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# Practice of prescribing antipsychotics in schizophrenia during 2013-2018 based on data from the National Health Fund

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**Summary**

**Aim.** The aim of the study was to analyse the prescribing pattern of antipsychotic drugs in patients with schizophrenia during the years 2013–2018.

**Method.** Schizophrenia is analysed as one of the diseases with the highest rate of Disability-Adjusted Life Years – DALY. In this study, the unitary data of the National Health Fund (NFZ) reported in the years 2013–2018 were used. Adult patients were identified by their Personal Identification Number (PESEL), and the antipsychotics were identified by the European Article Number (EAN). The study included 209,334 adults who were diagnosed with F20 to F20.9 (according to ICD-10) and were prescribed at least one antipsychotic within a year. The active substances of prescribed antipsychotic medication have been divided into typical (first generation), atypical (second generation) and long-acting injectable antipsychotics (both first and second generation). The statistical analysis contains descriptive statistics for selected sections. A linear regression, one-way analysis of variance and t-test were used in the study. All statistical analyses were performed using R, version 3.6.1 and Microsoft Excel.

**Results.** In the years 2013–2018, the number of patients in the public sector diagnosed with schizophrenia increased by 4%. The largest increase was recorded among persons diagnosed with other schizophrenia (F20.8). In the analysed years, the number of patients who were prescribed second-generation oral antipsychotics increased significantly as well as the number of patients who were prescribed long-acting antipsychotics, especially the second generation agents (risperidone LAI, olanzapine LAI). The most prescribed first-generation

antipsychotics included: perazine, levomepromazine and haloperidol with a downward trend for each; and the most common second-generation drugs included: olanzapine, aripiprazole and quetiapine. A noteworthy finding was an extremely high increase in the frequency of prescribing haloperidol in the form of depot.

**Conclusions.** Extending the study to include information on applied prescriptive practice in the private sector would provide a fuller picture of the studied phenomenon.

**Key words:** pharmacotherapy, schizophrenia, maps of health needs

## Introduction

Schizophrenia is a chronic, multidimensional mental disorder with a multifactorial aetiology and varying severity. Despite many years of observation and research, the debate on the nosological boundaries of schizophrenia is still underway. According to some researchers [1], the symptomatic polymorphism of schizophrenia can involve the interactive effects of a broad range of genetic, environmental, and developmental risk factors.

Due to heavy personal and social burden, schizophrenia is a major challenge in terms of health policy and public finances as well as the organisation and general functioning of the healthcare system [2, 3].

According to the literature, effective treatment of schizophrenia involves three main components – pharmacotherapy [4], psychotherapy [5] and psychosocial interventions [6, 7], the main goal of which is to ensure clinical, personal and social recovery of patients with schizophrenia [8, 9].

A significant breakthrough in the treatment of schizophrenia is attributed to pharmacotherapy, including first-generation antipsychotic drugs introduced in the 1950s and 1960s as well as second-generation drugs available since the 1990s. Detailed guidelines have been published in order to avoid adverse effects associated with the use of various drugs from both groups [10, 11].

Due to the diverse symptomatology, significant clinical heterogeneity of schizophrenia, and a wide range of available antipsychotic drugs, it became necessary to prepare treatment recommendations to optimise pharmacotherapy [4, 11-17]. Authors [18, 19] have adopted a clinical staging approach for standardising effective pharmacotherapy as they believe that this will allow the use of safer and more effective treatment based on biological markers.

Remarkably, there have been different concepts in clinical practice regarding the prescription of antipsychotic drugs to patients diagnosed with schizophrenia. Despite significant methodological differences in the following referenced studies, it is clear that most countries such as England and Wales [20], Austria, Belgium, Switzerland, Hungary, Germany [21, 22], India [23] and Nepal [24] opt for the use of second-generation antipsychotics which account for 59% – 80% of all prescriptions. Of those, the most prescribed drugs are olanzapine, risperidone, quetiapine and clozapine. In Nigeria [25], the most frequently prescribed drug is haloperidol (52%) and other first-generation drugs – 46%, while in Korea [26] they account for 39.43% of prescriptions.

In addition to its explanatory value, the multiannual analysis of prescribing trends of antipsychotic drugs in patients with schizophrenia may also have a practical relevance in terms of recommendations and reimbursement policy in Poland.

## Aim of the study

The aim of our study is to analyse the prescribing practice concerning antipsychotic drugs in patients with schizophrenia in the years 2013-2018.

## Material and methods

The starting point of our study is an online application launched in 2019 by the Ministry of Health to analyse the problem of schizophrenia in Poland as one of the five diseases with the highest rate of Disability-Adjusted Life Years – DALY [27]. The data presented in the application cover information on patient demographics, health services provided to patients, and prescription data.

We used individual-related data derived from the National Health Fund (NFZ) that were reported to NFZ by healthcare providers in 2013-2018. The NFZ database contains information on patients identified by individual numbers recorded in the Universal Electronic System for Registration of the Population (PESEL). Regarding the prescription data which have been collected since 2013, the European Article Number (EAN) was used to identify respective drugs. These were combined with the data on age, gender, primary diagnosis (according to ICD-10) and the patient's official place of residence (acknowledging the possibility of patient migration in any given year).

Our analysis concerns health services provided to adult patients, i.e. individuals who, according to their birth certificate, were at least 18 in the year of provision of the service. Patients were divided into three main age groups, namely: young adults (18-39 years old), middle-aged adults (40-59 years old) and seniors (60+) all of whom had schizophrenia as the primary diagnosis identified by different ICD-10 codes: F20.0 (paranoid schizophrenia), F20.1 (hebephrenic schizophrenia), F20.2 (catatonic schizophrenia), F20.3 (undifferentiated schizophrenia), F20.4 (post-schizophrenic depression), F20.5 (residual schizophrenia), F20.6 (simple schizophrenia), F20.8 (other schizophrenia), F20.9 (schizophrenia, unspecified). The F20 code was used where no extended disease code was reported. The study included patients who were prescribed at least one antipsychotic drug within a year.

The active substances of the prescribed antipsychotic drugs were divided into two classes:

(1) First-generation (typical) antipsychotics: perazinum, levomepromazinum, haloperidolum, chlorprothixeni hydrochloridum, sulpiridum, zuclopenthixoli dihydrochloridum, flupentixoli dihydrochloridum, chlorpromazini hydrochloridum and promazine;
(2) Second-generation (atypical) antipsychotics: olanzapinum, aripiprazolum, quetiapinum, risperidonum, clozapinum, amisulpride, ziprasidonum and sertindolum.

The active substances of long-acting injectable (LAI) antipsychotics were also divided into:

(1) Typical: zuclopenthixoli decanoas, haloperidoli decanoas, flupentixoli decanoas;
(2) Atypical: risperidonum, olanzapinum, aripiprazolum.

The statistical analysis contains descriptive statistics for selected sections. A linear regression was used to determine the dynamics of change in prescription patterns, including the number and type (generation) of the drugs. We used the one-way analysis of variance (one-way ANOVA) to compare the average doses (in milligrams) of the most prescribed active substances and the t-test to check the differences in the number of active substances of antipsychotic drugs prescribed in 2013 and 2018. The level of statistical significance was $p < 0.05$. All statistical analyses were prepared using the R application version 3.6.1 and Microsoft Excel.

## Results

### Patients – selected variables

The 2013 – 2018 analysis includes 209,334 patients diagnosed with schizophrenia. Although any given patient may appear more than once in subsequent years of the study, he/she still counts as a single case in each reporting year. The number of patients across the analysed years is presented in Table 1.

Table 1. **Number of patients diagnosed with schizophrenia in 2013 – 2018**

| ICD-10 | Year | | | | | | Change |
|---|---|---|---|---|---|---|---|
| | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2018 vs 2013 |
| F20 | 81,564 | 85,843 | 82,829 | 78,435 | 74,603 | 71,525 | -12% |
| F20.0 | 71,904 | 77,833 | 79,307 | 79,777 | 81,544 | 83,153 | 16% |
| F20.1 | 507 | 532 | 607 | 534 | 490 | 418 | -18% |
| F20.2 | 483 | 544 | 576 | 550 | 508 | 478 | – 1% |
| F20.3 | 1,720 | 1,859 | 1,829 | 1,960 | 2,019 | 2,082 | 21% |
| F20.4 | 1,533 | 1,622 | 1,654 | 1,601 | 1,519 | 1,497 | – 2% |
| F20.5 | 12,363 | 12,710 | 12,736 | 12,740 | 12,684 | 12,754 | 3% |
| F20.6 | 584 | 660 | 797 | 673 | 711 | 665 | 14% |
| F20.8 | 1,525 | 1,663 | 1,803 | 1,921 | 2,016 | 2,134 | 40% |
| F20.9 | 1,491 | 1,644 | 1,606 | 1,710 | 1,755 | 1,702 | 14% |
| Total | 138,843 | 147,277 | 146,950 | 146,591 | 145,565 | 143,743 | 4% |

The results indicate that in 2013 – 2018 there was a 4% increase in the number of patients diagnosed with schizophrenia. The highest increase in the number of patients was recorded in the groups diagnosed with F20.8 (other schizophrenia) – 40% and

F20.3 (undifferentiated schizophrenia) – 21%, while the largest decrease was seen in the F20.1 diagnosis (hebephrenic schizophrenia) – 18%.

The demographic variables (gender and age) for the analysed years are presented in Table 2.

Table 2. **Demographic variables of patients diagnosed with schizophrenia in 2013-2018**

| Variable | Year | | | | | | Change |
|---|---|---|---|---|---|---|---|
| | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2018 vs 2013 |
| Sex | | | | | | | |
| Women | 72,954 | 77,161 | 76,533 | 76,047 | 74,941 | 73,422 | 1% |
| % women | 53% | 52% | 52% | 52% | 51% | 51% | – 3% |
| Men | 65,889 | 70,116 | 70,417 | 70,544 | 70,624 | 70,321 | 7% |
| % men | 47% | 48% | 48% | 48% | 49% | 49% | 3% |
| Age | | | | | | | |
| 18-39 years | 40,355 | 44,681 | 44,264 | 43,169 | 42,051 | 40,564 | 1% |
| % 18-39 | 29% | 30% | 30% | 29% | 29% | 28% | – 3% |
| 40-59 years | 62,608 | 65,238 | 63,666 | 62,812 | 61,742 | 60,326 | – 4% |
| % 40-59 | 45% | 44% | 43% | 43% | 42% | 42% | – 7% |
| 60+ | 35,880 | 37,358 | 39,020 | 40,610 | 41,772 | 42,853 | 19% |
| % 60+ | 26% | 25% | 27% | 28% | 29% | 30% | 15% |
| Average age | 48.5 | 48.0 | 48.2 | 48.4 | 48.6 | 48.9 | 1% |

In the analysed years, the total number of female patients is greater than the number of male patients, but the proportions varied as the study progressed. Thus, in 2013 and 2018 women constituted 53% and 51% of patients vs 47% and 49% of men, respectively. Considering patient age, the greatest change in terms of the number of patients was seen for the 60+ group – an increase by 19%.

The data concerning patients' official place of residence in 2013-2018 are presented in Table 3.

Table 3. **Place of residence of patients diagnosed with schizophrenia in 2013-2018**

| Place of residence | Year | | | | | | Change |
|---|---|---|---|---|---|---|---|
| | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2018 vs 2013 |
| Large city (>100 thousand) | 45,264 | 47,933 | 47,458 | 47,131 | 46,366 | 45,219 | 0% |
| Residents of large cities [%] | 32.6% | 32.5% | 32.3% | 32.1% | 31.9% | 31.4% | -4% |
| Medium-sized town (20-100 thousand) | 29,974 | 31,893 | 31,584 | 31,440 | 30,963 | 31,198 | 4% |
| Residents of medium-sized towns [%] | 21.6% | 21.6% | 21.5% | 21.4% | 21.3% | 21.7% | 0% |

*table continued on the next page*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Small town (<20 thousand) | 18,806 | 19,830 | 19,751 | 19,819 | 19,422 | 19,469 | 4% |
| Residents of small towns [%] | 13.5% | 13.5% | 13.4% | 13.5% | 13.4% | 13.5% | 0% |
| Village | 44,845 | 47,679 | 48,237 | 48,308 | 48,634 | 47,982 | 7% |
| Residents of villages [%] | 32.3% | 32.4% | 32.8% | 32.9% | 33.5% | 33.4% | 3% |

The years 2013-2018 saw only a small change in the geographical structure of patients understood as the place (area) of official residence. The biggest increase in patients was observed in rural areas – 7% compared to year one of the analysis. There was also a slight increase (about 4%) for medium-sized and small-town populations.

## Prescribed antipsychotics

The number of active substances of antipsychotic drugs prescribed to patients per year and the number of patients who were prescribed the drugs are shown in Table 4.

Table 4. **Number of active substances of antipsychotic drugs prescribed to a patient and the number of patients in 2013-2018**

| Number of active substances | Year | | | | | | Change |
|---|---|---|---|---|---|---|---|
| | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2018 vs 2013 |
| | Number of patients | | | | | | |
| One | 62,174 | 62,914 | 60,917 | 57,775 | 55,359 | 54,717 | -12% |
| % of patients | 45% | 43% | 41% | 39% | 38% | 38% | -15% |
| Two | 50,246 | 54,647 | 55,496 | 55,633 | 56,293 | 56,137 | 12% |
| % of patients | 36% | 37% | 38% | 38% | 39% | 39% | 8% |
| Three or more | 26,423 | 29,716 | 30,537 | 33,183 | 33,913 | 32,889 | 24% |
| % of patients | 19% | 20% | 21% | 23% | 23% | 23% | 20% |

The results reflect a significant change in the number of active substances prescribed to patients over the years. According to the boundary values, the greatest increase (24%) is observed for three or more active substances. The analysis of the results by means of a linear regression in each of the three sections showed a statistically significant decrease in the number of patients prescribed a single active substance ($p < 0.001$, R2 = 0.89). At the same time, there was a statistically significant increase in the number of patients prescribed two active substances ($p = 0.05$, R2 = 0.57) and three active substances or more ($p < 0.001$, R2 = 0.77).

Figure 1 shows a comparison of the number of active substances prescribed to a patient in 2013 and 2018.

The violin plot shows the number of active substances prescribed in 2013 and 2018. The box plot marked in the centre shows prescribing frequency for neuroleptics, while the whiskers correspond to the 95% confidence interval and outliers, indicated by black dots. The marked area of the chart represents the density distribution for the

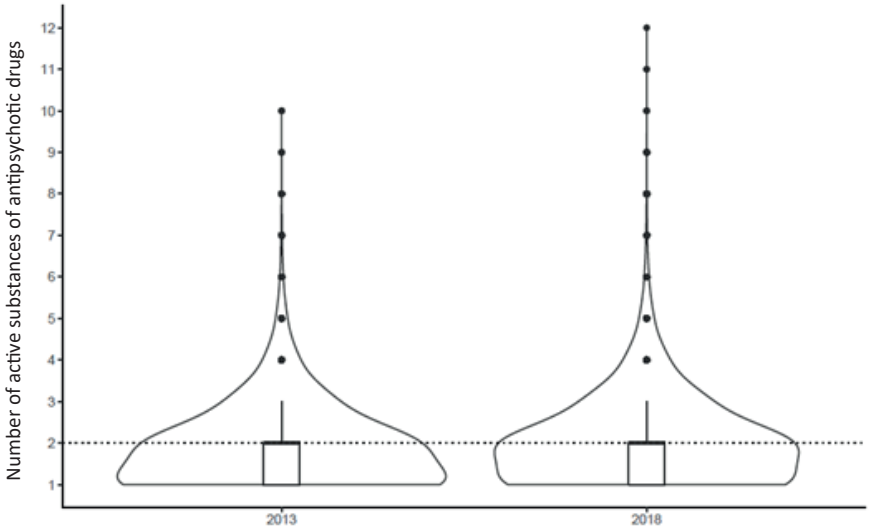


Figure 1. **Number of active substances of antipsychotic drugs prescribed to a patient in 2013 and 2018**

number of drugs prescribed to patients. A thin dashed line indicates the polytherapy threshold (in this case – two active substances). In 2013, median = 2, mean = 1.83; in 2018, median = 2, mean = 1.96 ($p < 0.001$; $t = 35.2$).

Figure 1 shows a statistically significant increase in the number of active substances of antipsychotic drugs prescribed to patients in 2018 (a maximum of 12 active substances were prescribed in 2018 vs 10 in 2013, considering the entire reporting year).

The number of patients who were prescribed active substances of antipsychotic drugs of different generations is presented in Table 5.

Table 5. **Number of patients and generation of active substances of antipsychotic drugs prescribed in 2013-2018**

| Drug generation | Year | | | | | | Change |
|---|---|---|---|---|---|---|---|
| | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2018 vs 2013 |
| First (typical) | 53,585 | 54,260 | 52,878 | 51,725 | 49,765 | 47,523 | -11% |
| % of first-generation active substances | 28% | 27% | 26% | 25% | 24% | 24% | -17% |
| Second (atypical) | 117,607 | 12,6257 | 126,566 | 127,173 | 127,187 | 125,851 | 7% |
| % of second-generation active substances | 62% | 62% | 62% | 62% | 62% | 63% | 1% |
| Long-acting antipsychotics | 17,634 | 23,150 | 24,981 | 25,668 | 27,002 | 27,609 | 57% |
| % of active substances of long-acting antipsychotics | 9% | 11% | 12% | 13% | 13% | 14% | 47% |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Long-acting antipsychotics (typical) | 10,313 | 15,028 | 16,230 | 16,077 | 16,088 | 15,738 | 53% |
| Long-acting antipsychotics (atypical) | 7,767 | 8,735 | 9,486 | 10,404 | 11,888 | 12,885 | 66% |
| % of typical/atypical long-acting antipsychotics | 44% | 38% | 38% | 41% | 44% | 47% | 6% |

Between 2013 and 2018, the number of patients prescribed antipsychotic drugs containing first-generation active substances declined by 11%. At the same time, the number of patients prescribed antipsychotics containing second-generation active substances and long-acting injectable antipsychotics increased by 7% and 57%, respectively. It is worth noting that the number of patients who were prescribed second-generation long-acting antipsychotics increased by as much as 66%. The linear regression analysis of the data showed a statistically significant difference between the first-generation drugs and the long-acting injectable drugs ($p < 0.005$, R2 = 0.85 and $p < 0.01$, R2 = 0.79, respectively).

The percentage of the first – and second-generation antipsychotics and long-acting antipsychotics prescribed in respective years is shown in Figure 2.

According to the results, there has been an upward trend in prescribing long-acting antipsychotics, from 9% in 2013 to 14% in 2018. In the case of prescribing drugs with first-generation active substances, a decrease was observed from 28% in 2013 to 24% in 2018.

The trends in prescribing first – and second-generation antipsychotic drugs and long-acting antipsychotics in 2013-2018 are illustrated in Figures 3-5.

The active substances of first-generation drugs most frequently prescribed in 2013-2018 were perazine, levomepromazine and haloperidol, with a visible declining trend for each of the compounds (by 26%, 15% and 10%, respectively).

The most prescribed active substances of second-generation drugs included olanzapine (6% increase) and aripiprazole. Compared to 2013, the prescription frequency of the latter substance increased almost twofold.

With respect to the long-acting drugs, risperidone LAI was the most prescribed formulation, showing a significant (30%) increase between 2013 and 2018. However, the greatest increase in prescribing frequency was observed for depot haloperidol (zero patients in 2013 vs 6.5 thousand patients in 2018). There was also a systematic increase in the prescribing frequency of olanzapine LAI (up 463% compared to 2013).

The average doses of the prescribed active substances of antipsychotic drugs in 2013-2018 (in milligrams) are presented in Table 6. The active substances included in the analysis account for 80% of those most frequently prescribed in 2018.

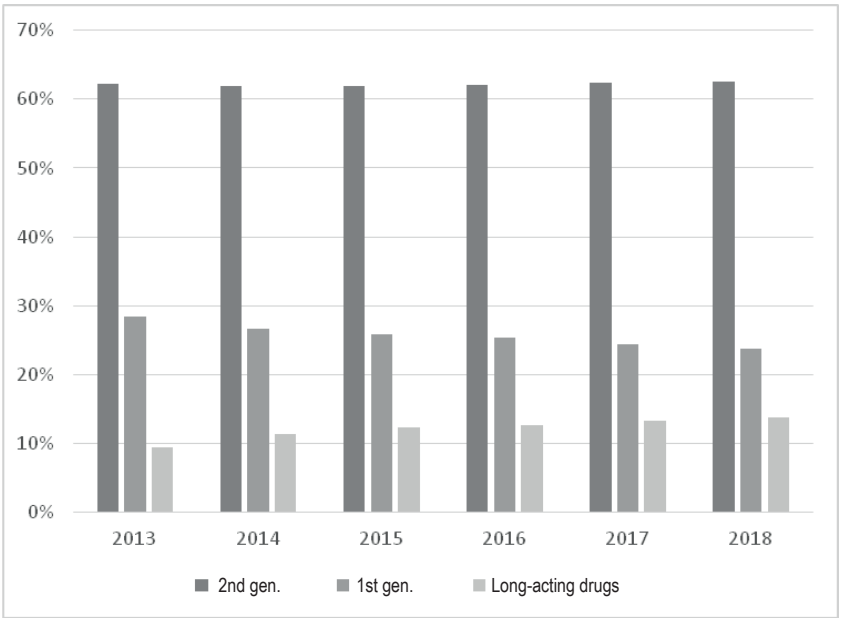
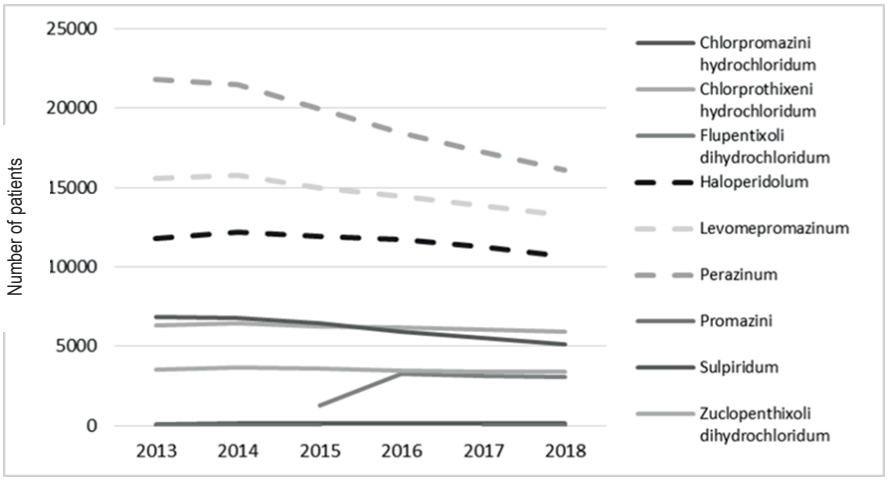



Figure 2. **Percentage of the first – and second-generation antipsychotic drugs and long-acting antipsychotics (first and second generation) prescribed in 2013-2018**

Table 6. **Average doses of the active substances of antipsychotic drugs prescribed in 2013-2018 (in mg)**

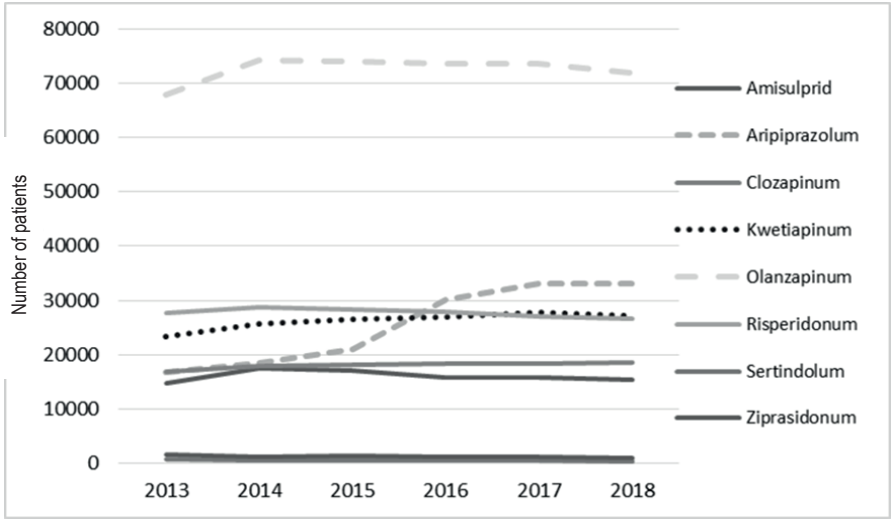
| Active substance | Year | | | | | | Change | ANOVA | P value |
|---|---|---|---|---|---|---|---|---|---|
| | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2018 vs 2013 | | |
| Amisulpride | 282.5 | 278.6 | 279.1 | 279.7 | 279.0 | 278.4 | -1% | F (5, 38341) = 3.4 | <0.005 |
| Aripiprazolum | 15.0 | 15.0 | 14.8 | 14.7 | 15.0 | 15.3 | 2% | F (5, 63512) = 215.7 | <0.001 |
| Clozapinum | 76.0 | 76.1 | 76.3 | 76.0 | 76.5 | 76.2 | 0% | F (5, 28656) = 0.7 | 0.61 |
| Quetiapinum | 145.8 | 149.5 | 165.3 | 168.5 | 169.6 | 167.5 | 15% | F (5, 60797) = 402.7 | <0.001 |
| Levomepromazinum | 25.0 | 25.0 | 25.0 | 25.0 | 25.0 | 25.0 | 0% | F (5, 33009) = 0.9 | 0.46 |
| Olanzapinum | 9.7 | 9.9 | 10.1 | 10.2 | 10.2 | 10.4 | 7% | F (5, 126267) = 289.9 | <0.001 |
| Perazinum | 70.1 | 72.1 | 73.0 | 73.2 | 73.2 | 73.5 | 5% | F (5, 44317) = 23.7 | <0.001 |
| Risperidonum | 2.2 | 2.2 | 2.2 | 2.2 | 2.2 | 2.2 | 0% | F (5, 61268) = 0.5 | 0.81 |

The results show significant dosage variations between the active substances over the years of the study. The largest difference in the average prescribed dose was found in the case of quetiapine (15% increase) and olanzapine (7% increase). The average dose of clozapine (76 mg) and levomepromazine (25 mg) remained unchanged.




The dashed lines indicate the three most frequently prescribed active substances in 2018.

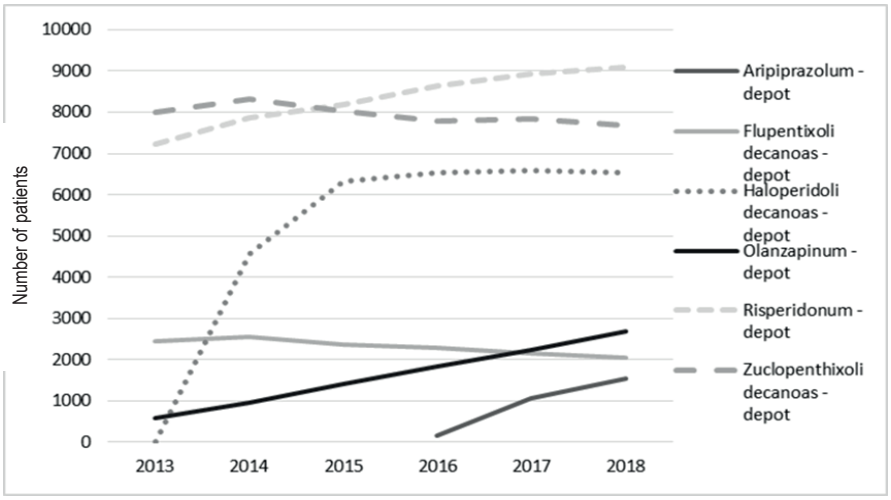
Figure 3. **Active substances of first-generation antipsychotic drugs prescribed in 2013-2018**




The dashed lines represent the three most frequently prescribed active substances in 2018.

Figure 4. **Active substances of second-generation antipsychotic drugs prescribed in 2013-2018**

The difference in the average prescribed dose size is statistically significant for most of the active substances (i.e. amisulpride, aripiprazole, quetiapine, olanzapine and perazine).




The dashed lines represent the three most frequently prescribed active substances in 2018.

Figure 5. **Active substances of long-acting antipsychotic drugs prescribed in 2013-2018**

## Discussion

The use of safe and effective pharmacological treatment in patients with schizophrenia is one of the biggest challenges for healthcare professionals. To the best of our knowledge, our study is the first ever investigation of the prescribing trends for antipsychotic drugs in patients diagnosed with schizophrenia in 2013-2018. It can be used to verify whether the current prescribing practices are universal in nature and shed more light on the preferred direction of the reimbursement practices.

The study included 209,334 patients diagnosed with schizophrenia. It is worth noting that this number increased by 4% in the period of the analysis. This observation is consistent with the estimates of some epidemiological researchers [2] who assume that the number of people suffering from schizophrenia will continue to increase along with population growth and ageing of society. However, in the analysed group of patients, the largest increase (40%) was recorded for patients diagnosed with F20.8 (other schizophrenia). At the same time, the largest decrease (18%) was observed in the F20.1 group (hebephrenic schizophrenia), which was also noted by researchers analysing the years 1920-1966 [28] and 1900-1979 [29] who stressed a declining trend in diagnosing this form of schizophrenia.

The socio-demographic data indicate that the number of female patients treated for schizophrenia is greater than the number of males. In 2013-2018, the most marked change in the number of patients occurred in the 60+ age group – an increase by 19%, while the largest increase in the overall number of patients was found in rural areas – 7%. Given the fact that these registered prevalence figures derive solely from the data reported to the National Health Fund, their face-value interpretation is questionable.

One of our main findings in this study is the increase in the number of patients prescribed second-generation antipsychotics. This trend is also observed in other countries [20-24]. Although the National Health Fund's database does not contain detailed clinical particulars, the diagnosis of residual schizophrenia as the third largest group of schizophrenic disorders (almost 13 thousand patients) is in line with the recommendations of the Polish Psychiatric Association [17].

Also, a significant (57%) increase in the number of patients prescribed long-acting antipsychotics, especially second-generation drugs (66% increase), can be viewed as a desired direction of change for a number of reasons: their use ensures a stable concentration of the active substance in the body, improves patient compliance, and reduces caregiver stress regarding compliance with medical recommendations [14, 30, 31]. Long-acting antipsychotics also reduce the risk of death by about 30% compared to oral formulations [32].

Between 2013 and 2018, the most frequently prescribed first-generation drugs in the investigated group of patients were: perazine, levomepromazine and haloperidol. Each of these drugs showed a downward trend by 26%, 15% and 10%, respectively. It can be assumed that the less frequent use of first-generation drugs was associated with concerns over possible adverse effects in the ageing patient population. Interestingly, perazine has been regarded for years by Polish psychiatrists as an effective and well-tolerable drug [33] with an additional benefit of full reimbursability.

In the group of second-generation drugs, the most frequently prescribed were olanzapine, aripiprazole and quetiapine. Interestingly, according to Huhn et al. [4], olanzapine was among only five neuroleptics which were evaluated as significantly more effective in reducing schizophrenia symptoms than the remaining twenty-seven first – and second-generation drugs (the other four were clozapine, amisulpride, zotepine and risperidone). At this point, it is worth noting that the pharmacological action of olanzapine may lead to rapid, adverse changes in the regulation of hunger and satiety, control of energy expenditure and body weight, peripheral release of insulin and glucose tolerance [11], and hence its use is encumbered with the risk of substantial weight gain and metabolic syndrome.

In the analysed years, the frequency of prescribing aripiprazole (considered a third-generation drug due to its unique mechanism of action) almost doubled. This is a positive trend which was also found in the AMSP study [21]. The third position of quetiapine on the list of the most frequently prescribed drugs comes as a surprise given the results of a study by Leucht et al. [34] which indicated its lower clinical efficacy compared to other antipsychotics.

The choice of risperidone LAI and olanzapine LAI (a significant increase between 2013 and 2018 by 30% and 463%, respectively) could be a deliberate, evidence-based clinical practice [14, 35]. In this context, the observed extremely high increase in the frequency of prescribing depot haloperidol is difficult to explain – no use in 2013 versus 6.5 thousand patients in 2018.

The increase in the number of different active substances prescribed to patients which was observed in 2018 is challenging to explain. This may be related to more frequent changes than in 2013 of primarily prescribed antipsychotics due to low efficacy

or adverse effects, or possibly to more frequent use of adjuvant therapies, insufficient drug doses, or the patient's general health condition. Data from the National Health Fund database, which do not contain information on comorbidities, course/duration of illness, and patients' test results, do not allow for unequivocal interpretation of results concerning the drug doses used. For example, the mean dose of clozapine, recommended in drug-resistance, remained unchanged at 76 mg. Perhaps the use of low doses of clozapine was dictated by concern over life-threatening adverse effects, especially granulocytopaenia and agranulocytosis. It was found that the number of patients treated with clozapine monotherapy decreased (by 11%), and slightly increased (by 7%) with polytherapy. It is also difficult to interpret the increase in the average prescribed dose observed for quetiapine in 2018, although in the analysed years the drug was used in a dose below the recommended therapeutic range.

Conducting the study among psychiatrists would allow significant expansion of knowledge regarding the rules and prescriptive practice in schizophrenia. The most important limitation of our study is that it considers only the information originating from the reports submitted to the public sector of health services (National Health Fund). The databases contain only very basic socio-demographic variables with incomplete medical information (e.g. without comorbidities, illness duration and course), which makes it impossible to analyse the factors behind the choice of different antipsychotic drugs. Therefore, including information on prescribing practices prevailing in the private sector of mental health services would provide a more comprehensive picture. Another limitation is the fact that the analysis did not feature a division into healthcare facilities providing services during different stages of illness.

## Conclusions

1. In the years 2013 – 2018, the number of patients with schizophrenia treated in public healthcare facilities increased by 4%. The largest increase in the number of patients was reported for the diagnosis of F20.8 (other schizophrenia).
2. In the years 2013 – 2018, there was an increase in the number of patients prescribed second-generation oral antipsychotics in the public sector.
3. The years 2013 – 2018 saw a significant increase in the number of patients prescribed long-acting antipsychotic drugs, particularly second-generation antipsychotics.
4. The most frequently prescribed first-generation drugs in the analysed group of patients were perazine, levomepromazine and haloperidol, with a downward trend for each of the products.
5. The most frequently prescribed second-generation drugs in the analysed group of patients were olanzapine, aripiprazole and quetiapine.
6. The most frequently prescribed long-acting antipsychotic drugs in the analysed group of patients were risperidone LAI, olanzapine LAI and depot haloperidol.
7. Supporting the study with information on the prescribing patterns in the private sector healthcare facilities would provide a more comprehensive picture.

## References


1. Green IW, Glausier JR. *Different paths to core pathology: The equifinal model of the schizophrenia syndrome.* Schizophr. Bull. 2016; 42(3): 542–549.
2. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG et al. *Global epidemiology and burden of schizophrenia: Findings from the Global Burden of Disease Study 2016.* Schizophr. Bull. 2018; 44(6): 1195–1203.
3. Millier A, Schmidt U, Angermeyer MC, Chauhan D, Murthy V, Toumi M et al. *Humanistic burden in schizophrenia: A literature review.* J. Psychiatr. Res. 2014; 54: 85–93.
4. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N et al. *Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis.* Lancet 2019; 394(10202): 939–951. Doi: 10.1016/S0140-6736(19)31135-3.
5. Dickerson FB, Lehman AF. *Evidence-based psychotherapy for schizophrenia: 2011 update.* J. Nerv. Ment. Dis. 2011; 199(8): 520–526.
6. Nowak I, Świtaj P, Sabariego C, Oberhauser C, Anczewska M. *Development and evaluation of a recovery-oriented cognitive behavioural workshop for people diagnosed with schizophrenia.* Behav. Cogn. Psychother. 2019; 47(3): 400–406. Doi: 10.1017/S1352465818000607.
7. Cechnicki A, Bielańska A. *The influence of early psychosocial intervention on the long-term clinical outcomes of people suffering from schizophrenia.* Psychiatr. Pol. 2017; 51(1): 45–61.
8. Roosenschoon BJ, Kamperman AM, Deen ML, Weeghel JV, Mulder CL. *Determinants of clinical, functional, and personal recovery for people with schizophrenia and other severe mental illnesses: A cross-sectional analysis.* PLoS One 2019; 14(9): e0222378. Doi: 10.1371/journal.pone.0222378.
9. Tyszkowska M, Jarema M. *Between health and schizophrenia.* Psychiatr. Pol. 2013; 47(4): 587–597.
10. Stroup TS, Gray N. *Management of common adverse effects of antipsychotic medications.* World Psychiatry 2018; 17(3): 341–356. Doi: 10.1002/wps.20567.
11. Wichniak A, Dudek D, Heitzman J, Kapłon-Cieślicka A, Mamcarz A, Samochowiec J et al. *Metabolic risk reduction in patients with schizophrenia treated with antipsychotics: recommendations of the Polish Psychiatric Association.* Psychiatr. Pol. 2019; 53(6): 1191–1218.
12. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA et al. Schizophrenia Patient Outcomes Research Team (PORT). *The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements.* Schizophr. Bull. 2010; 36(1): 71–93. Doi: 10.1093/schbul/sbp116.
13. Jarema M, Rabe-Jabłońska J. *Schizofrenia.* In: Jarema M. ed. *Standardy leczenia farmakologicznego niektórych zaburzeń psychicznych.* Gdańsk: Via Medica; 2011. p. 1–46.
14. Jarema M, Wichniak A, Dudek D, Samochowiec J, Bieńkowski P, Rybakowski J. *Guidelines for the use of second-generation long-acting antipsychotics.* Psychiatr. Pol. 2015; 49(2): 225–241.
15. Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M. *Guidelines for the pharmacotherapy of schizophrenia in adults.* Can. J. Psychiatry 2017; 62(9): 604–616. Doi: 10.1177/0706743717720448.
16. Szulc A, Samochowiec J, Gałecki P, Wojnar M, Heitzman J, Dudek D. *Recommendations for the treatment of schizophrenia with negative symptoms. Standards of pharmacotherapy by the Polish Psychiatric Association (Polskie Towarzystwo Psychiatryczne), part 1*. Psychiatr. Pol. 2019 ONLINE FIRST Nr 128: 1–28. Doi: 10.12740/PP/OnlineFirst/100698.

17. Szulc A, Dudek D, Samochowiec J, Wojnar M, Heitzman J, Gałecki P. *Recommendations for the treatment of schizophrenia with negative symptoms. Standards of pharmacotherapy by the Polish Psychiatric Association (Polskie Towarzystwo Psychiatryczne), part 2.* Psychiatr. Pol. 2019 ONLINE FIRST Nr 129: 1–16. Doi: 10.12740/PP/OnlineFirst/100697.
18. Galletly C, Castle D, Dark F, Humberstone V, Jablensky A, Killackey E et al. *Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders.* Aust. N. Z. J. Psychiatry 2016; 50(5): 410–472. Doi: 10.1177/0004867416641195.
19. Wójciak P, Remlinger-Molenda A, Rybakowski J. *Stages of the clinical course of schizophrenia – staging concept.* Psychiatr. Pol. 2016; 50(4): 717–730.
20. Roberts R, Neasham A, Lambrinudi C, Khan A. *A quantitative analysis of antipsychotic prescribing trends for the treatment of schizophrenia in England and Wales.* JRSM Open 2018; 9(4): 1–7. Doi: 10.1177/2054270418758570.
21. Toto S, Grohmann R, Bleich S, Frieling H, Maier HB, Greil W et al. *Psychopharmacological treatment of schizophrenia over time in 30 908 inpatients: Data from the AMSP Study.* Int. J. Neuropsychopharmacol. 2019; 22(9): 560–573. Doi: 10.1093/ijnp/pyz037.
22. Weinbrenner S, Assion HJ, Stargardt T, Busse R, Juckel G, Gericke CA. *Drug prescription patterns in schizophrenia outpatients: Analysis of data from a German Health Insurance Fund.* Pharmacopsychiatry 2009; 42(2): 66–71.
23. Rode SB, Salankar HV, Verma PR, Sinha U, Ajagallay RK. *Pharmacoepidemiological survey of schizophrenia in Central India.* Int. J. Res. Med. Sci. 2017; 2(3): 1058–1062.
24. Banergee I, Roy B, Sathian B, Banergee I, Chakraborty PK, Saha A. *Sociodemographic profile of utilization pattern of antipsychotic drugs among schizophrenic inpatients: A cross sectional study from western region of Nepal.* BMC Psychiatry 2013; 13: 96.
25. Okpataku CI, Tawani D. *Psychotropic prescriptions for the treatment of schizophrenia in an outpatient clinic.* Trends Psychiatry Psychother. 2017; 39(3): 165–172.
26. Park SC, Lee MS, Kang SG, Lee SH. *Pattern of antipsychotic prescription to patients with schizophrenia in Korea: Results from the health insurance review & assessment service-national patient sample.* J. Korean Med. Sci. 2014; 29(5): 719–728.
27. GBD 2016 DALYs and HALE Collaborators, 2017.
28. Morrison JR. *Changes in subtype diagnosis of schizophrenia: 1920–1966.* Am. J. Psychiatry 1974; 131(6): 674–677.
29. Templer DI, Veleber DM. *The decline of hebephrenic schizophrenia.* Journal of Orthomolecular Psychiatry 1982; 11(2): 100–102.
30. Faden J. *How do we select an antipsychotic for those with schizophrenia?* Expert Opin. Pharmacother. 2019; 20(18): 2195–2199. Doi: 10.1080/14656566.2019.1674284.
31. Pietrini F, Albert U, Ballerini A, Calò P, Maina G, Pinna F et al. *The modern perspective for long-acting injectables antipsychotics in the patient-centered care of schizophrenia.* Neuropsychiatr. Dis. Treat. 2019; 15: 1045–1060. Doi: 10.2147/NDT.S199048.
32. Taipale H, Mittendorfer-Rutz E, Alexanderson K, Majak M, Mehtälä J, Hoti F et al. *Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia.* Schizophr. Res. 2018; 197: 274–280.
33. Jarema M, Meder J, Araszkiewicz A, Tyszkowska M. *Antipsychotics in clinical practice. The refractory schizophrenic patients treatment*. Psychiatr. Pol. 2008; 42(6): 841–858.
34. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F et al. *Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis.* Lancet 2013; 382(9896): 951–962.

35. Graffino M, Montemegni C, Mingrone C, Rocca P. *Long-acting injectable antipsychotics in the treatment of schizophrenia: A review of literature.* Riv. Psichiatr. 2014; 49(3): 115–123.

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