The characteristics of outpatient treatment of patients with schizophrenia in Lithuania

Šizofrenija sergančių pacientų ambulatorinio gydymo ypatumai Lietuvoje

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SUMMARY

Background. Long-term outpatient treatment plays the main role in schizophrenia's relapse prevention. The fast development of antipsychotics leads to various treatment choices.

The aim. To evaluate the association between schizophrenia patients' sociodemographic/clinical characteristics, outpatient treatment regimens and prescribed psychotropic medications.

Methods. One-year data of schizophrenia patients' medical records of visits to the primary mental health center were collected in one Lithuanian region. Data included: age, gender, treating psychiatrist, duration of the mental disorder, frequency of visits to the primary mental health care center, number of hospitalizations and the psychopharma -cological treatment. Particular attention was devoted to antipsychotic medications, their dosages, forms and types, concomitant psychotropic medications prescription and treatment correction.

Results. The study evaluated 172 participants with the mean age 51.5±13.8. The average duration of the mental disorder was 18.3±10.5, while the mean number of visits to the primary mental health center – 8±3,4. The range of hospitalizations varied around 0 to 4. The study revealed the negative relations between age of the patient and the number of visits (r=–0.253 (p<0.01)). Only 41.9 % of cases included monotherapy, while polytherapy – 58.1 % of cases. Longer illness duration led to a higher number of antipsychotic (r=0.212 (p<0.06)) and concomitant psychotropic medications (r=0.156 (p<0.05)). The study showed that treatment corrections were more common with a lower number of hospitalizations (p<0.001). The most frequent prescribed medication was Olanzapine oral (14.5 %). Longacting injectable antipsychotics were chosen in 22.1% of the cases: the mean age of patients receiving this treatment was 10.6 years lower, compared with oral, however, there was no statistically significant difference between the age of the patient and longacting antipsychotics prescription (p<0.99). Other psychotropic medications, were prescribed to 63.4 % of participants, they visited the primary mental health care center more often (p<0.004). In 67.6 %of corrected treatment cases included concomitant psychotropic medications.

Conclusions. In more than half of schizophrenia cases outpatient treatment included polytherapy. The number of antipsychotic and other psychotropic medications got higher with a more frequent visits to the primary mental health care center and longer duration of mental illness.

Key words: schizophrenia, polytherapy, antipsychotics, outpatient treatment, psychotropic medications

SANTRAUKA

Įvadas. Ilgalaikis ambulatorinis šizofrenijos gydymas yra vienas iš svarbiausių veiksnių ligos atkryčių prevencijai. Dėl didėjančios antipsichotinių vaistų įvairovės ambulatorinis gydymas įvairiais atvejais skiriasi.

Tikslas. Įvertinti sąsajas tarp šizofrenija sergančiųjų sociademografinių -klinikinių charakteristikų, ambulatorinio gydymo režimo bei skiriamų psichotropinių vaistų.

Metodai. Analizuoti šizofrenija sergančiųjų vienerių metų ambulatorinių apsilankymų psichikos sveikatos centre medicininiai įrašai viename Lietuvos rajone. Sukaupta informacija apie paciento amžių, lytį, gydantį gydytoją, ligos trukmę, lankymosi pirminiame psichikos sveikatos priežiūros centre dažnį, stacionarizavimo dažnį ir psichofarmakologinį gydymą. Atkreiptas dėmesys į skiriamus antipsichozinius vaistus, jų dozes, skyrimo formą ir rūšį, papildomų psichotropinių vaistų skyrimą ir gydymo koregavimą.

Rezultatai. Vertinti 172 pacientai, amžiaus vidurkis – 51,5±13,8 metai. Vidutinė ligos trukmė – 18,3±10,5 metų, o apsilankymų pirminiame psichikos sveikatos priežiūros centre dažnio vidurkis – 8±3,4 kartai. Stacionarizavimo dažnis 0–4 kartų. Nustatyta, kad didėjant paciento amžiui, ambulatorinių apsilankymų skaičius reikšmingai mažėjo (r=–0,253 (p<0,01)). Tik 41,9 proc. atvejų pasirinktas gydymas monoterapija, tuo tarpu politerapija – net 51,8 proc. atvejų. Ilgesnė ligos trukmė siejosi su didesniu antipsichotinių (r= 0,212 (p<0,06)) ir kitų psichotropinių vaistų kiekiu (r= 0,156 (p<0,05)). Gydymo koregavimas siejosi su mažesniu hospitalizacijų skaičiumi (p<0,001). Dažniausiai skiriamas antipsichozinis vaistas – geriamasis Olanzapinas (14,5 proc.). Ilgai veikiantys injekuojami antipsichoziniai vaistai buvo skirti 22,1 proc. atvejų. Juos vartojantys buvo vidutiniškai 10,6 metais jaunesni, lyginus su geriamųjų antipsichozinių vaistų vartotojais, tačiau jų skyrimas nuo amžiaus statistiškai reikšmingai nesiskyrė (p<0,99). Kiti psichotropiniai vaistai buvo skirti 63,4 proc. atvejų, juos vartojantys klinikoje lankėsi reikšmingai dažniau (p<0,04). Pacientams, kuriems gydymas koreguotas, 67,6 proc. atvejų buvo skirti kiti psichotropiniai vaistai.

Išvados. Daugiau nei pusė šizofrenija sergančiųjų ambulatoriškai buvo gydomi politerapija. Antipsichozinių ir kitų psichotropinių vaistų kiekis didėjo sąsajoje su ilgėjančia ligos trukme ir dažnesniu apsilankymu pirminiame psichikos sveikatos priežiūros centre.

Raktiniai žodžiai: Šizofrenija, ambulatorinis gydymas, politerapija, antipsichotikai, psichotropiniai vaistai

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INTRODUCTION

Schizophrenia is a severe mental disorder with a lifetime risk of about 1%, characterized by hallucinations, delusions and cognitive deficits with heritability estimated at up to 80% [1, 2]. It is believed to have a complex aetiopathogenesis and to affect widely distributed neural circuitry [3, 4]. The disorder is typically associated with a significant functional disability and usually manifests in the early 20s. Such a change in a young age crucially affects the quality of life and requires an immediate reaction from both patient and a treating physician. Permanent outpatient treatment plays the main role in schizophrenia's relapse prevention. Although there are other treatment methods, like electroconvulsive therapy, antipsychotic medications have been a mainstay of treatment for more than half a decade. The fast development of antipsychotics leads to various treatment choices. For example, there are more options for choosing the form and duration of action of the antipsychotic. It can be used orally every day or injected for a longer period. The long-acting injection is usually chosen when a patient has troubles taking their medication daily. Furthermore, the development of a range of antipsychotic medications has provided individuals with schizophrenia some relief from the cardinal symptoms of the illness [5] and reduced the number of recurrent psychotic episodes [6]. Such wide medication options give an opportunity to apply a suitable and effective treatment to prevent hospitalization caused by psychosis or its complications. It is known that substantial numbers of suicide victims with schizophrenia are receiving inadequate antipsychotic treatment [7]. Moreover, recent findings suggest that formerly widespread use of very high doses antipsychotics, has been replaced by an increased use of more than one antipsychotic agent at the same time, usually at moderate doses of each agent, as well as their combination with other types of psychotropic drugs (especially mood-altering and sedative agents)[8, 9]. These practices can be considered as examples of 'polytherapy'.

Our study was performed to evaluate the association of schizophrenia patients' sociodemographic/clinical characteristics, outpatient treatment regimes and psychotropic medications.

METHODS

The study was performed in the primary mental health care center in Lithuania (served the population of the area – 48 000 inhabitants). The study and its consent procedures were approved by a Human Subjects Bioethics Review Committee (No. BEC-MF-22). One-year data of schizophrenia patients' medical records of outpatients' visits to the primary mental health care center were collected (particularly from 2017 July to 2018 June). Data included: age, gender, treating psychiatrist (coded 1–4), duration of the mental disorder, frequency of visits to the primary mental health care center, number of hospitalizations and the psychopharmacological treatment the patient received for the last year period.

Particular attention was devoted to psychopharmacological treatment. Firstly, we observed the number of all psychotropic medications a patient received, including antipsychotics, sedatives, antidepressants and hypnotics. According to this, the data were distributed into two groups: monotherapy and polytherapy. Furthermore, the form and generic name of prescribed antipsychotics were identified. Lastly, the treatment changes during one-year period were evaluated.

The statistical analysis was performed using SPSS 19.0. Scale variables (age, duration of the disorder, number of visits to the primary mental health care center, etc.) were described as means and standard deviation. Nominal variables were described by distribution – in numbers (n) and percentages (%). The frequency rates were compared using Chi-square. For comparison the means the independent t-test was used. Other statistical tools were also performed: correlations between variables using Spearman's correlation for significance evaluation and tests of nonparametric independent samples. Statistical significance was set at the 5% level ($p<0.05$).

RESULTS

Of all 172 participants, included in the study (0.7% of region population), 57.6% were men. Other sociodemographic/clinical characteristics of study patients are presented in Table 1. The study revealed the significant negative correlations between age of the patients and the number of outpatient visits ($r= –0.253$ ($p<0.01$)). Study participants used from 1 to 3 different antipsychotics at the same time (range 1–4, including other psychotropic medications). In most cases, one (54.3 %) or two (44. 2 %) antipsychotic medications were received. In addition, prescription of three antipsychotics was unusual in this study (1.5 %). Only 41.9 % of cases included monotherapy, while polytherapy – 58.1 %.

The study showed the relations among the number of antipsychotics and all other psychotropic medications with the clinical characteristics of schizophrenia patients (Table 2).

More than 40 different options for antipsychotic treatment were observed. The most frequent prescribed antipsychotic medications and the combinations are shown in table 3. Clozapine, antipsychotic used for treatment-resistant schizophrenia, was prescribed for 5.8% patients, the majority of them (70%) used Clozapine in monotherapy. Furthermore, long-acting injectable antipsychotics were chosen in 22.1% of the cases. The mean age of patients receiving it was 10.6 years lower, compared with oral, however, there was no statistically

Table 1. **Sociodemographic characteristics of schizophrenia patients**

Sociodemographic characteristics	Mean	Standard deviation
Age, years	51.5	13.8
Duration of the mental disorder, years	18.3	10.5
Number of visits to the primary mental health center	8	3.4
Number of hospitalizations	0.2	0.6
Number of antipsychotic medications	1.4	0.6
Number of all psychotropic medications	2.2	0.8

Table 2. **The relations between received medications number and clinical characteristics**

Clinical characteristics	Number of antipsychotic medications	Number of all psychotropic medications
	rs	
Duration of the mental disorder	0.188*	0.131
Number of visits to the primary mental health care center	–0.290	0.195*
Number of hospitalizations	0.011	0.021

*p<0.05

significant difference between the age and long-acting injectable antipsychotics prescription (p<0.99). The most frequent prescribed long-acting injectable antipsychotic was Haloperidol Decanoate in combination with oral Olanzapine. The second popular long-term injectable antipsychotic was Paliperidone Palmitate (3.5 %).

In addition, other psychotropic medications, such as antidepressants or sedatives, were prescribed to 63.4% of patients. It was noticed that patients who used concomitant psychotropic medications visited the primary mental health care center significantly more often (p<0.01).

The outpatient treatment was adjusted to 37 participants (21.5%) during a one-year period. The study showed that more common corrections related to a lower number of hospitalizations (p<0.001). Antipsychotic medication changes were performed only in 23.4% of corrected treatment cases. The most common change was either to Quetiapine oral (13.5%) or combination of oral Olanzapine and Aripiprazole (13.5%). Moreover, 67.6% of corrected treatment cases included adding concomitant medications. The study showed a statistically significant difference between different doctors and the number of prescribed concomitant psychotropic medications (p<0.001).

Table 3. **The most frequent outpatient antipsychotic treatment among study participants**

Antipsychotic medications	Frequency, %
Olanzapine	14.5
Quetiapine	14.0
Quetiapine and Risperidone	9.9
Olanzapine and Risperidone	8.7
Risperidone	5.2
Haloperidol Decanoate and Olanzapine	4.7
Olanzapine and Aripiprazole	4.7
Quetiapine and Aripiprazole	4.7
Paliperidone palmitate	3.5
Haloperidol and Olanzapine	2.3
Quetiapine and Ziprazidone	1.7
Quetiapine and Amisulpiride	1.2
Amisulpiride	1.2
Haloperidol Decanoate and Risperidone	1.2
Risperidone and Levomepromazine	1.2

DISCUSSION

We have analyzed the characteristics of outpatient treatment of schizophrenia patients in one Lithuanian region: regarding age, gender, duration of the mental disorder, visits to the primary mental health center and hospitalizations. The main finding in our study was that in outpatient treatment the polytherapy (combination) of antipsychotics with other psychotropic medications was chosen almost as frequently as monotherapy. Comparing to a study in Palestine, where 50,4 % of study patients received antipsychotic combinations, prescribing two or more antipsychotics in Lithuania is is slightly less prevalent [10]. The number of all prescribed psychotropic medications rose with the duration of the mental disorder and with the number of visits to the primary mental health center. Similar results were found of Sim K et al study. They enrolled 300 patients with schizophrenia in Singapore. The polytherapy was encountered in 71.7% of participants and it was associated with longer mental illness duration [11]. Although we do not analyze different concomitant psychotropic medications, one of the most popular groups of psychotropic medications prescribed are antidepressants. Along with antipsychotics they are more effective in treating the negative symptoms of schizophrenia than antipsychotics alone [12]. According to Harvey PD et al., longer illness duration might indicate older age, which leads to more negative symptoms [13]. Considering that, we can presume that polytherapy for patients with longer illness duration might be chosen because of more frequent manifestation of negative symptoms. However, our study showed that the number of visits to the primary mental health center decreases with age, so the true reasons of polytherapy remain unclear and need further investigation.

In addition, our study showed that oral treatment was prescribed significantly more frequent than the injectable long-acting one. Long-acting injectable antipsychotics are less popular in Lithuania, comparing to other countries. For example, in Sweden almost half of schizophrenia patients receive long-acting injectable antipsychotics [14]. An important note is that injectable long-acting antipsychotics were chosen more often to younger patients. Younger age is known to be associated with earlier treatment discontinuation [15]. In Tiihonen J et al. cohort study results showed a significantly lower risk of discontinuation and rehospitalization with injectable long-acting antipsychotic formulation [16]. Moreover, long-acting antipsychotic use (compared with oral) is associated with about 30 % lower risk of death, says a nationwide cohort of 29 823 patients with schizophrenia [17]. Malla A et al. in their recommendations for clinicians suggest that long-acting injectable antipsychotic should be offered as a treatment option to all individuals, receiving antipsychotic treatment [18]. The most frequent prescribed injectable long-acting antipsychotics in our study was Haloperidol decanoate and Paliperidone palmitate. Similar results are seen in an American study, where Haloperidol decanoate is the most popular prescribed antipsychotic [19]. McEvoy JP et al. study, comparing Haloperidol decanoate and Paliperidone palmitate showed that Haloperidol decanoate more frequent induced

akathisia [20]. Many physicians talk about the advantages of long-acting injectable antipsychotics, however data from randomized controlled trials comparing long-acting versus the oral formulation of the same antipsychotic showed that there is no robust evidence to support doctors in choosing long-acting injectable instead of oral formulations in order to gain better tolerability and efficacy [21].

Over 40 different treatment options in our study simply confirm, that choosing suitable antipsychotic is very individual and depends on various patients and illness features. Nevertheless, some treatment tendencies are noticeable. Since extrapyramidal adverse effects are one of the most uncomfortable reactions, it seems quite clear why atypical antipsychotic Olanzapine oral is the most popular prescribed antipsychotic in this study. Similar results are seen in Tiihonen et al. study, where Olanzapine is also the most frequent received oral antipsychotic [14]. Duggan L et al. Cochrane review showed that patients receiving Olanzapine experienced fewer extrapyramidal side effects compared to other atypical or typical antipsychotics [22]. It is also very important that nowadays more authors are talking about sustaining cognitive functions when treating schizophrenia. Despite the fact that in Neil D. Woodward et al meta-analysis study no pairwise contrasts in overall cognition between atypical neuroleptics were observed, olanzapine and quetiapine (second most popular neuroleptic in our study) outperformed vigilance and selective attention [23].

There is little evidence in supporting the combination of antipsychotics in schizophrenia [24], but more than 45% of participants in our study were treated with two or more antipsychotics at the same time. As in polytherapy treatment cases, the association between a higher number of antipsychotics and mental illness duration is noticed. Review of various published clinical data on treatment-resistant schizophrenic and schizoaffective patients suggested that combinations were beneficial in patients with a reduction of positive symptoms and occasionally negative symptoms [25]. The most common antipsychotic combinations in our study were oral forms of either Olanzapine or Quetiapine with Risperidone. In their practice guideline for the treatment of patients with schizophrenia Lehman AF et al. claimed that several antipsychotics may be beneficial to those patients, who did not respond adequately to antipsychotic monotherapy [26]. Another reason could be the prevention of an acute exacerbation while switching medications. It might also explain why Olanzapine and Aripiprazole combination is widely used for correction in our study. In meta-analysis investigating antipsychotic co-treatment versus monotherapy, 12 of 18 subgroup analyses showed antipsychotic combinations were associated with significantly greater efficacy [27]. Talking about particular antipsychotic combinations, augmentation of Clozapine remains the most widely studied antipsychotic combination. It is a generally accepted treatment option for select patients [26], although in our study Clozapine with or without any additives was prescribed only for 5.8% of patients.

In this study, we have learned, that polytherapy is a widespread outpatient treatment for patients diagnosed with schizophrenia in Lithuania. However, there is a necessity to ascertain the true reasons for this kind of treatment. According to study results, we can presume that prescribing additional antipsychotic or psychotropic medications is the most frequent solution for insufficient treatment response. In addition, instead of oral antipsychotic adjustment or prescription of injectable long-acting antipsychotic, polytherapy remains a popular treatment for patients with longer illness duration. One of the weaknesses of this study is that the dosages of antipsychotic medications aren't analyzed. This kind of information would allow us to consider the possibility of inadequate antipsychotic treatment. Moreover, the identification of the most frequently prescribed concomitant psychotropic medications would be beneficial. Our study also showed the association between treatment correction and a lower number of hospitalizations. This finding proves a necessity of careful supervision in schizophrenia treatment cases in order to prevent exacerbations. However, identifying psychotropic medications received before the correction would allow us to extend our study and analyze the most frequent ineffective treatment.

CONCLUSION

In more than half of schizophrenia cases outpatient treatment included polytherapy. The number of antipsychotic and other psychotropic medications got higher with a more frequent visits to the primary mental health care center and longer duration of mental illness.

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