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Comparative analysis of EEG in patients with schizophrenia receiving various atypical antipsychotics

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ABSTRACT

Aim. To conduct a comprehensive analysis of EEG recordings of schizophrenia patients receiving atypical antipsychotics as monotherapy.

Materials and methods. We examined 94 patients with schizophrenia aged 33 [28; 40] years with a disease duration of 10 [4; 15] years. The patients were divided into 5 groups depending on the antipsychotic drugs they took: 1) risperidone – 31 patients; 2) quetiapine – 20 patients; 3) aripiprazole – 11 patients; 4) olanzapine – 13 patients; 5) clozapine – 19 patients. EEG was recorded during wakefulness with closed eyes (background test), 3-minute hyperventilation, and rhythmic photostimulation in all patients. To describe and interpret the received recordings, the EEG classification according to J. Micoulaud – Franchi et al. was used.

Results. EEG modifications (score > 1A) were observed in 61.7% (n = 58) of patients. In the group of patients receiving risperidone, EEG modifications were found in 48.4% of cases, in patients taking quetiapine – in 70% of cases, aripiprazole – in 63.6% of cases, olanzapine – in 61.5% of cases, clozapine – in 73.7% of cases. The frequency of epileptiform patterns in patients receiving olanzapine was significantly higher than in those taking risperidone (p = 0.033) and clozapine (p = 0.032). Slowing in the EEG (score > 1) was more often observed in patients taking clozapine – 63.2% (n = 12), olanzapine – 61.5% (n = 8), and quetiapine – 60% (n = 12). Slower EEG waves were less common in patients receiving aripiprazole – 45.5% (n = 5) and risperidone – 45.2% (n = 14). In the group of patients with EEG slowing (score > 1), the dose of chlorpromazine equivalent was significantly greater compared to patients with normal EEG (p = 0.00046).

Conclusion. The data obtained demonstrate changes in EEG parameters during monotherapy with atypical antipsychotics and indicate their dose-dependent effect on the bioelectrical activity of the brain.

Keywords: schizophrenia, antipsychotics, therapy, electroencephalography, slowing, paroxysmal activity

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study and have their personal data processed. The study was approved by the local Ethics Committee at Mental Health Research Institute of Tomsk NRMC (Protocol No. 157 of 18.11.2022).

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Сравнительный анализ электроэнцефалограммы у больных шизофренией, получающих различные атипичные антипсихотики

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РЕЗЮМЕ

Цель. Провести комплексный анализ записей электроэнцефалограммы (ЭЭГ) больных шизофренией, получавших атипичные антипсихотики в режиме монотерапии.

Материалы и методы. Обследованы 94 больных шизофренией в возрасте 33 [28; 40] лет с длительностью заболевания 10 [4; 15] лет. Сформировано пять групп пациентов на основании принимаемых ими антипсихотических препаратов: 1) рисперидон – 31 пациент; 2) кветиапин – 20; 3) арипипразол – 11; 4) оланзапин – 13; 5) клозапин – 19 пациентов. ЭЭГ регистрировалась во время бодрствования с закрытыми глазами (фоновая проба), 3-минутной гипервентиляции и ритмической фотостимуляции у всех пациентов. Для описания и интерпретации полученных записей использовалась классификация ЭЭГ по J. Micoulaud-Franchi и соавт.

Результаты. Изменения (модификации) на ЭЭГ (класс > 1А) наблюдались у 61,7% (n = 58) пациентов. В группе пациентов, принимавших рисперидон, модификации ЭЭГ были обнаружены у 48,4%, кветиапин – 70%, арипипразол – 63,6%, оланзапин – 61,5%, клозапин – 73,7%. Частота эпилептиформных паттернов у пациентов была статистически значимо выше при приеме оланзапина по сравнению с рисперидоном (p = 0,033) и клозапином (p = 0,032). Замедление ЭЭГ (класс > 1) чаще наблюдалось у больных, принимавших клозапин – 63,2% (n = 12), оланзапин – 61,5% (n = 8) и кветиапин – 60% (n = 12). Реже медленные волны на ЭЭГ встречались у больных, принимавших арипипразол – 45,5% (n = 5) и рисперидон – 45,2% (n = 14). В группе больных с замедлением ЭЭГ (класс > 1) хлорпромазиновый эквивалент оказался статистически значимо выше по сравнению с пациентами с нормальной ЭЭГ (p = 0,00046).

Заключение. Полученные данные демонстрируют изменения показателей ЭЭГ в процессе терапии отдельными атипичными антипсихотиками и свидетельствуют об их дозозависимом эффекте на биоэлектрическую активность мозга.

Ключевые слова: шизофрения, антипсихотики, терапия, электроэнцефалография, замедление, пароксизмальная активность

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Исследование проведено в рамках выполнения госзадания № 075–01392–23–00 «Персонализированная диагностика и терапия больных полиморбидными расстройствами шизофренического и аффективного спектра», № 123041900006–4.

Соответствие принципам этики. Все пациенты подписали согласие на участие в исследовании и обработку персональных данных. Исследование одобрено локальным этическим комитетом при НИИ психического здоровья Томского НИМЦ (протокол № 157 от 18.11.2022).

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INTRODUCTION

The study of the effect of psychotropic drugs on the human electroencephalogram (EEG) began in the first half of the 20th century. In 1933, the founder of electroencephalography H. Berger described the changes in the EEG caused by barbiturates and morphine [1]. The first studies that reported anomalies caused by antipsychotic drugs appeared in the early 1970s and used phenothiazine as an example [2]. In 1970–1971, H. Dasberg and S. Robinson described changes related to the toxic effects of drugs, which turned out to be secondary to pre-existing cerebral disorders [2, 3]. Phenothiazine antipsychotics caused slight slowing, an increase in amplitude, synchronization, and expansion of alpha activity in the EEG [2, 3]. H. Dasberg [3] explained that human behavior changes through the effect of antipsychotics in the EEG.

As is known, many patients with mental disorders have various changes in the EEG [4–8]. Approximately 20–40% of patients with mood disorders and 20–60% of patients with schizophrenia have persistent disturbances in the bioelectric activity of the brain [8, 9]. In a relatively big proportion of patients with schizophrenia, changes in the EEG are detected in the form of generalized slowing (delta and theta waves), asymmetry, the presence of sharp waves and spike-and-wave complexes (paroxysmal patterns) [9].

However, a meta-analysis by S. O'Sullivan et al. suggested that most of the changes in the EEG in patients with mental disorders can be explained by taking psychotropic drugs and in this case the EEG cannot be used for the diagnosis of mental disorders [10]. However, EEG can help in determining whether patients suffering from mental disorders are taking prescribed medications, or whether different doses of medications cause side effects in the central nervous system (CNS) [10, 11].

One way or another, taking antipsychotics of different classes is accompanied by changes in the EEG. The literature mainly reports generalized slowing in background activity, an increase in paroxysmal theta or delta activity, and the development of epileptiform discharges [12–14]. Despite the appearance of various new antipsychotics over the past thirty years, only a few studies have been devoted to changes in the EEG caused by atypical antipsychotics [13, 15–18]. Some authors suggest that changes in the EEG caused by taking certain antipsychotics are associated with a good therapeutic response [14].

F. Centorrino et al. [15] showed that EEG changes were more severe when using second-generation antipsychotics than the first-generation ones, with a high risk of EEG modifications when using clozapine (47.1%) and olanzapine (38.5%), and a moderate risk when using risperidone (28%). In their study, severe modifications (spike discharges) were observed in patients taking clozapine (5.9%), olanzapine (7.7%), and risperidone (4.0%), but not in individuals taking haloperidol [15]. Risk factors contributing to significant changes in the EEG were the presence of arterial hypertension, the use of an atypical antipsychotic, the presence of bipolar affective disorder, and old age.

F. Pillmann et al. [16] analyzing the EEG in 43 patients treated with olanzapine showed an increase in diffuse slowing (48.8%), intermittent slowing (34.9%), and epileptiform activity in some patients (9.3%). A study involving 54 patients treated with olanzapine found significant slowing in the EEG (70.4%), the appearance of sharp waves (22.2%), and paroxysmal discharges of slow waves (14.8%) [17]. The combination of olanzapine with other antipsychotics increased the number of EEG modifications, while co-treatment with benzodiazepines reduced the number of EEG changes [17].

In another study, EEG was evaluated in 81 patients receiving quetiapine, olanzapine or haloperidol as monotherapy [18]. Adverse EEG changes were detected in one patient (5%) receiving quetiapine, in 13 (35%) patients receiving olanzapine, and in 5 (22.8%) patients receiving haloperidol. Epileptiform activity was observed only in 4 patients (10.8%) treated with olanzapine [18].

Thus, the prevalence of EEG modifications seems to vary depending on the type of antipsychotic drug taken. According to studies, the prevalence of EEG changes in people taking clozapine ranges from 25 to 53% [13, 15]. Quetiapine causes fewer changes in the EEG [18]. However, the number of EEG studies is very limited.

In this regard, the aim of the study was to conduct a comprehensive analysis of EEG recordings in patients with schizophrenia receiving atypical antipsychotic as monotherapy. We suggested that changes in the EEG may depend on the dose of antipsychotics taken.

MATERIALS AND METHODS

The study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki of the World Medical Association in 1964, as amended in 1975–2013, and approved by the local Ethics Committee at Mental Health Research Institute of Tomsk NRMC (Protocol No. 157 of 18.11.2022).

All the examined patients signed an informed consent to participate in the study and have their personal data processed.

The selection of patients to participate in the study was carried out at the clinic of the Mental Health Research Institute of Tomsk NRMC of the Russian Academy of Sciences. The study included 94 patients with schizophrenia (50 men and 44 women) aged 33 [28; 40] years; the duration of the disease was 10 [4; 15] years, and the age of schizophrenia onset was 23 [20; 28] years. The inclusion criteria were: age of patients 18–60 years, a verified diagnosis of schizophrenia according to the criteria of ICD–10, and an informed consent to participate in the study. The exclusion criteria were: the presence of pronounced organic, neurological, and somatic symptom disorders leading to organ failure, and refusal to participate in the study.

All patients at the time of inclusion in the study received basic antipsychotic therapy at therapeutic doses approved by the Ministry of Health of Russia; the therapy lasted for 4 [1; 9] years. We formed 5 groups of patients based on the antipsychotic drugs they took: 1) risperidone – 31 patients, 2) quetiapine – 20 patients, 3) aripiprazole – 11 patients, 4) olanzapine – 13 patients, 5) clozapine – 19 patients. All doses of medications taken were brought to uniformity in terms of a chlorpromazine equivalent (CPZeq).

Electroencephalography was performed in an electrically shielded room with dim lighting. During the study, patients were sitting in a state of calm, relaxed wakefulness. The EEG was recorded using the NEUROFAX EEG–1200K encephalograph (Nihon Kohden, Japan) according to the International 10–20 system, with monopolar connections in 16 standard leads: Fp_1, Fp_2, F_3, F_4, F_7, F_8, C_3, C_4, P_3, P_4, O_1, O_2, T_3, T_4, T_5 and T_6, with a sampling frequency of 1 kHz, Fz as a grounding electrode and reference electrodes on the earlobes. EEG of all patients was recorded during wakefulness with closed eyes (background test), 3-minute hyperventilation, and rhythmic photostimulation. EEGs were recorded in the morning (between 9 and 12 o'clock), after breakfast. The total duration of the EEG recording was at least 15 minutes.

All patients during the EEG recording were under the supervision of a functional diagnostics doctor, and in case of signs of falling asleep or EEG signs of drowsiness, the recording was stopped. The analysis and interpretation of EEG data was carried out separately by two experienced certified neurophysiologists. In case of disagreement in the interpretation of the data, the EEGs were re-evaluated and discussed to reach a consensus. The EEG Classification by Micoulaud–Franchi et al. was used to describe and interpret the obtained recordings [19], developed to assess the effect of psychotropic drugs (Table 1).

Table 1

EEG modifications using the classification of Micoulaud – Franchi et al.

Slowing score		Excitability score	
Class	Description	Class	Description
1	Absent (predominant alpha)	A	Absent
2	Theta slowing	B	Sporadic epileptiform discharges or sharp waves during hyperventilation or photostimulation
3	Theta slowing with delta bursts	C	Sporadic epileptiform discharges or sharp waves throughout the recording
4	Delta slowing	D	Long lasting epileptiform discharges

The statistical analysis was performed using the Statistica for Windows V. 12.0 software (Statsoft Inc.). Compliance with the law of normal distribution was checked using the Lilliefors-corrected Kolmogorov – Smirnov test and the Shapiro–Wilk test. Data with a normal distribution were presented as the mean and the standard deviation $M \pm SD$. In the absence of a normal distribution, data were presented as the median and the interquartile range Me [Q_1; Q_3]. Qualitative variables were represented by frequency parameters in absolute and relative units n (%). To compare EEG parameters (EEG types according to the EEG classification of Micoulaud–Franchi et al.), the $\chi 2$ test was used. Average daily doses of antipsychotics were compared in accordance with EEG changes using the Student's t-test. The Spearman's rank correlation coefficient was used to identify the relationships between the studied parameters. The threshold level of statistical significance p was assumed to be 0.05.

RESULTS

According to the data obtained, EEG modifications (class >1A) were observed in 61.7% (n = 58) of the patients included in this study. In the group of patients receiving risperidone, EEG modifications were found in 48.4% of cases, in patients taking quetiapine – in 70% of cases, aripiprazole – in 63.6% of cases, olanzapine – in 61.5% of cases, clozapine – in 73.7% of cases (Table 2).

Epileptiform patterns (class B and C) were more often detected in the group of patients taking olanzapine – 30.7% (n = 4). Less frequently, paroxysmal activity was detected in 20% of patients taking quetiapine (n = 4), in 18.2% of patients taking aripiprazole (n = 2), in 12.9% of individuals taking risperidone (n = 4), and in 10.5% of patients taking clozapine (n = 2). The frequency of epileptiform patterns was significantly higher in patients taking olanzapine compared with risperidone (p = 0.033) and clozapine (p = 0.032).

EEG slowing (class >1) was more often observed in patients taking clozapine – 63.2% (n = 12), olanzapine – 61.5% (n = 8), and quetiapine – 60% (n = 12). EEG slowing was less common in patients taking aripiprazole – 45.5% (n = 5) and risperidone – 45.2% (n = 14). However, according to the $\chi 2$ test, these differences did not reach statistical significance ($p > 0.05$). Extremely severe EEG modifications (class 4C or 4D) were not found in the study sample.

We also failed to find correlations between the presence (class >1A) and severity of EEG changes (classes 2 and 3, B and C) and clinical data (age, duration of the disease, age of schizophrenia onset and the duration of therapy) collected from patient clinical records ($p > 0.05$).

The results of comparing the average daily doses of antipsychotics, depending on the presence or absence of EEG changes, are presented in Table 3.

Table 2

Percentage of EEG changes (class >1A) depending on the type of the atypical antipsychotic taken in patients with schizophrenia

Antipsychotic	n	Age of patients, Me [Q_1; Q_3]	Dose CPZeq, mg/day, $M \pm SD$	EEG modifications (class >1A)	
				n	%
Risperidone	31	35 [29; 39]	290.3 ± 89.8	15	48.4
Quetiapine	20	33 [25; 45]	598.6 ± 455.3	14	70
Aripiprazole	11	30 [21; 35]	193.9 ± 80	7	63.6
Olanzapine	13	34 [27; 40]	307.7 ± 171.8	8	61.5
Clozapine	19	33 [32; 44]	163.3 ± 79.9	14	73.7

Table 3

Comparison of average daily doses of atypical antipsychotics in accordance with the presence (class >1A) and absence of EEG changes in patients with schizophrenia

Antipsychotic	EEG modifications (class >1A)		Absent (class = 1A)		p
	n	Dose (CPZeq, mg/day), $M \pm SD$	n	Dose (CPZeq, mg/day), $M \pm SD$	
Risperidone	15	296.7 ± 81.2	16	284.4 ± 99.5	0.452
Quetiapine	14	657.9 ± 503.4	6	460.3 ± 310	0.291
Aripiprazole	7	190.4 ± 103.1	4	199.9 ± 101.2	0.993
Olanzapine	8	262.5 ± 178.8	5	380 ± 148.3	0.754
Clozapine	14	168.1 ± 82.4	5	150 ± 79.5	0.909
All	58	335.3 ± 272.6	36	298.9 ± 176.1	0.00029*

Here and in Table 5, * the reliability of statistical differences at $p < 0.05$.

There were no statistically significant differences in the average daily doses (mg per day) of atypical antipsychotics between patients without and with EEG modifications (risperidone: p = 0.452; quetiapine: p = 0.291; aripiprazole: p = 0.993; olanzapine: p = 0.754; clozapine: p = 0.909). However, when the doses of all antipsychotics were averaged, it could be seen that in patients with EEG changes (class >1A), the dose of chlorpromazine equivalent was significantly greater (p = 0.00029).

Tables 4 and 5 contain the results of comparing the average daily doses depending on the assessment of paroxysmal activity and EEG slowing.

The average daily doses of antipsychotics did not significantly differ in patients depending on the presence or absence of paroxysmal activity (risperidone: p = 0.191; quetiapine: p = 0.261; aripiprazole: p = 0.177; olanzapine: p = 0.848; clozapine: p = 0.725) (Table 4), as well as on the presence or absence of EEG slowing (risperidone: p = 0.386; quetiapine: p = 0.154; aripiprazole: p = 0.374; olanzapine: p = 0.754; clozapine: p = 0.588) (Table 5). However, taking into account the average doses of all atypical antipsychotics, it was found that in the group of patients with EEG slowing (class >1), the dose of the chlorpromazine equivalent was significantly higher (p = 0.00046).

Table 4

Comparison of average daily doses of atypical antipsychotics depending on the assessment of paroxysmal activity

Antipsychotic	EEG modifications (class >A)		Absent (class = A)		*p*
	n	Dose CPZeq, mg/day, *M* ± *SD*	*n*	Dose CPZeq, mg/day, *M* ± *SD*	
Risperidone	4	250 ± 129.1	27	296.3 ± 84.3	0.191
Quetiapine	4	631.9 ± 132.5	16	590.3 ± 126.8	0.261
Aripiprazole	2	199.9 ± 41.4	9	170.3 ± 45.5	0.177
Olanzapine	4	200 ± 141.4	9	225.5 ± 168.5	0.848
Clozapine	2	121.8 ± 39.8	17	168.2 ± 82.7	0.725
All	16	323.2 ± 153.8	78	320.9 ± 156.3	0.171

Table 5

Comparison of average daily doses of atypical antipsychotics depending on the assessment of paroxysmal activity

Antipsychotic	EEG modifications (class >1)		Absent (class = 1)		*p*
	n	Dose CPZeq, mg/day, *M* ± *SD*	*n*	Dose CPZeq, mg/day, *M* ± *SD*	
Risperidone	14	289.3 ± 78.9	17	291.2 ± 100.4	0.386
Quetiapine	12	709.4 ± 517.7	8	432.5 ± 298.4	0.154
Aripiprazole	5	146.6 ± 50.6	6	133.3 ± 81.6	0.374
Olanzapine	8	262.5 ± 178.8	5	280 ± 148.3	0.754
Clozapine	12	175.8 ± 86.2	7	141.9 ± 68.3	0.588
All	51	343.2 ± 233.93	43	295.4 ± 176.5	0.00046*

DISCUSSION

In the present study, the EEG data of 94 patients with schizophrenia who received clozapine, olanzapine, quetiapine, aripiprazole or risperidone as monotherapy were studied. The largest percentage of EEG modifications (class >1A) was found in the group of patients taking clozapine (73.7%), which is slightly higher than in other studies [13, 15, 18]. However, severe modifications (class 4C and 4D) were not detected in any of the patient groups.

The frequency of modifications associated with the presence of epileptiform patterns when taking the above antipsychotics is consistent with research data [13, 15, 16]. However, in contrast to the results of the study conducted by F. Centorrino et al. [15], the frequency of paroxysmal activity for clozapine was significantly lower (10.5%,) whereas for olanzapine it was higher (30.7%).

It is known that the risk of seizures caused by antipsychotics is higher for patients taking olanzapine and clozapine than for those taking risperidone and aripiprazole [20]. In this regard, EEG monitoring is recommended when the average daily dose is 20 mg for olanzapine and 400 mg for clozapine [21, 22]. Like clozapine, olanzapine can cause EEG changes, such as the appearance of slow waves, sharp waves, and paroxysmal slow-wave discharges, but the risk of seizures is considered low [22].

We found no differences in the frequency of paroxysmal activity depending on the average daily doses of any antipsychotic. Thus, it can be assumed that there is no dose-dependent effect of antipsychotics on convulsive activity. However, the number of patients with epileptiform patterns in our study was small. Studies on larger samples could confirm or refute this assumption.

EEG slowing was observed in the majority of the studied patients – 51 (54.3%), which is also consistent with the literature data [15–18]. The most common EEG modification in patients taking antipsychotics was diffuse slowing of bioelectrical activity (73.9%). Diffuse EEG slowing is often associated with the effect of psychotropic drugs and compared with the effect of electroconvulsive therapy [23]. There is an assumption that diffuse or paroxysmal EEG slowing during antipsychotic therapy may indicate a favorable outcome of the therapy [14]. However, some researchers [12, 13] found that patients with a long duration of therapy had EEG slowing and explained this phenomenon by an increase in the severity of the disease [13].

In our opinion, it is impossible to exclude the influence of the disease duration on these parameters, since schizophrenia is a pathology requiring specific

treatment [24, 25]. In our study, we found no differences in the frequency of EEG slowing depending on the average daily doses of any atypical antipsychotic. However, taking into account the average doses of all antipsychotics, it was found that the dose of the chlorpromazine equivalent was significantly higher in the group of patients with EEG slowing. Thus, we assume that with an increase in the therapeutic dose of antipsychotics, we can expect an increase in slow-wave activity in the EEG and, as a consequence, generalized slowing in the bioelectrical activity of the brain. Another important result of the study was the fact that the effect of antipsychotics on the EEG was found to correspond to the spectrum of their atypia described by M. Carli et al. [26].

CONCLUSION

The study revealed several interesting results. Firstly, the most frequent EEG changes were observed in patients taking clozapine compared to other atypical antipsychotics. These changes were more related to EEG slowing. Secondly, epileptiform patterns were most often detected in the group of patients taking olanzapine compared to other antipsychotics, although olanzapine also caused EEG slowing. Thirdly, we found a dose-dependent effect of atypical antipsychotics in relation to EEG slowing. A higher percentage of EEG slowing episodes appears to be associated with higher doses of the chlorpromazine equivalent. Thus, the data obtained indicate the need for the use of electroencephalography in monitoring antipsychotic therapy.

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Authors' contribution

Galkin S.A. – neurophysiological examination of patients, analysis and interpretation of the data, drafting of the manuscript. Kornetova E.G. – conception and design, clinical, psychopathological, and psychometric examination of the sample, critical revision of the manuscript for important intellectual content. Ivanova S.A. – final approval of the manuscript for publication.

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