Real-world evidence of antipsychotic monotherapy vs. polypharmacy in the treatment of schizophrenia spectrum disorders: Risk of hospitalisation from the emergency department

ŞÜKRÜ ALPEREN KORKMAZ[1], Esra Koca[2], Özge Yılmaz[2], Tayfun Özbek[2], and Muhammed Güçlü[2]

[1]Affiliation not available
[2]Ankara Bilkent City Hospital

August 30, 2023

Abstract

Introduction: Although it is known that antipsychotic non-compliance increases the risk of emergency department (ED) utilisation, presentation with agitation/aggression and rehospitalisation in schizophrenia spectrum disorders (SSD) patients, it is unwell known whether antipsychotic monotherapy vs. polypharmacy differs in terms of efficacy in these domains. This study aimed to determine the effectiveness of antipsychotic monotherapy and polypharmacy for the prevention of hospitalisation who admitted to the ED in the real-world. Methods: The study was conducted with electronic health records of 669 SSD patients admitted to the ED between 2019 and 2022. Patients were evaluated in four groups according to antipsychotic use at the first admission to the ED: antipsychotic non-compliance for more than 90 days, antipsychotic non-compliance for 15-90 days, antipsychotic monotherapy and polypharmacy. All antipsychotics and other psychotropic drugs used by the patients were also recorded and followed up for at least one year after index admission. Results: The groups, including patients with antipsychotic non-compliance, had higher ED visits, more hospitalisations and more admissions with agitation/aggression compared to antipsychotic monotherapy or polypharmacy. However, no differences were found between monotherapy and polypharmacy groups regarding these outcomes. Patients discharged with monotherapy or polypharmacy also had similar re-hospitalisation rates at follow-up. Conclusions: There is no positive evidence that recommending polypharmacy over antipsychotic monotherapy is superior in the frequency of ED visits, ED admissions with agitation/aggression, hospitalisation and re-hospitalisation. In this context, it may be more feasible to clozapine monotherapy before antipsychotic polypharmacy in treatment-resistant patients due to more significant evidence.

1. Introduction

Schizophrenia spectrum disorders (SSDs) include schizophrenia, schizophreniform disorder, schizoaffective disorder and other psychotic disorders, according to current diagnostic classification systems (American Psychiatric Association, 2013). The pharmacological treatment for SSDs consists of antipsychotic medications. Antipsychotic treatments are not only effective on psychotic symptoms but are also reported to reduce hostility, violence, suicide and even all-cause mortality (Faay et al., 2018; Huang et al., 2021; Strassnig et al., 2020; Volavka et al., 2014; Zuschlag, 2021). It is also reported that antipsychotic treatments reduce the burden related to the illness (James et al., 2018). Although antipsychotics are known to be effective in both acute and maintenance treatment of SSD, response and tolerability vary between patients. This variability of individual response means that there is no clear first-line antipsychotic drug of choice for everyone (Taylor et al., 2021).

Treatment guidelines recommended antipsychotic monotherapy as the first line of treatment for SSD (Barnes

et al., 2020; Hasan et al., 2012;*Psychosis and Schizophrenia in Adults: Prevention and Management Clinical Guideline* , 2014). Recommendations following an inadequate antipsychotic monotherapy response include waiting for a delayed response, adjusting the dose, switching to another antipsychotic, and in the case of treatment resistance, "clozapine" treatment is recommended in the absence of a response to at least two inadequate antipsychotic treatments (Buchanan et al., 2010; Hasan et al., 2012; Keepers et al., 2020). Antipsychotic polypharmacy is another method used in cases of inadequate response (Gallego et al., 2012). The concurrent use of two or more antipsychotic treatments is defined as antipsychotic polypharmacy (Weissman, 2002). Although it is recommended as a last-step treatment strategy in treatment guidelines and there is limited evidence regarding the treatment of patients, antipsychotic polypharmacy is a frequently used and increasing strategy in clinical practice (Keepers, 2020; Buchanan, 2010; Faries, 2005; Faden, 2021). The global pooled median rate of antipsychotic combination treatment is estimated to be approximately 20 per cent (Gallego, 2012). Antipsychotic polypharmacy also increases the risk of treatment-related side effects (Haddad & Dursun, 2008; Haddad & Sharma, 2007; Lähteenvuo & Tiihonen, 2021). More importantly, it is not well known whether it is more effective than monotherapies in reducing the frequency of unplanned hospitalisations and ED visits (Boskailo et al., 2017; Faden et al., 2021; Kasteridis et al., 2019). This situation shows that empirical research is needed to put the benefits and drawbacks of antipsychotic polypharmacy into perspective (Gören et al., 2013).

Antipsychotic effectiveness is the integrating assessment of antipsychotic efficacy, tolerability and compliance and is used to evaluate treatment in the "real world" (Faden et al., 2021). Although it is known that antipsychotic non-compliance increases the risk of ED utilisation, presentation with agitation/aggression and rehospitalisation in SSD patients, it is not well known whether antipsychotic monotherapy vs. polypharmacy differs in terms of efficacy in these domains. For this reason, our study aimed to determine the effectiveness of antipsychotic monotherapy and polypharmacy for the prevention of hospitalisation who admitted to the ED in the real-world in Turkey. Another aim of the study was to determine whether there was a difference in the frequency of presentation to the ED with agitation/aggression or suicide attempts in patients taking antipsychotic monotherapy and polypharmacy. The last aim of the study was to determine whether antipsychotic monotherapy or polypharmacy discharge of patients hospitalised from the ED influences re-hospitalisation at follow-up.

2. Methods

2.1. Data Sources and Setting

The study was conducted using hospital electronic health records (EHR) data of patients evaluated in the Emergency Department (ED) of Ankara Bilkent City Hospital, Ankara, Turkey, between 21 February 2019 and 25 February 2022. The first admission of all patients to this hospital's emergency department was recorded as "index admission", and one-year follow-up of all patients after the index admission continued to be performed from the EHR. Ankara Bilkent City Hospital is a centre that admits patients who seek psychiatric treatment independently or with their relatives and patients brought in for evaluation by the police and/or emergency health services. In addition, outpatient clinic records before the index admission were examined from the e-pulse system, the patient registration system of the Ministry of Health of the Republic of Turkey, in eligible patients.

The EHR includes a unique patient number, date of presentation to the emergency department, age, gender, date of birth, occupation, marital status, medications used in the past or currently, and psychiatric diagnosis according to the International Classification of Disease 10th version (ICD-10), the reason for admission to the emergency department, current and previous suicidal ideation, current and recent homicidal thoughts and aggressive behaviours, number of admissions to the emergency department on different days, total duration of illness, age at onset of illness, number of hospitalisation, history of smoking, alcohol and substance use, and comorbidities. In addition, whether the patient was hospitalised after the examination in the emergency department (index hospitalisation), and if so, the start and end of hospitalisation and discharge prescription are recorded in the EHR. Hospital Discharge registers of patients hospitalised after the index admission were also used. All patients' subsequent visits to the outpatient clinic and changes in treatment during the

one-year after index admission were also registered. If there was re-hospitalization within a year, this was also recorded.

2.2. Study Design and Sample

The retrospective follow-up study included all adult patients (?18 years) with schizophrenia spectrum disorders who had at least one visit to the emergency department. Patients diagnosed with schizophrenia spectrum disorder by the psychiatrist(s) at previous follow-ups and whose diagnosis was confirmed by assessing a psychiatrist in the emergency department were included in the study. The diagnoses of the patients with SSD regarding the ICD-10 codes were Schizophrenia (F20), Brief psychotic disorder (F23), Schizoaffective disorders (F25), Other psychotic disorder not due to a substance or known physiological condition (F28) and Unspecified psychosis not due to a substance or known physiological condition (F29). These patients had to have at least one year of registration in the EHR. We obtained information on the diagnosis of the patients directly from the EHR. Following a routine comprehensive psychiatric assessment, the clinician entered the psychiatric diagnosis into the EHR.

For the purposes of this study, patients were categorised into the following four groups based on antipsychotic use. The first group had non-compliance with discontinued antipsychotic medications for more than 90 days before index admission at the emergency department (Group 1). The second group had non-compliance with discontinued antipsychotic medicines for two weeks to 90 days before index admission (Group 2). Group 3 consisted of patients taking a single antipsychotic regularly (with at least 75% medication compliance) for at least one month (Group 3). The fourth group consisted of patients receiving antipsychotic polypharmacy treatment. There is no consensus on polypharmacy; in this study, we defined the concurrent use of more than one distinct antipsychotic medication (with at least %75 medication compliance) for at least one month as polypharmacy (Group 4). In addition to antipsychotics, other psychotropic drugs, such as antidepressants, benzodiazepines, anticholinergics, and mood stabilisers, were also recorded in Group 3 and Group 4 patients.

Antipsychotic doses were equivalent to chlorpromazine (CPZE) of all patients receiving antipsychotic monotherapy, and polypharmacy was calculated (Leucht et al., 2016). In some cases, the CPZE 100 mg may not have the exact intention of their antipsychotic effects (Stephen M. Stahl, 2021). For this reason, antipsychotic polypharmacy was calculated in two ways: The first calculation included all antipsychotics at all doses. The second calculation included only those antipsychotics at higher doses than the 100 mg chlorpromazine equivalent dose (Yazici et al., 2017). Exceeding 1000 mg CPZE daily or more was considered a “high dose usage” (Yorston & Pinney, 2000). Moreover, dose equivalents to lithium for mood stabilisers, fluoxetine for antidepressants, diazepam for benzodiazepines and biperiden for anticholinergics were recorded (Baldessarini, 2013; *Choosing Equivalent Doses of Oral Benzodiazepines* , 2023; Hayasaka et al., 2015).

All-cause psychiatric hospitalisations from the emergency department were evaluated. The reasons for hospitalisation were psychotic exacerbation, suicide attempt or deliberated self-harm, catatonia, anxiety/depression or insomnia, alcohol or substance use, medical conditions, adverse events, and other causes. Only the psychiatric hospitalisation of seven days or longer during the study period was included for each patient (Abdullah-Koolmees et al., 2021; Laan et al., 2010).

2.3. Outcome Measures

The primary outcomes determined the association between antipsychotic monotherapy vs. polypharmacy and all-cause psychiatric hospitalisation between the groups after ”index admission” in the SSD. A re-admission within 14 days after discharge with the same principal diagnosis was defined as the same (one) hospitalisation episode.

The second outcome measure was the association between monotherapy vs. antipsychotic polypharmacy use and emergency department admission for acute agitation/aggressive behaviour or suicide attempt. Another secondary outcome was whether hospitalised patients receiving monotherapy vs. polypharmacy after index admission were re-hospitalised in the first six months. The final secondary outcome was whether antipsychotic use at index admission was associated with multiple hospitalisations in the following year.

2.4. Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 28.0 (IBM Corporation, New York, USA), and the graphic was drawn using GraphPad Prism 9.2.0 software (Dotmatics, Boston, USA). Before analysing the data, they were checked for loss and extreme values. The skewness and kurtosis values were checked to determine whether the groups were normally distributed. The data were normally distributed if the skewness and kurtosis values were between -1.5 and +1.5, as suggested by Tabachnick and Fidell (Barbara G. Tabachnick & Linda S. Fidell, 2013). For normally distributed continuous characteristics, means and standard deviations (SD) were calculated through T-tests or analysis of variance (ANOVA) and for non-normally distributed continuous characteristics, median and interquartile ranges (IQR) were calculated through Mann-Whitney U or Kruskal-Wallis H tests. Categorical and dichotomous variables were presented with numbers and percentages per category, and Chi-square tests with Bonferroni correction were performed to assess differences. Binary logistic regression analyses using the "enter" method were conducted to examine the impact of antipsychotic use of the patients and other characteristics of the patients on hospitalisation from ED after index admission and on presentation to ED with agitation/aggression. Odds ratio (OR) with a 95% confidence interval (CI) and p-values were reported. Statistically significant p-values with effect sizes (Cohen's d or Phi coefficient) are given. The significance level was set at $\alpha = 0.05$, and all the tests were two-tailed.

3. Results

3.1 Characteristics of patients with SDD admitted to the ED

A total of 696 patients were admitted to the ED within the study period, and 657 identified patients who met the inclusion criteria were included. The mean age was 40.0 years [standard deviation (SD): 12.1 years, min-max: 18-73 years], 413 (62.9%) were male, and most patients (83.7%, n=545) were diagnosed with schizophrenia, see Table 1. It was the first psychotic episode in 8.3% (n=53) of all patients (drug-naive patients). Of all patients, 30.7% (n = 202) had at least one medical comorbidity. The rates of smoking, alcohol and substance use of the patients were 65.8% (n=432), 23.6% (n=155) and 18.3 % (n=120), respectively.

3.2. Psychotropic drug use and equivalent doses in patients admitted with ED

When grouped according to antipsychotic use, 41.46% of the patients (n= 273) had antipsychotic treatment non-compliance for more than 90 days (Group 1), while %15.8 of the patients (n=104) had antipsychotic treatment non-compliance for 15-90 days (Group 2). 24.4% of the patients (n=160) were receiving antipsychotic monotherapy (Group 3), and 18.3% (n=120) were receiving antipsychotic polypharmacy (Group 4). As expected, patients in Group 1 were more frequently admitted to the ED than others ($p < 0.001$). The mean CPEZ antipsychotic dose of those receiving antipsychotic monotherapy was 378.9 mg/day (SD: 194), while that of those receiving polypharmacy was 817.3 mg/day (SD: 369), and there was a statistically significant difference ($p < 0.001$; Cohen's $d = 1.56$). Patients in Group 1 attended the psychiatry outpatient unit fewer times in the six months before admission to the ED than others ($p < 0.001$). LAI was used by 24.4% ($n = 39$) of monotherapy antipsychotic users and 46.7% of ($n = 56$) polypharmacy users ($p<0.001$; Phi = 0.23). There was no significant difference between the two groups regarding clozapine use (8.8 vs. 11.7%, p= 0.44). Intriguingly, only 23.9% of the patients receiving antipsychotic polypharmacy treatment at ED admission had previously received clozapine treatment.

The mean non-antipsychotic psychotropic medication use was 0.53 drug (SD: 0.74) in the monotherapy group and 0.61 (SD: 0.8) in the polypharmacy group ($p = 0.413$). The rate of mood-stabiliser use was %13.5 (n=22) in the monotherapy group and %14.2 ($n = 17$) in the polypharmacy group and no difference was found between the groups ($p = 0.654$). The rate of antidepressant use was %15 (n=24) in the monotherapy group and %13.3 (n=16) in the polypharmacy group and no statistical difference was detected ($p = 0.796$). Monotherapy antipsychotic users took anticholinergic drugs less frequently than polypharmacy users (10.6 vs. 19.2%, $p = 0.03$; Phi = 0.13), but there were no differences in the daily dose of anticholinergic drugs [benztropine equivalent dose: 3.4 (SD:1.4) mg vs 2.9 (SD:1.16), respectively; $p = 0.253$). Benzodiazepine

use was not significantly different between the two groups in terms of use rate (6.3 vs 5.8%, p = 0.88).

3.3. Hospitalisation of patients admitted to the ED

Of all patients with SSD, 39.8% (n = 260) were hospitalised after index admission. 66.67% of the patients (n = 182) in Group 1; 35.6% of the patients (n = 37) in Group 2; 13.8% of the patients (n = 22) in Group 3, and 15.8% of the patients (n = 19) in Group 4 were hospitalised in the psychiatry clinic. According to the post-hoc tests, the hospitalisation rate in group 1 was statistically higher than all other groups (all p <0.001); see Figure 1. Group 2 was hospitalised significantly more than Group 3 (p <0.001) and Group 4 (p <0.001). However, no difference was determined between patients receiving monotherapy antipsychotics (Group 3) and those receiving polypharmacy (Group 4) in terms of hospitalisation from ED, which was the primary outcome of the study (p = 0.62).

When patients receiving monotherapy and polypharmacy were compared with patients receiving only antipsychotics at doses higher than the equivalent dose of 100 mg chlorpromazine, there was again no difference in hospitalisation between the groups (p = 0.434). Moreover, the high dose usage (exceeding CPZE 1000 mg daily) among those receiving antipsychotic polypharmacy treatment did not reduce the risk of hospitalisation. Those on clozapine or LAI treatment at admission to the ED did not have a reduced risk of hospitalisation, regardless of whether they used monotherapy or polypharmacy (p = 0.09 and p = 0.456, respectively). LAI or clozapine use was also not associated with a lower risk for psychiatric hospitalisation in the monotherapy and polypharmacy groups (p = 0.11 and p = 0.333, respectively). In addition, there was no significant difference in the hospitalisation rate between first-generation LAI users and second-generation LAI users (p = 0.624). More patients were hospitalised in the 2nd year of COVID-19 than in the 1st year of the pandemic and the year before the pandemic (p = 0.043). However, no difference was found in hospitalisation according to months and seasons (p = 0.086, p= 0.076, respectively).

There was a significant difference in ED admissions for acute agitation/aggression (p <0.001): patients in the two antipsychotic non-adherent groups (groups 1 and 2) presented with acute agitation/aggression at a higher rate than those on monotherapy and polypharmacy but no significant difference was found between the monotherapy and polypharmacy groups (p = 0.562). Moreover, concerning ED admissions for suicide attempts, there was no difference between the groups (p = 0.083), see Table 2. In addition, no correlation was found between CPZE dose and admissions to the ED with agitation/aggression and suicide attempts in patients in the monotherapy and antipsychotic polypharmacy groups (all p> 0.05). Being a clozapine user also did not reduce the likelihood of admission for suicide (p = 0.743).

Multivariate binary logistic regression showed that non-adherence to antipsychotic medications for at least 90 days (p <0.001, OR = 7.72), non-adherence to medications for 15-90 days (p= 0.017, OR = 2.36), first psychotic episode (p <0.001, OR = 6.7), admission with agitation/aggression (p <0.001, OR = 3.54) and total duration of illness (p = 0.043, OR = 1.02) were associated with increased risk of hospitalisation from ED after index admission. In addition, there was no difference in the risk of hospitalisation in monotherapy antipsychotic users compared to polypharmacy users (p = 0.61, OR = 0.83); see Table 3.

Further, non-adherence to antipsychotic treatment for more than 90 days (p <0.001, OR = 3.61), non-adherence to antipsychotic treatment for 15-90 days (p= 0.004, OR = 2.44), and the presence of a diagnosis of the disease for less than one year (p= 0.003, OR = 3.58) were associated with the presentation to the ED with agitation/aggression. In contrast, monotherapy or polypharmacy treatments were not superior to each other (p = 0.97, OR = 1.01) regarding visits with agitation/aggression; see Table 4.

3.4. Follow-up of patients after hospitalisation discharge and re-hospitalisation

Antipsychotic treatment at discharge from psychiatric hospitalisation was analysed in 260 patients. Of the patients, 54.6% (n= 142) were discharged with monotherapy and 44.7% (n = 118) with polypharmacy (p = 0.484). Of the hospitalised patients in Group 1, 104 (57.1%) patients were discharged with monotherapy and 79 (42.6%) patients with polypharmacy, whereas, in Group 2, 45.9% (n=17) were discharged with monotherapy and 54.1% (n=20) with polypharmacy. Those discharged from hospitals with antipsychotic

polypharmacy had more hospitalisation days than those discharged with monotherapy (p <0.001; r = 0.28). Most patients initiated LAIs when they were not compliant with previous antipsychotic treatment before the hospitalisation (61.2% vs. 37.3%, p <0.001). It was also found that those discharged with polypharmacy received more LAIs than those discharged with antipsychotic monotherapy (71.9 vs 51.9%, p <0.001); however, there was no difference in terms of clozapine initiation (10 vs 4.7%, p = 0.116).

Those discharged with polypharmacy had a higher total number of hospitalisations (4.14 + 4.67 vs 2.49 + 1.9, p <0.001), an earlier age at disease onset (25.79 + 7.25 years vs 30.01 + 0.4 years, p <0.001), and a higher total duration of illness (14.12 + 9.86 years vs 10.26 + 10.05 years, p = 0.003).

Three months after discharge, follow-up records of 34 of 260 patients could not be reached (13.1%). The records of 226 patients whose follow-up records could be accessed were analysed. Drug treatment compliance was poor in 32 patients in the third month after discharge (14.2%). There was no difference between monotherapy and polypharmacy groups regarding poor medication adherence (p = 0.6) at three months post-discharge. It was also found that 65.5% (n = 148/226) of the patients did not change the number of antipsychotic drugs. 35.2 % of patients using antipsychotic polypharmacy (n = 32/91) switched to antipsychotic monotherapy, and 11.6% of patients using antipsychotic monotherapy (n = 14/121) switched to antipsychotic polypharmacy. Antipsychotic treatment status at three months post-discharge did not predict re-hospitalisation in the first six months post-discharge (p = 0.282). In addition, medication adherence was similar between those discharged with LAI use and those discharged with oral antipsychotic use three months after discharge (p = 0.66).

In the first six months after index admission to the ED, 61 patients were hospitalised. Nineteen of these patients were re-hospitalised after index admission to ED. No difference existed between the rehospitalisation rates of the groups previously discharged with antipsychotic monotherapy and polypharmacy in the first six months (p = 0.117). However, re-hospitalised patients were younger (p = 0.024). None of the 16 patients previously discharged with clozapine treatment were re-hospitalised in the first six months. However, previous discharge on depot antipsychotics did not result in fewer hospitalisations in the first six months after discharge (8.8 vs. 6.9%, p = 0.607). As the final secondary outcome measure, there was no association between antipsychotic use at index admission to ED and multiple hospitalisations after index admission (p = 0.787).

4. Discussion

This study used real-world data with naturalistic follow-up to understand the links between antipsychotic monotherapy or polypharmacy and ED admission and subsequent hospitalisation in patients with SSD. One of the study's main findings was that non-compliance with antipsychotic treatment for more than 15 days increased the risk of hospitalisation from ED. In contrast, antipsychotic polypharmacy was not associated with fewer hospitalisations than antipsychotic monotherapy in patients with SSD after ED admissions. Similarly, non-compliance with antipsychotic treatment led to more ED admissions with agitation/ aggression, whereas antipsychotic monotherapy or polypharmacy use was associated with a similar risk of emergency department visits for this reason. Contrary to expectations, the rate of suicide attempts among SSD patients who took antipsychotic treatment did not decrease compared to those who did not take antipsychotic treatment. Being discharged from the hospital with antipsychotic monotherapy, polypharmacy, or LAI antipsychotics does not affect markedly re-hospitalisation risk in the following six months.

In the current study, almost two-thirds of the study population were non-compliant with their antipsychotic medication and non-compliance with antipsychotics was associated with more ED admissions, more hospitalisations and more ED visits with aggression/agitation. Among these patients, 58% were hospitalised from the ED; those who were non-compliant with antipsychotic treatment for 15-90 days had 1.4-fold increased odds of hospitalisation, and those who were non-compliant with antipsychotic treatment for more than 90 days had 6.7-fold increased odds. Our findings align with previous studies showing that non-compliance with antipsychotic treatment significantly contributes to relapse and hospitalisation (Abdullah-Koolmees et al., 2021; Morken et al., 2008; Novick et al., 2010). In addition, non-compliance to antipsychotic medication was reported to be an essential risk factor for presentation with aggression/agitation, which is consistent

with our study (Strømme et al., 2022; Wu et al., 2018). Thus, antipsychotic medication is the most effective intervention to prevent hospitalisation and admission with agitation/aggression in SSD patients. Identifying modifiable risk factors for medication non-compliance may improve patient outcomes by increasing treatment compliance.

Current guidelines for patients with SSD recommend antipsychotic monotherapy as a first-line treatment option (Galletly et al., 2016; Keepers et al., 2020; *Psychosis and Schizophrenia in Adults: Prevention and Management Clinical Guideline* , 2014), and our findings provide further evidence of a negative association between antipsychotic monotherapy and hospitalisation. Even though antipsychotic polypharmacy is recommended as the last choice in treatment guidelines, it is known that antipsychotic polypharmacy is widely practised in Turkey (up to 71%) and worldwide (Kasteridis et al., 2019; Yazici et al., 2017). These recommendations in the treatment guidelines are based on the limited evidence for the superior efficacy of polypharmacy compared with monotherapy and concerns that antipsychotic polypharmacy is associated with an increased risk of adverse effects (Kasteridis et al., 2019). Antipsychotic polypharmacy was not associated with fewer hospitalisations from ED compared to antipsychotic monotherapy as an outcome in our study. In previous studies, similar to our findings, it was concluded that antipsychotic polypharmacy did not decrease the frequency of hospitalisation and ED visits (Baker & Aebi, 2017; Boskailo et al., 2017; Kadra et al., 2018; Kasteridis et al., 2019; Sun et al., 2014). Moreover, we found that antipsychotic polypharmacy at discharge did not reduce re-hospitalisation risk over six months. Consistent with our results, studies reported that antipsychotic polypharmacy does not minimise rehospitalisation (Boskailo et al., 2017; Kadra et al., 2018). Thus, it suggests that the discharge of SSD patients with more than one antipsychotic does not provide an additional benefit in preventing relapse.

Antipsychotic polypharmacy is frequently used in treating agitation/aggression in SSD patients (Zhang et al., 2019). In fact, most clinical trials have failed to show more benefits of antipsychotic polypharmacy in these patients (Ritsner, 2013). Our findings suggest antipsychotic polypharmacy is not advantageous over monotherapy in ED admission with agitation/aggression. Clinicians may consider this despite the lack of evidence to support the assumption that antipsychotic polypharmacy is better for agitation, aggression or violence. Our study did not show that clozapine users presented with significantly fewer suicide attempts, probably because of the small number of patients receiving clozapine treatment (n=28). There is not enough evidence to suggest that non-clozapine antipsychotics reduce the risk of suicide (Taipale et al., 2021). Although it is known that SSD patients are at high risk of suicide, effective treatments have not been identified yet (Qin & Nordentoft, 2005).

The risks of antipsychotic polypharmacy include non-compliance with treatment, as well as an overall increase in the total dose of antipsychotic medication, increased drug interactions and worsening of side effects (Faden et al., 2021; Procyshyn et al., 2010). Our study found that those receiving antipsychotic polypharmacy treatment received significantly higher mean CPZE antipsychotic doses than those receiving monotherapy treatment. Moreover, antipsychotic polypharmacy is associated with a higher overall burden of side effects than monotherapy. The most robust evidence is reported for Parkinsonian side effects and the use of anticholinergics (Centorrino et al., 2004; Gallego et al., 2012). Although we did not assess the Parkinsonian side effects in our study, we found an association between antipsychotic polypharmacy and the additional use of anticholinergic drugs. This result suggests that patients may have an increased frequency of troublesome extrapyramidal side effects while on antipsychotic polypharmacy and may require intervention. Apart from more side effects, antipsychotic polypharmacy was associated with additional costs associated with prescribing, higher bed occupancy and length of inpatient stay, consistent with our results (Baandrup et al., 2012; Gilmer et al., 2007; Velligan et al., 2015).

4.1. Strenghts and Limitations

This study had several strengths. It is common to exclude those who are too psychotic, substance dependent, aggressive or treatment-resistant to fulfil the inclusion criteria. The fact that a naturalistic follow-up was performed with real-world clinical practice with few exclusion criteria enabled this group of patients to be included in the study. The second strength of the study is that it is a large study conducted in a European

country, analysing three years of electronic health records. Third, another strength of the study is that not only the risk of hospitalisation from ED but also the reasons for ED presentation were compared between the groups. Not only the antipsychotic treatments used by the patients but also all other psychotropic drugs were utilised in the outcome measures.

The limitations of this study should be noted. First, one of the methodological limitations of the study design is that, as a retrospective study, no information was collected directly from patients, but information was collected from medical records. This resulted in our inability to provide sufficient information about the severity of the disorder (e.g. PANSS score). Second, there is no way to show or control for individual differences in disease before the index date or to assess the effectiveness of treatments in the subsequent time. Many individual characteristics of the patients, such as their health status and the time since their first diagnosis, are not available in the data. Therefore, their effect on the study's results is unknown. Third, the patients included in the study were recruited from a single centre, and the results obtained may not be generalisable to all patients. Fourth, the results cannot be generalised to all patients as the influence of many confounding factors cannot be excluded. Last, we did not detect co-prescribing of non-psychotropic medications, which could have affected outcome measures.

5. Conclusions

There is no controversy about the efficacy of antipsychotic treatments in patients with SSD. The "real-world" pharmacotherapy of patients with SSD has developed its well-established practice, which may have exceeded available data support (Pickar et al., 2008). However, there is no positive evidence that recommending polypharmacy over antipsychotic monotherapy is superior in the frequency of emergency department visits, emergency department admissions with agitation/aggression, hospitalisation and re-hospitalisation. In this context, it may be more feasible to administer antipsychotic monotherapy in treatment-non-resistant patients and clozapine monotherapy before antipsychotic polypharmacy in treatment-resistant patients due to more significant evidence (Velligan et al., 2015). Although the results do not show that all types of polypharmacy are beneficial, rational approaches such as combining clozapine with aripiprazole, which has been shown to reduce the risk of hospitalisation, may be recommended in ultra-resistant patients (Tiihonen et al., 2019). Moreover, supporting the notion that antipsychotic polypharmacy may not be necessary for most patients, recent studies have shown that two-thirds of patients treated with antipsychotic polypharmacy can be successfully switched to monotherapy (Essock et al., 2011; Suzuki et al., 2004). It may be possible to switch to a single antipsychotic in the outpatient setting for patients discharged on multiple antipsychotics. The conclusions further demonstrate that the required interventions to increase the treatment compliance of the patients are more critical in terms of prognosis than the number of antipsychotics used by the patients. Indeed, these results do not rule out antipsychotic polypharmacy, and further research is needed to identify rational polypharmacy choices for antipsychotics.

Acknowledgements: Not applicable.

Author Contributions: ŞAK designed the research; ŞAK, EK, ÖY, TÖ, and MAG performed the research; ŞAK analysed the data; ŞAK, EK, ÖY, TÖ and MAG wrote the manuscript.

Ethical Approval: The study was conducted according to the Declaration of Helsinki and approved by the Ankara City Hospital Ethics Committee (decision number E2-22-2574) on 12.10.2022. Individual patient consent was not obtained, as this was a database study. The information was de-identified to protect privacy.

References

Abdullah-Koolmees, H., Nawzad, S., Egberts, T. C. G., Vuyk, J., Gardarsdottir, H., & Heerdink, E. R. (2021). The effect of non-adherence to antipsychotic treatment on rehospitalization in patients with psychotic disorders. *Therapeutic Advances in Psychopharmacology* , *11* , 204512532110274.*https://doi.org/10.1177/20451253211027449*

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5).* American Psychiatric Association.

Baandrup, L., Sørensen, J., Lublin, H., Nordentoft, M., & Glenthoj, B. (2012). Association of antipsychotic polypharmacy with health service cost: a register-based cost analysis. *The European Journal of Health Economics* , *13* (3), 355–363.*https://doi.org/10.1007/s10198-011-0308-0*

Baker, J., & Aebi, C. (2017). Comparison of readmission data between different categories of antipsychotic drugs at a state psychiatric hospital in Oregon. *Mental Health Clinician* , *7* (3), 124–130.*https://doi.org/10.9740/mhc.2017.05.124*

Baldessarini, R. J. (2013). *Chemotherapy in Psychiatry* . Springer New York.*https://doi.org/10.1007/978-1-4614-3710-9*

Barbara G. Tabachnick, & Linda S. Fidell. (2013). *Using Multivariate Statistics* . Pearson.

Barnes, T. R., Drake, R., Paton, C., Cooper, S. J., Deakin, B., Ferrier, I. N., Gregory, C. J., Haddad, P. M., Howes, O. D., Jones, I., Joyce, E. M., Lewis, S., Lingford-Hughes, A., MacCabe, J. H., Owens, D. C., Patel, M. X., Sinclair, J. M., Stone, J. M., Talbot, P. S., ... Yung, A. R. (2020). Evidence-based guidelines for the pharmacological treatment of schizophrenia: Updated recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology* ,*34* (1), 3–78.*https://doi.org/10.1177/0269881119889296*

Boskailo, E., Malkoc, A., McCurry, D. B., Venter, J., Drachman, D., & Ramos, G. M. (2017). Assessment of inpatient psychiatric readmission risk among patients discharged on an antipsychotic polypharmacy regimen: A retrospective cohort study. *Acta Medica Academica* ,*46* (2), 133–144.*https://doi.org/10.5644/ama2006-124.198*

Buchanan, R. W., Kreyenbuhl, J., Kelly, D. L., Noel, J. M., Boggs, D. L., Fischer, B. A., Himelhoch, S., Fang, B., Peterson, E., Aquino, P. R., & Keller, W. (2010). The 2009 Schizophrenia PORT Psychopharmacological Treatment Recommendations and Summary Statements.*Schizophrenia Bulletin* , *36* (1), 71–93.*https://doi.org/10.1093/schbul/sbp116*

Centorrino, F., Goren, J. L., Hennen, J., Salvatore, P., Kelleher, J. P., & Baldessarini, R. J. (2004). Multiple Versus Single Antipsychotic Agents for Hospitalized Psychiatric Patients: Case-Control Study of Risks Versus Benefits. *American Journal of Psychiatry* ,*161* (4), 700–706.*https://doi.org/10.1176/appi.ajp.161.4.700*

Choosing equivalent doses of oral benzodiazepines . (2023, June 2). Specialist Pharmacy Service.*https://www.sps.nhs.uk/*

Essock, S. M., Schooler, N. R., Stroup, T. S., McEvoy, J. P., Rojas, I., Jackson, C., & Covell, N. H. (2011). Effectiveness of Switching From Antipsychotic Polypharmacy to Monotherapy. *American Journal of Psychiatry* , *168* (7), 702–708.*https://doi.org/10.1176/appi.ajp.2011.10060908*

Faay, M. D. M., Czobor, P., & Sommer, I. E. C. (2018). Efficacy of typical and atypical antipsychotic medication on hostility in patients with psychosis-spectrum disorders: a review and meta-analysis.*Neuropsychopharmacology* , *43* (12), 2340–2349.*https://doi.org/10.1038/s41386-018-0161-2*

Faden, J., Kiryankova-Dalseth, N., Barghini, R., & Citrome, L. (2021). Does antipsychotic combination therapy reduce the risk of hospitalization in schizophrenia? *Expert Opinion on Pharmacotherapy* , *22* (5), 635–646.*https://doi.org/10.1080/14656566.2020.1847274*

Gallego, J. A., Bonetti, J., Zhang, J., Kane, J. M., & Correll, C. U. (2012). Prevalence and correlates of antipsychotic polypharmacy: A systematic review and meta-regression of global and regional trends from the 1970s to 2009. *Schizophrenia Research* , *138* (1), 18–28.*https://doi.org/10.1016/j.schres.2012.03.018*

Galletly, C., Castle, D., Dark, F., Humberstone, V., Jablensky, A., Killackey, E., Kulkarni, J., McGorry, P., Nielssen, O., & Tran, N. (2016). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. In *Journal of Psychiatry* (Vol. 50, Issue 5).

Gilmer, T. P., Dolder, C. R., Folsom, D. P., Mastin, W., & Jeste, D. V. (2007). Antipsychotic Polypharmacy Trends Among Medi-Cal Beneficiaries With Schizophrenia in San Diego County, 1999–2004. *Psychiatric Services* , *58* (7), 1007–1010.*https://doi.org/10.1176/ps.2007.58.7.1007*

Gören, J. L., Meterko, M., Williams, S., Young, G. J., Baker, E., Chou, C.-H., Kilbourne, A. M., & Bauer, M. S. (2013). Antipsychotic Prescribing Pathways, Polypharmacy, and Clozapine Use in Treatment of Schizophrenia. *Psychiatric Services* , *64* (6), 527–533.*https://doi.org/10.1176/appi.ps.002022012*

Haddad, P. M., & Dursun, S. M. (2008). Neurological complications of psychiatric drugs: clinical features and management. *Human Psychopharmacology: Clinical and Experimental* , *23* (S1), S15–S26.*https://doi.org/10.1002/hup.918*

Haddad, P. M., & Sharma, S. G. (2007). Adverse Effects of Atypical Antipsychotics. *CNS Drugs* , *21* (11), 911–936.*https://doi.org/10.2165/00023210-200721110-00004*

Hasan, A., Falkai, P., Wobrock, T., Lieberman, J., Glenthoj, B., Gattaz, W. F., Thibaut, F., & Möller, H.-J. (2012). World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 1: Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *The World Journal of Biological Psychiatry* , *13* (5), 318–378.*https://doi.org/10.3109/15622975.2012.696143*

Hayasaka, Y., Purgato, M., Magni, L. R., Ogawa, Y., Takeshima, N., Cipriani, A., Barbui, C., Leucht, S., & Furukawa, T. A. (2015). Dose equivalents of antidepressants: Evidence-based recommendations from randomized controlled trials. *Journal of Affective Disorders* ,*180* , 179–184.*https://doi.org/10.1016/j.jad.2015.03.021*

Huang, C.-Y., Fang, S.-C., & Shao, Y.-H. J. (2021). Comparison of Long-Acting Injectable Antipsychotics With Oral Antipsychotics and Suicide and All-Cause Mortality in Patients With Newly Diagnosed Schizophrenia. *JAMA Network Open* , *4* (5), e218810.*https://doi.org/10.1001/jamanetworkopen.2021.8810*

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, Z., Abera, S. F., Abil, O. Z., Abraha, H. N., Abu-Raddad, L. J., Abu-Rmeileh, N. M. E., Accrombessi, M. M. K., ... Murray, C. J. L. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* , *392* (10159), 1789–1858.*https://doi.org/10.1016/S0140-6736(18)32279-7*

Kadra, G., Stewart, R., Shetty, H., MacCabe, J. H., Chang, C.-K., Kesserwani, J., Taylor, D., & Hayes, R. D. (2018). Antipsychotic polypharmacy prescribing and risk of hospital readmission.*Psychopharmacology* , *235* (1), 281–289.*https://doi.org/10.1007/s00213-017-4767-6*

Kasteridis, P., Ride, J., Gutacker, N., Aylott, L., Dare, C., Doran, T., Gilbody, S., Goddard, M., Gravelle, H., Kendrick, T., Mason, A., Rice, N., Siddiqi, N., Williams, R., & Jacobs, R. (2019). Association Between Antipsychotic Polypharmacy and Outcomes for People With Serious Mental Illness in England. *Psychiatric Services* , *70* (8), 650–656.*https://doi.org/10.1176/appi.ps.201800504*

Keepers, G. A., Fochtmann, L. J., Anzia, J. M., Benjamin, S., Lyness, J. M., Mojtabai, R., Servis, M., Walaszek, A., Buckley, P., Lenzenweger, M. F., Young, A. S., Degenhardt, A., & Hong, S.-H. (2020). The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. *American Journal of Psychiatry* ,*177* (9), 868–872.*https://doi.org/10.1176/appi.ajp.2020.177901*

Laan, W., Does, Y. van der, Sezgi, B., Smeets, H., Stolker, J., Wit, N., & Heerdink, E. (2010). Low Treatment Adherence with Antipsychotics is Associated with Relapse in Psychotic Disorders within Six Months after Discharge. *Pharmacopsychiatry* , *43* (06), 221–224.*https://doi.org/10.1055/s-0030-1254090*

Lähteenvuo, M., & Tiihonen, J. (2021). Antipsychotic Polypharmacy for the Management of Schizophrenia: Evidence and Recommendations.*Drugs* , *81* (11), 1273–1284.*https://doi.org/10.1007/s40265-021-01556-4*

Morken, G., Widen, J. H., & Grawe, R. W. (2008). Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. *BMC Psychiatry* , *8* (1), 32.*https://doi.org/10.1186/1471-244X-8-32*

Novick, D., Haro, J. M., Suarez, D., Perez, V., Dittmann, R. W., & Haddad, P. M. (2010). Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. *Psychiatry Research* , *176* (2–3), 109–113.*https://doi.org/10.1016/j.psychres.2009.05.004*

Pickar, D., Vinik, J., & Bartko, J. J. (2008). Pharmacotherapy of Schizophrenic Patients: Preponderance of Off-Label Drug Use. *PLoS ONE* , *3* (9), e3150.*https://doi.org/10.1371/journal.pone.0003150*

Procyshyn, R. M., Honer, W. G., Wu, T. K. Y., Ko, R. W. Y., McIsaac, S. A., Young, A. H., Johnson, J. L., & Barr, A. M. (2010). Persistent Antipsychotic Polypharmacy and Excessive Dosing in the Community Psychiatric Treatment Setting. *The Journal of Clinical Psychiatry* , *71* (05), 566–573.*https://doi.org/10.4088/JCP.08m04912gre*

Psychosis and schizophrenia in adults: prevention and management Clinical guideline . (2014). *www.nice.org.uk/guidance/cg178*

Qin, P., & Nordentoft, M. (2005). Suicide Risk in Relation to Psychiatric Hospitalization. *Archives of General Psychiatry* ,*62* (4), 427.*https://doi.org/10.1001/archpsyc.62.4.427*

Ritsner, M. S. (2013). *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies: Vol. Volume I* (M. S. Ritsner, Ed.). Springer Verlag. Stephen M. Stahl. (2021). *Stahl's Essential Psychopharmacology. Neuroscientific Basis and Practical Applications.*(Fifth Edition). Cambridge University Press.

Strassnig, M. T., Nascimento, V., Deckler, E., & Harvey, P. D. (2020). Pharmacological treatment of violence in schizophrenia. *CNS Spectrums* , *25* (2), 207–215.*https://doi.org/10.1017/S1092852919001226*

Strømme, M. F., Bartz-Johannesen, C., Kroken, R. A., Mehlum, L., & Johnsen, E. (2022). Overactive, aggressive, disruptive and agitated behavior associated with the use of psychotropic medications in schizophrenia. *Schizophrenia Research* , *248* , 35–41.*https://doi.org/10.1016/j.schres.2022.07.014*

Sun, F., Stock, E. M., Copeland, L. A., Zeber, J. E., Ahmedani, B. K., & Morissette, S. B. (2014). Polypharmacy with antipsychotic drugs in patients with schizophrenia: Trends in multiple health care systems.*American Journal of Health-System Pharmacy* , *71* (9), 728–738.*https://doi.org/10.2146/ajhp130471*

Suzuki, T., Uchida, H., Tanaka, K. F., Nomura, K., Takano, H., Tanabe, A., Watanabe, K., Yagi, G., & Kashima, H. (2004). Revising polypharmacy to a single antipsychotic regimen for patients with chronic schizophrenia. *The International Journal of Neuropsychopharmacology* , *7* (2), 133–142.*https://doi.org/10.1017/S1461145703004012*

Taipale, H., Lähteenvuo, M., Tanskanen, A., Mittendorfer-Rutz, E., & Tiihonen, J. (2021). Comparative Effectiveness of Antipsychotics for Risk of Attempted or Completed Suicide Among Persons With Schizophrenia.*Schizophrenia Bulletin* , *47* (1), 23–30.*https://doi.org/10.1093/schbul/sbaa111*

Taylor, D., Barnes, T. R. E., & Young, A. H. (2021). *The Maudsley prescribing guidelines in psychiatry.* (14th edition). John Wiley & Sons.

Tiihonen, J., Taipale, H., Mehtälä, J., Vattulainen, P., Correll, C. U., & Tanskanen, A. (2019). Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia. *JAMA Psychiatry* , *76* (5), 499.*https://doi.org/10.1001/jamapsychiatry.2018.4320*

Velligan, D. I., Carroll, C., Lage, M. J., & Fairman, K. (2015). Outcomes of Medicaid Beneficiaries With Schizophrenia Receiving Clozapine Only or Antipsychotic Combinations. *Psychiatric Services* , *66* (2), 127–133.*https://doi.org/10.1176/appi.ps.201300085*

Volavka, J., Czobor, P., Citrome, L., & Van Dorn, R. A. (2014). Effectiveness of antipsychotic drugs against hostility in patients with schizophrenia in the Clinical Antipsychotic Trials of Intervention Effectiveness

(CATIE) study. *CNS Spectrums* , *19* (5), 374–381.*https://doi.org/10.1017/S1092852913000849*

Wu, Y., Kang, R., Yan, Y., Gao, K., Li, Z., Jiang, J., Chi, X., & Xia, L. (2018). Epidemiology of schizophrenia and risk factors of schizophrenia-associated aggression from 2011 to 2015. *Journal of International Medical Research* , *46* (10), 4039–4049.*https://doi.org/10.1177/0300060518786634*

Yazici, E., S. Cilli, A., Yazici, A. B., Baysan, H., Ince, M., Bosgelmez, S., Bilgic, S., Aslan, B., & Erol, A. (2017). Antipsychotic Use Pattern in Schizophrenia Outpatients: Correlates of Polypharmacy. *Clinical Practice & Epidemiology in Mental Health* , *13* (1), 92–103.*https://doi.org/10.2174/1745017901713010092*

Yorston, G., & Pinney, A. (2000). Chlorpromazine equivalents and percentage of *British National Formulary* maximum recommended dose in patients receiving high-dose antipsychotics. *Psychiatric Bulletin* , *24* (4), 130–132.*https://doi.org/10.1192/pb.24.4.130*

Zhang, S.-Z., Mu, Y.-G., Liu, Q., Shi, Y., Guo, L.-H., Li, L.-Z., Yang, F.-D., Wang, Y., Li, T., Mei, Q.-Y., He, H.-B., Chen, Z.-Y., Su, Z.-H., Liu, T.-B., Xie, S.-P., Tan, Q.-R., Zhang, J.-B., Zhang, C.-P., Sang, H., … Zhang, H.-Y. (2019). Prescription practices in the treatment of agitation in newly hospitalized Chinese schizophrenia patients: data from a non-interventional naturalistic study. *BMC Psychiatry* , *19* (1), 216.*https://doi.org/10.1186/s12888-019-2192-6*

Zuschlag, Z. D. (2021). Second-Generation Antipsychotics and Suicide. *The Journal of Clinical Psychiatry* , *82* (5).*https://doi.org/10.4088/JCP.21ac13955*

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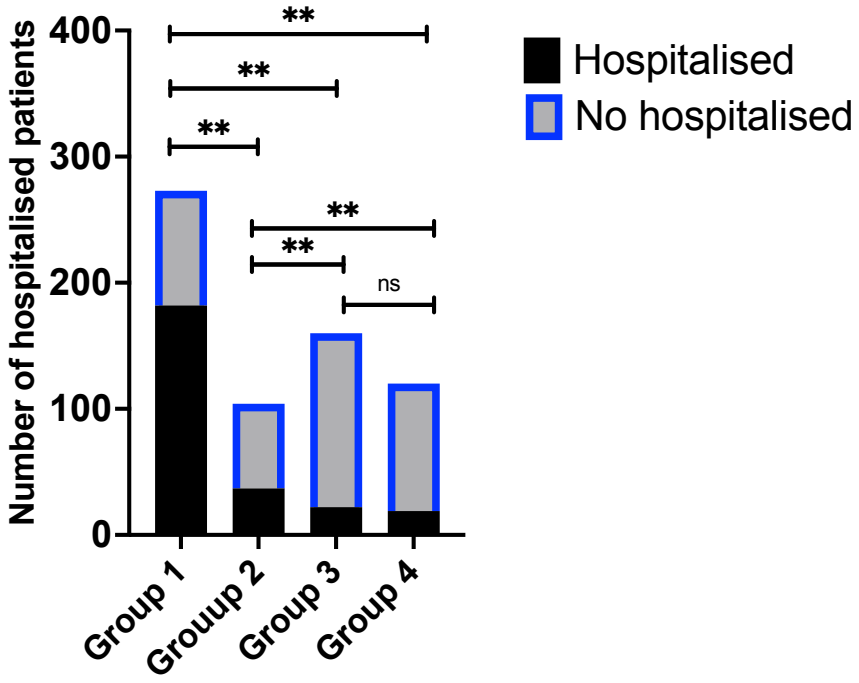
Figure 1. Hospitalisation of the groups



Note. ** p < 0.001, ns=non-significant. Group 1: Patients with non-compliance antipsychotic treatments for more than 90 days; Group 2: Patients with non-compliance antipsychotic treatments for 15-90 days; Group 3: antipsychotic monotherapy users; Group 4: antipsychotic polypharmacy users.