus atypical). However, the patients treated with olanzapine had the lowest severity of negative symptoms.

The severity of negative symptoms was correlated with the duration of the disease, in all the study subgroups, except from the one, treated with olanzapine. This indicates that the treatment with olanzapine is related to a lower frequency of negative symptoms, and also, with a possible arrest of the development of these symptoms. The patients with long-term schizophrenia treated with atypical antipsychotics displayed the best compliance with the treatment. In contrast, the worst attitude toward the medication was noted in younger patients, treated with haloperidol, with an early onset of schizophrenia, severe disease symptoms, and severe akathisia.

The patients treated with clozapine had worse compliance with the antipsychotic at the beginning of treatment. In case of olanzapine, no differences in compliance with the medication, related to the disease duration, time of onset, severity of symptoms, or medication intolerance were observed.

No relations were found between the drug attitude and the negative or parkinsonian-like symptoms, in any of the study groups.

Comparison with prior studies

Numerous studies have indicated the importance of the role of positive attitude toward the treatment for the outcome of schizophrenia. Patients who understand their disease process, and accept the gains from the treatment achieve better therapeutic success, and are capable to fulfill their life aims (Lysaker et al. 2004).

Awareness of the disease has the great impact on the drug attitude, better insight and acceptance of the long-term treatment regime. All those factors contribute to a better compliance and prevention of schizophrenia relapse (Lysaker et al. 2004, Kako et al. 2014).

Long-term study of Murawiec and Boutros (2012) showed that better attitude toward the drug, assessed with DAI, correlated with reduced number of days spent in the psychiatric hospitals. It was also proved that higher scores in DAI corresponded with the therapeutic adherence in schizophrenia patients (Yang et al. 2012). The EUFEST study confirmed the usefulness of DAI score as the predictor of the treatment effectiveness in the first episode of schizophrenia (Gaebel et al. 2010).

As the lack of compliance has become the crucial problem of contemporary psychiatry, an attempt to identify the risk factors for negative drug attitude appears to be helpful for finding strategies to improve patient outcomes. The worst attitude toward the antipsychotic treatment in our study group was expressed by the patients receiving a classical neuroleptic (haloperidol), and by the treatment resistant ones. According to our results, the worse compliance was observed in younger age subjects, and with early onset of the disease. Similarly, Chandra et al. (2014) showed that poorer compliance relates to early age of schizophrenia onset and younger age of patients. The study of Chandra et al. was operating on another inclusion criteria: the patients were suffering from schizophrenia for no longer than 6 months and were in acute psychotic state, but his results are consistent with our study. In Chandra's study, the lack of compliance and worse drug attitude was related to higher PANSS severity. Brain et al. (2013) indicated the same correlation – the higher severity of positive symptoms was the predictor of non-adherence. In the presented study the worse drug attitude was observed in patients with more intensive schizophrenia symptoms and with shorter duration of the disease. Our results replicate the observation from CATIE study, where patients with lower PANSS score at the beginning of the study expressed better attitude toward drug (Lieberman et al. 2005). As in the study of Chandra et al. (2014) we also showed that bad attitude to the drug was related to the severity of antipsychotic side effect – akathisia.

The interdependence of the earlier onset of schizophrenia and the worse drug attitude indicates the importance of early education in young schizophrenia patients. The better acceptance of the disease improves the attitude to the treatment and improves live competence (Mintz et al. 2003).

In the subsequent study Mintz et al. showed that better insight in schizophrenia symptoms improves their reception by patients (Mintz et al. 2004). Moreover, the CATIE study showed that the improvement of insight in schizophrenia correlates with the better compliance (Lieberman et al. 2005).

Among the results of the present study the interesting finding was that though the intensity of negative symptoms both in the treatment resistant patients and in subjects treated with haloperidol was higher than in clozapine and olanzapine groups, the drug attitude did not correlate with negative symptoms. Because the negative symptoms in the study correlated with severity of extrapyramidal symptoms, their character may be secondary to the antipsychotic treatment. The relation between the negative symptoms and drug attitude during longer time periods requires further studies.

In the treatment resistant patients, negative symptoms were worsening with the longer duration of schizophrenia. In contrast, in the symptomatic remission (SR) groups, the intensity of negative symptoms decreased with the duration of the disease. This may bring some optimism in terms of the long-term treatment outcomes in chronic schizophrenia, providing that the patients remain compliant with the treatment.

The drug attitude in the study group was better in patients treated with atypical drugs. It is worth reminding that proscribing typical neuroleptics is indicated as the main reason of poor adherence in the treatment of schizophrenia, beside the poor insight and lack of therapeutic alliance between patient and his therapist (Dassa et al. 2010).

Strengths and limitations

Strengths

To our knowledge, the present study is one of very few studies that explores several clinical parameters of patients with long-term treated chronic schizophrenia. In contrast, the majority of published studies on schizophrenia have been focused on early phases of this disease.

In addition, in our study, we investigated a homogenous group of schizophrenic patients, in symptomatic remission, who were treated with different antipsychotics for many years. In this way, the results of this study can be relevant to different clinical situations, encountered in a daily management of such patients.

Limitations

We are aware of some important limitations of our study, such as lack of reliable methods for direct assessment of the patient compliance with medications (this is common in studies exploring drug adherence). In particular, the DAI-10 scale, which we used, can only indirectly indicate whether or not the patient will be taking a given medication. For instance, a patient may be perfectly educated about schizophrenia symptoms, and about the importance of therapeutic adherence, and may even express the best drug attitude in front of an examiner. However, in the real world, he or she might still be noncompliant. Although there is no perfect way to assess the drug compliance, the DAI-10 still remains the most reliable tool in clinical practice.

Our study included patients of similar age, who had comparable duration and onset of schizophrenia. However, we were unable to involve patients with a similar number of hospitalizations. For this reason, there is a concern that differences in the number of hospitalizations could potentially impact the schizophrenia course, and thus, might be a source of bias in interpreting of the study data.

Since in the present study, one classic and two atypical antipsychotics were used, it might be impossible to generalize the study results to therapy with other antipsychotic agents. Nevertheless, the antipsychotics used in this study are common in psychiatric practice, and thus, they should be representative in terms of their clinical efficacy, safety, and mechanisms of action.

Clinical implications

The results of this study provide at least two valuable messages for clinicians. First, it is possible to identify risk factors, predicting undesirable attitude toward medications, such as: earlier onset of schizophrenia, younger patient age, shorter duration of the disease, higher severity of symptoms, treatment with typical neuroleptics, and higher severity of akathisia. Patients with such characteristic should be specifically supervised to improve their treatment adherence. Second, the study findings indicate that olanzapine is well received by patients with chronic schizophrenia and has particularly beneficial impact on exacerbation of negative symptoms in such patients.

CONCLUSIONS

An analysis of clinical parameters, and attitudes toward medication, in a group of patients with chronic schizophrenia allows to identify factors that might increase risk of undesirable attitude to pharmacologic treatment, and in turn, also a worse adherence to treatment. Antipsychotic medications, despite their similar clinical efficacy in treatment of schizophrenia symptoms, have been differently perceived by patients. Among the analyzed study medications, atypical antipsychotics (olanzapine and clozapine) were best perceived by the patients. In particular, using olanzapine was beneficial for improvement of negative symptoms, and good tolerability of the treatment. Moreover, taking olanzapine might arrest the development of negative symptoms in patients with chronic schizophrenia.

Contribution of individual authors:

Marek Krzystanek: design of the study, literature researches and analyses, statistical analyses, interpretation of data, manuscript writing.

Krzysztof Krysta & Małgorzata Janas-Kozik: literature researches and analyses, manuscript writing

Małgorzata Janas-Kozik: literature researches and analyses, manuscript writing.

Ewa Martyniak: manuscript writing.

Janusz Rybakowski: interpretation of data, manuscript writing.

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