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Comparison of Polypharmacy in Schizophrenia and Other Psychotic Disorders in Outpatient and Inpatient Treatment Periods: A Naturalistic One Year Follow-up Study

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ÖZET:

Şizofreni ve diğer psikotik bozukluklarda çoklu antipsikotik ilaç kullanımının yatış ve ayaktan izlem dönemlerinde karşılaştırılması: Bir yıllık doğal izlem çalışması

Amaç: Şizofreni tedavisinde çoklu antipsikotik ilaç kullanımı, tedavi rehberlerinde yer almamasına ve kanıta dayalı yeterli bulgu olmamasına rağmen giderek artmaktadır. Çalışmamızda bu konudaki kesitsel çalışmalardan farklı olarak, bir yıl süreyle izlenen hastalarda çoklu ilaç kullanım oranı ve ilgili etkenlerin saptanması, hastalık şiddeti ve eşdeğer doz ilişkisinin araştırılması amaçlanmıştır.
Yöntem: Ankara Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi Psikiyatri Kliniğinde 2008-2009 arasında şizofreni ve diğer psikotik bozukluklar tanılarıyla yatarak tedavi gören hastalardan (n=261) taburculuk sonrası ayaktan düzenli izlemi olan hastalar (n=192) çalışmaya alındı. Hastalar birinci yılın sonunda tedavi uyumu, çoklu ilaç kullanımı ve dozları ile hastalık şiddeti açısından değerlendirildi. **Bulgular:** Çalışma grubunun çoklu antipsikotik kullanım oranı taburculuk sırasında %52.1 (n=100) iken, bir yıl sonra ayaktan kontrolde %44.3 (n= 85) oranındaydı (χ^2=2.97, df=1, p=0.001). Tekli ve çoklu antipsikotik grupları arasında eştanı varlığı, hastalık ve tedavi süresi, önceki yatış sayısı, kliniğe geliş biçimi, genel tıbbi durum açısından fark bulunmazken, antipsikotik ilaçların grupları arasında istatistiksel olarak farklı olduğu saptandı. Yatan hastalarda şiddetli olarak tanımlanan hasta oranı ayaktan izleme dönemine göre anlamlı olarak yüksekti. Ayaktan izlemde remisyon grubunda yer alan hastalar durumlarını korurken, orta ve ağır gruptakilerin hastalık şiddetinde artış gözlendi. İlaç tedavi uyumu hem yatan hasta (χ^2 =12.99; df=1; p=0.001) hem ayaktan hasta gruplarında (χ^2 =12.81; df=1; p=0.001) çoklu ilaç kullanan hastalarda anlamlı olarak düşüktü. Yan etki sıklığı açısından gruplar benzerdi. Etki yokluğu ve yan etki olması en sık ilaç değişikliği nedenleri olarak bildirildi. Yatan hastalarda atipik ve tipik antipsikotik ilaç kombinasyonu alan grubun hastalık şiddeti ve antipsikotik ilaç eşdeğer dozu diğer ilaç kombinasyon tiplerine göre daha yüksekti; ayaktan hasta grubunda hastalık şiddeti açısından fark yokken eşdeğer dozlardaki farklılık korunuyordu.
Sonuç: İyi klinik uygulama rehberlerinde çoklu ilaç kullanımı çok sınırlı olarak önerilmektedir, ancak bu konudaki klinik pratik çalışmaların verileri çoklu ilaç kullanımının önerilenin üzerinde olduğunu göstermektedir. Diğer yandan tedaviye dirençli ve uyumu az olan gruplarda klozapin ve uzun etkili antipsikotiklerin kullanım oranları, bu grupların yaygınlık oranlarının altındadır. Klinisyene yol göstermek açısından, şizofreni tedavi algoritmalarının çoklu antipsikotik kullanımı, klozapin ve uzun etkili antipsikotik ilaç formları açısından güncellenmesi gereklidir.

Anahtar sözcükler: Antipsikotik polifarmasi, hastalık şiddeti, tedaviye direnç, yatan, ayaktan hasta

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ABSTRACT:

Comparison of polypharmacy in schizophrenia and other psychotic disorders in outpatient and inpatient treatment periods: a naturalistic one year follow-up study

Objective: Polypharmacy of antipsychotic drugs has been increasing although there are not enough evidence based data and recommendations in the treatment algorithms. The current study differs from cross-sectional studies as it aimed at observing the same patient population during their in- and out-patient periods for one year follow-up and investigated the frequency of polypharmacy and related factors in terms of clinical correlates and equivalent doses.
Method: The patients admitted to Psychiatry Service of Dışkapı Yıldırım Beyazıt Trainig and Research Hospital, Ankara in the 2008-09 period with the diagnosis of schizophrenia and other psychotic disorders (n=261) were reviewed and patients with regular follow up visits in the outpatient clinic (n=192) were included in the study. At the end of the first year, participants were evaluated for their treatment compliance, use of polypharmacy, drug doses, and severity of the disorder.
Results: The rate of polypharmacy was 52.1% (n=100) at the time of discharge from hospital while it was 44.3% (n=85) during the one year-follow up visit (χ^2=2.97, df=1, p=0.001). The polypharmacy and monotherapy groups were not statistically different in terms of comorbidity, disorder and treatment duration, number of previous hospitalizations, type of admission, and general medical condition. However, the monotherapy and polypharmacy groups were statistically different in terms of the use of antipsychotic type. The ratio of patients with severe disorder was statistically higher in the inpatient group. While the clinical severity impression (CGI) of patients in remission did not change during the follow-up period, the moderate to severe patient groups' severity increased during that time. Drug compliance of the polypharmacy group was statistically lower than the monotherapy group both in the inpatient (χ^2 =12.99; df=1; p=0.001) and outpatient (χ^2 =12.81; df=1; p=0.001) periods. Adverse event frequency was the same for both groups. Adverse events and lack of efficacy were the most frequent reasons for drug prescription change. Both inpatients and outpatients receiving antipsychotic combination therapy had statistically higher equivalent antipsychotic drug doses. Severity scores of inpatients receiving combination therapy were higher than the patients receiving other drug regimens
Conclusion: Use of polypharmacy is limited in good clinical practice guidelines but surveys on clinical practices show that the use of polypharmacy is more frequent than the suggested levels in the guidelines. On the other hand, use of clozapine and long-term effective antipsychotics are below the incidence of suggested groups. In order to guide clinicians better, schizophrenia treatment algorithms need to emphasize the use of clozapine and long acting antipsychotics more.

Key words: Antipsychotic polypharmacy, severity, treatment resistance, inpatient, outpatient

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INTRODUCTION

Antipsychotic polypharmacy in schizophrenia and psychotic disorders has been increasing although there are not enough evidence-based data and a lack of treatment algorithms in guidelines on this issue. The rates of antipsychotic use change according to countries and years. It varies between 18% and 50% in Europe and USA and is considerably high in East Asian countries around 78.6% both for outpatients and inpatients (1,2). The studies conducted in Turkey found similar results (3-6).

American and British treatment guidelines suggest a limited use of polypharmacy while changing the drug regimen or in treatment resistant cases. However, high usage rates indicate that there is substantial use outside of these indications (7-10). Despite the view that polypharmacy is not necessary according to good clinical practice guidelines ("there is no need to utilize two drugs with similar mechanisms, which might result in an increase not in desired but in the side effects"), Pandurangi and Dalkilic (11) noted that rational polypharmacy is applied in areas such as epilepsy, hypertension (HTN), and diabetes (DM) and may be practiced in psychiatry rationally if necessary. Some studies report that antipsychotic polypharmacy has certain advantages for schizophrenic patients, such as a quick recovery time, a decrease in side effects and decreased time spent in hospital. On the other hand, numerous other studies claim that polypharmacy is responsible for high doses, treatment noncompliance, metabolic side effects, and mortality (14).

Different findings of previous studies about antipsychotic polypharmacy show the need of further studies for investigating effectiveness and adverse events of polypharmacy (11,15,16,17). In particular, clinicians who are obliged to change treatments as a result of partial or complete treatment resistance and/or serious side effects, are in need of evidence based algorithms (10).

Since findings on rates of antipsychotic use and related factors are so different in previous studies, study designs need to be discussed in terms of factors that may affect study results such as: methodology, sample, diagnostic groups, and health services (9,11,17). It is reported that the results do not reflect continual use tendencies, because these studies are generally cross-sectional or carried out in a very limited time. As a result, these studies cover short terms such as drug changing phases or exacerbation periods (18,19). Also it is worth noting that polypharmacy is hardly continuous and there exist almost no certain criteria about duration or drug combinations in most studies.

Our study differs from other cross-sectional ones as it aims at observing the same patient population during their inpatient and outpatient periods for a one year follow-up period and determining the changes and factors related to polypharmacy. The study also aims to investigate the difference between inpatient and outpatient groups in terms of monotherapy and polypharmacy and their relation with the severity of the disorder.

MATERIALS and METHOD

Sampling

A total of 261 patients diagnosed with schizophrenia or other psychotic disorders and admitted to the psychiatry unit of our hospital in the years of 2008-2009 were followed up. At the end of the first year, 204 patients with follow-up data were assessed for treatment compliance, use of polypharmacy, antipsychotic drug doses, and severity of the disorder. Data regarding 12 patients were excluded from the analysis because of death or interruption of treatment (death: 1.51%, n=4; not using drug: 3%, n=8). Of the excluded patients, 4.9% (n=10) was in remission and 0.5% (n=2) was in partial remission according to the Clinical Global Impression Scale (CGI). Evaluation of the patients (n=162, 84.4%) was carried out at outpatient clinics. Those attending follow- up visits irregularly (n=30, 15.6) were contacted at the end of the year and assessed through interviews with themselves or their relatives. The study was approved by the Ethics Committee of the hospital and written informed consents of patients to participate in the study were obtained at admission. Method. A total of 561 inpatients throughout the period of 2008-2009 were screened. 261 of 300 patients diagnosed according to the DSM-IV criteria with schizophrenic, brief psychotic disorder, schizophreniform disorder, delusional disorder, schizoaffective, and psychotic disorder, not-otherwise specified were included in the study. A total of 39 patients were excluded due to lack of complete data. The patients were diagnosed at rounds by at least three psychiatrists and the psychiatrists working in the unit have not changed within 5 years. The rounds were made routinely twice a week.

Data regarding demographic features, admission and discharge dates to and from hospital, CGI scorings at inpatient and outpatient periods, treatment compliance, side effects, medication changes if any, and date and reason for

the changes were recorded. Drug regimens were not altered. Patients were grouped as either being on monotherapy or polypharmacy (those taking two or more antipsychotics). The patients were then compared in terms of socio-demographic features, treatment compliance, existing comorbidity, length of treatment, number of previous admissions, duration of drug use before the admission, drug use and equivalent doses after the admission, use of additional drugs for side effects, and the severity of the disorder.

Statistical Analysis

Statistical analysis was carried out through parametric and non-parametric tests by employing the SPSS 13.0.

RESULTS

The study population consisted of patients aged 15-75 years, with a mean age of 37.5 (SD: 12.3). The group included 103 male patients (53.6%) and 89 female patients (46.4%). Patients in the scope of the study were categorized as monotherapy and polypharmacy groups according to the drugs prescribed during discharge from hospital and to the drugs prescribed in the outpatient period. There were no significant differences between the monotherapy and polypharmacy antipsychotic groups in terms of gender, marital status, education, profession, and residential area by chi-square and student t-tests statistical analysis. The groups were similar also in terms of psychiatric comorbidity, duration of disorder and treatment, number of previous admissions, type of admission, and general medical comorbidity parameters. However, there was a significant difference between groups in drug compliance (chi-square test, pearson χ^2=12.81, df=1, p=0.001) (Table 1).

In the study group (n=192) the polypharmacy antipsychotic use rate was 52.1% (n=100) while it

Table 1: Comparison of socio-demographic and clinical features in monotherapy and polypharmacy groups in terms of initial data

	Type of Medication				Statistical analysis
	Monotherapy (n= 107)		Polypharmacy (n= 85)		
	Frequency	Percentage	Frequency	Percentage	
Gender					
Male	53	49.5	50	58.8	*χ^2=1.64 df=1 p=0.20
Female	54	50.5	35	41.2	
Marital status					
Married	50	46.7	34	40.4	*χ^2=0.87 df=1 p=0.35
Divorced/Bachelor	57	50.3	51	60.0	
Age year±sd	37.6 ± 12.6		37.4±12.0		**t= 0.15 df=190 p=0.88
Education year±sd	8.0 ± 3.9		8.2 ± 3.6		**t= -0.25 df=190 p= 0.79
Profession					
Employed	20	64.5	11	35.5	*χ^2=1.15 df=1 p=0.28
Unemployed	87	81.3	74	87.1	
Duration of disorder					
<1 year	19	70.4	8	29.6	*χ^2=2.93 df=3 p=0.40
1-5 year	35	55.6	28	44.4	
5-10 year	16	51.6	15	48.4	
>10 year	37	52.1	34	47.9	
New Diagnosis	34	31.8	18	21.2	*χ^2=2.69 df=1 p=0.10
Number of Previous Admission					
No admission	49	45.8	28	32.9	*χ^2=3.37 df=2 p=0.18
1-2 admissions	38	35.5	39	45.9	
≥3 admissions	20	18.7	18	21.2	
Reasons for Admission					
Voluntary	36	33.6	31	36.5	*χ^2=1.96 df=2 p=0.37
By the will of relatives	66	61.7	53	62.4	(exact test p= 0.41)
Administrative	5	4.7	1	1.2	
General medical condition					
No	46	43.0	39	45.9	*χ^2=1.23 df=2 p=0.55
1 chronic illness	38	35.5	33	38.8	
2 chronic illnesses	23	21.5	13	15.3	

*Chi-square test, if needed fisher exact test is given.; ** Student t-test

Table 2: Comparison of clinical features in monotherapy and polypharmacy groups

	Type of Medication				Statistical analysis
	Monotherapy (n= 107)		Polypharmacy (n= 85)		
	Frequency	Percentage	Frequency	Percentage	
Admission CGI					
Scores 1-3	3	2.8	0	0	*χ^2=13.24 df=2 p=0.001
Score 4	22	20.6	4	4.7	
Scores 5-7	82	76.6	81	95.3	
Discharge CGI					
Scores 1-3	82	76.6	55	64.7	*χ^2=5.5 df=2 p=0.058
Score 4	23	21.5	23	27.1	
Scores 5-7	2	1.9	7	8.2	
Follow-up CGI					
Scores 1-3	82	76.6	54	63.5	*χ^2=5.32 df=2 p=0.051
Score 4	14	13.1	23	27.1	
Scores 5-7	11	10.3	8	9.4	
Long-term effective antipsychotic users	23	21.5	64	75.3	**χ^2=55.32 df=1 p=0.001
Treatment compliance during follow-up	79	67.2	42	49.4	**χ^2=12.82 df=1 p=0.001
Antipsychotic change during follow-up	37	34.8	50	58.8	**χ^2=11.23 df=1 p=0.001
Reasons for drug change (antipsychotics or other drugs)					
No effect	21	19.6	27	31.8	**χ^2=8.98 df=4 p=0.062
Side effect	10	9.3	8	9.4	
Non-compliance	6	5.6	11	12.9	
Others	9	8.4	6	7.1	
No change	61	57.0	33	38.8	

*Chi square test, ** Fisher exact test

decreased to 44.3% (n=85) after a year of outpatient treatment (chi-square test, pearson χ^2=2.97, df=1, p=0.001). According to the CGI scores during admission to hospital, 1.6% (n=3) of the group were in remission or in partial remission (scores 1-3), while 13.5% (n=26) were scored as moderate (score 4) and 84.9% (n=163) were scored as serious (scores 5-7). The last group which had scores of 5-7 during admission was statistically high in terms of polypharmacy but this difference disappeared at discharge (Table 2). After a period of one year, a significant difference was shown between the monotherapy and polypharmacy groups for CGI scores; those rated to be in 1-3 phases were stable whereas severity of those in mid and severe phases worsened (Table 2). About 31.3% (n=60) of the patients were re-hospitalized during follow-up; the monotherapy and polypharmacy groups were similar to each other in this parameter.

During outpatient follow-up after discharge, it was found out that in 51% (n=98) of the cases drug regimens were changed and 88.3% of these (n=87) were antipsychotic drug changes. About 65.4% (n=70) of the monotherapy group kept their condition in this period, while the rest changed from monotherapy to combination therapy. Seventyfour point one percent (n=63) of the polypharmacy group stayed on polypharmacy, whereas 25.9% of them changed to monotherapy (chi square test, pearson χ^2=26.7, df=1, p=0.001). As far as the time of drug change, it was observed that 5.2% (n=10) of the drugs were changed within the first two months after discharge while the rest were changed after the third month or later. The ratio for drug change was 34.6% (n=37) in the monotherapy group and it was 58.8% (n=50) in the polypharmacy group (chi square test, pearson χ^2=11.23, df=1, p=0.001). It was found that both antipsychotic drug changes and change between the monotherapy and polypharmacy groups were statistically significant (Table 2).

Fortysix (35.1%) of non-compliant patients (n=124, 64.9 %) were still not adhering to treatment in the follow up assessment. The adherence rate was meaningfully lower in the polypharmacy group both during the admission

Table 3: Comparison of antipsychotic drug combinations in outpatient and inpatient groups in terms of severity of disorder and equivalent drug dosages (one-sided Anova Test)

	Inpatient group				Outpatient group			
	n	%	CGI* average±s.d.	Equivalent dosage** average±s.d.	n	%	CGI average±s.d.	Equivalent dosage *** average±s.d., median
Typical (a)	8	4.2	5.6 ± 0.5	557.5±138.0	10	5,2	3.0 ± 1.2	150.0±126.9; 20.90
Atypical (b)	82	42.7	5.1 ± 0.9	532.9±279.4	97	50,5	2.9 ± 1.3	341.6±155.3; 72.76
Atypical and typical (c)	41	21.4	5.7 ± 0.7	815.4±316.2	39	20,3	3.2 ± 1.0	574.7±303.7; 124;88
Atypical and atypical (d)	45	23.4	5.4 ± 0.7	726.7±225.3	39	20,3	3.3 ± 0.9	666.8±228.9; 149.78
Typical and typical (e)	16	8.3	5.0 ± 0.9	507.8±259.1	7	3,6	3.7 ± 0.8	364.3±224.9; 78.43
Total	192	100	5.3 ± 0.9	637.6±295.5	192	100	3.1 ± 1.1	445.8±258.8

*One-way anova test F=3.85, p=0.005; Levene test = 1.24, sig= 0.31; posthoc Bonferoni and Tukey HSD b<c
** One-way anova test F= 9.80, p=0.001; Levene test= 1.12, sig= 0.35; posthoc Bonferoni and Tukey HSD a=b<c=d, e<d
*** Kruskal Wallis test x2= 25.6, p=0.001; posthoc Bonferoni and Tukey HSD d>b, c=d>e
a = b > c=d, e<d.

(chi square test, pearson χ^2=12.99; df=1; p=0.001) and in the follow up phases (chi square test, pearson χ^2=12.81; df=1; p=0.001). The non-compliance rate in the polypharmacy group was statistically high in both periods. During the follow up period, it was seen that the CGI scores were high for those whose antipsychotic drugs were changed (student t-test, t=3.94 df=190 p=0.001) and who were not adhering to treatment (student t-test, t= 6.86 df=189 p= 0.001).

About 47.5% (n=87) of the patients had been discharged with a prescription for a long-acting antipsychotic drug. 73.6% (n=64) of the patients on polypharmacy and 26.4% (n=23) of patients on monotherapy were prescribed long-acting antipsychotic drugs. The use of a long-acting antipsychotic drug was significantly higher in the polypharmacy group (chi square, fisher exact test χ^2=55.33 df=1 p=0.001) (Table 2). When patients on long-acting drugs were assessed in terms of the severity of the disorder, they were rated significantly higher (student test t= -3.29 df=190 p=0.001) on admission but this difference vanished after the visits carried out during discharge and a year after. Another significant point was the combination use of long-acting risperidone (25.9%, n=22) with oral risperidone.

Side effect frequency was similar in the groups and reasons for changing the drug were either lack of effectiveness or the occurrence of side effects (Table 2). The rate of using additional drugs for side effects was 44.7% in the polypharmacy group while it was 34.6% in the monotherapy group. The groups were rated similarly in that sense (Pearson chi square χ^2= 2.04 df=1 p=0.15). The most frequently prescribed drug for side effects was biperiden.

The drug dosages were compared by computing the equivalent dose of chlorpromazine. The mean equivalent drug dose was 323.7±162.3 mg in the monotherapy group and was 599.1±275.8 mg in the polypharmacy group during the follow up period and the difference was statistically significant (student-t test, for equal variances not assumed t= -8.17 df=128.85 p=0.001). As there was an almost two-fold dose difference between the groups the difference in side effect frequency could be related to higher drug doses. The groups with and without reported side effects were compared in terms of equivalent doses. Within this context, no statistically significant difference was seen (student-t test t= 0.18, df=190; p=0.86) between the groups with side effects (449.9±256.5) and without (443.2±261.3).

The study population was grouped according to the combination type of the antipsychotic drug in order to assess the relation between the severity of the disorder and the choice of monotherapy or polypharmacy antipsychotic use. A one-sided anova test was used to compare combination groups in terms of equivalent doses of

antipsychotic drug doses and scores of the CGI both in outpatient and inpatient periods. The Levene test was used for analyzing variance equality, or if it could not be employed, the Kruskal Wallis test was used. For post-hoc comparisons, the Tukey HSD and the Bonferoni correction was performed (Table 3).

Post-hoc analysis showed that severity of the disorder in the group receiving an atypical-typical drug combination during their admission was meaningfully higher than those receiving atypical monotherapy, while there were no differences among other groups. From the point of view of equivalent dose of antipsychotic drugs, meaningfully higher doses were present in atypical-atypical and atypical-typical combination groups than atypical and typical monotherapy groups; moreover, typical drug combinations had lower dose levels than atypical ones (Table 3).

No significant relation was found between the severity of the disorder and drug combination in the outpatient group. As far as equivalent doses of antipsychotics are concerned, meaningfully higher doses were present in the polypharmacy groups when compared with the same in the inpatient group (Table 3).

DISCUSSION

The rate of polypharmacy in outpatients and inpatients was 52.1% and 44.3% respectively. For the inpatient group in our clinic the rate was found 11.6% in 1999 and 20% in 2004 (4). Despite the fact that treatment guidelines do not recommend polypharmacy, nor are there enough data based on evidence, antipsychotic drugs are increasingly being used in our clinical practice as in the rest of the world (4,6). University and community-based clinical studies show the polypharmacy rate to be 15.6% for outpatients but it is reported that this does not reflect the actual reality at all (20). Although we found that the polypharmacy rate lowered significantly in outpatient setting than inpatient setting, it is still above the level of suggested by treatment algorithms.

Polypharmacy in inpatient groups is reported to be related with acute treatment, severity of disorder, high number of treatment resistant patients, and inability of managing drug regimens due to short duration of inpatient stays. In the studies carried out at inpatient clinics, polypharmacy of antipsychotics was found to be related with male gender, duration of disorder, number of previous admissions, lack of insight, and severity of the disorder parameters (6,21). In fact recent meta-analysis and studies carried out with inpatients have revealed that polypharmacy might be more effective than monotherapy in some cases (2,3,12,22). Essock et al. showed that in cases changed from polypharmacy to monotherapy many patients required to restart using polypharmacy (23).

In the current study it is shown that there is transition between the monotherapy and polypharmacy groups and that there is change of antipsychotic group. 37% of the polypharmacy group changed to monotherapy while 23.9% of the monotherapy group started using polypharmacy within one year follow-up period. When the cross-sectionally determined 44.3% rate was analyzed for a year, it was thought that this high rate covered both polypharmacy users and those in drug transition phase. Considering these data, as Pandurangi and Dalkilic (11) emphasized, it would be an incomplete assessment to state that all polypharmacy and changes of antipsychotics are irrational clinical applications.

A study carried out with outpatients in Canada for a year indicated that more than half of the patients used polypharmacy and that 60% of them maintained their drug treatment; that antipsychotic drug change rate (45.3%) was similar to our study and that there was no difference between the monotherapy and polypharmacy groups in terms of the severity of the disorder by the BPRS, CGI, and GAF (18,19). In our study it was seen that the severity of the disorder was higher in the polypharmacy group in inpatients whereas there was no difference in outpatients.

The CGI carried out during the admission of patients showed that 84.9% of the patients were severely sick. On follow-up patients discharged with remissions kept their statuses, whereas those discharged with partial remissions worsened clinically both in monotherapy and polypharmacy groups. The severity of the disorder seems to be a significant parameter at this point and observations show that there were patients at the 4-7 scores on the CGI in the monotherapy and polypharmacy groups. As far as the combination types of antipsychotics are concerned, it was seen that clinicians preferred using atypical and typical drug combinations for patients with more severe symptoms. Another difference shown between the groups in the study was that high equivalent doses of antipsychotics and long-term effective forms were used more in the polypharmacy group. When drug combinations were analyzed for doses,

it was found that the highest mean dose was used in the atypical/atypical and atypical/typical combinations. As for outpatients, no difference occurred between drug combinations in the CGI measurements but higher equivalent dose combinations were seen in atypical-typical and atypical-atypical drug combinations. Considering the data above, it could be said that clinicians preferred using high doses of atypical-typical polypharmacy combinations for inpatients with severe symptoms and those resistant to treatment and that they partly succeeded in managing the symptoms. Another point to be discussed is questioning the effectiveness of atypical antipsychotic combinations in the treatment resistant group and asking would the rational combinations be working through effective dosing or by increasing efficiency at receptor level. The study carried out by Ranceva et al. revealed that 61.1% of outpatients using polypharmacy are on medication for reasons not listed in treatment guidelines (9). Studies on clinician preferences show that clinicians are of the opinion that 65% of the patients on polypharmacy are resistant to treatment (17,24).

The study by Tsutsumi et al. reported that clinicians decide to change to polypharmacy after using a single antipsychotic for two months and before utilizing the benefits of full doses (25). Another reason that impacts on the decisions of clinicians is their distrust in treatment algorithms (21,25). Antipsychotic drug change rate in our study for the first two months is 5.2%, other than this group waiting time for the change is 3 to 12 months, which is long enough to do so.

In polypharmacy it is a source of concern that, with high doses, side effects and mortality increase and that clinicians have not noted these problems. There are certain data stating that polypharmacy does not increase the efficacy but does increase side effects and length of stay at hospital by exposing patients to higher doses (11,26,27,28). Careful monitoring is suggested for side effects in polypharmacy of antipsychotics including the use of ECGs. In our study side effects are noted but no detailed assessment of side effects was carried out. In terms of side effect frequency no difference was detected between the monotherapy and polypharmacy groups. However, data was checked as equivalent dosage was significantly higher in polypharmacy groups. As there are no detailed data regarding side effects and assessment of ECG and biochemistry, it is not possible to discuss the issue thoroughly within the frame of this study.

Treatment guidelines state that another antipsychotic could be utilized when clozapine on its own is not enough and when antipsychotics from different groups do not work (7,8,10). In our study the rate of patients using clopazine was quite small (6.8%) and there was no combination use. And as such, the data from our clinic do not confirm to treatment guidelines. We believe side effects of clozapine and low levels of patient adaptation to follow-up protocol might have contributed to this result.

Although in treatment guidelines the use of long term antipsychotics is suggested when patients prefer to do so (10), it is shown to be related with race, comorbidity, use of substances and severe psycho-pathology (16). Shi et al. have reported that typical depot medication use is related with previous admission to hospital, judicial involuntary admission, severe levels of psychopathology and positive and disorganized behaviors; they also say that treatment of 68% of the patients was supported with oral antipsychotics for a long time (29). Polypharmacy in those on long-term effective antipsychotic medication was significantly high in our study.

Depot antipsychotic use is reported to be related to high doses of medication and polypharmacy (6,29,30,31). Although they had been in use for almost 30 years, use of depot medication was decreasing gradually until long-acting risperidone, which is an atypical depot antipsychotic, appeared in the market (32). Recent studies have shown that there exists a relation between the use of long-acting risperidone and polypharmacy (9). Ranceva et al., in their study dealing with the adherence to treatment algorithms, report that long-acting antipsychotics are jointly used with oral antipsychotics in 40% of cases (9). Similar studies were carried out with inpatients in Turkey also showed that joint use of atypical and long-acting antipsychotic drugs was 40.2% (5). In our study the group that started treatment with a long-acting antipsychotic form initially was more stable. However, this treatment option is suggested "to be decided by the patient" in treatment guidelines. Thus, it could be proposed the said treatment mode should be revised in the light of clinical data. On the other hand, since it is orally used around 45% and this is more than the suggested dosage, it can be stated that discussion regarding the useful dosage of risperidone's long-acting version was justified. This is an indication showing that this treatment option should be revised both for its indications and for its

effective dosages in the guidelines.

As the current study deals with inpatients, who were a more severe group in terms of disorder, it is difficult to make generalizations about outpatients. This may be considered as a limitation but it is significant since it gives information about treatment resistant or partially respondent patients as well. Since the current study is a natural follow-up study it aims to identify the current situation rather than establishing causality. The results may be useful in the decision making process of patient groups to be studied for polypharmacy, severity of the disorder, high equivalent dosages, and side effects. Another limitation of the study was including all patients diagnosed with schizophrenia and other psychotic disorders. No comparison could be performed in the sub-diagnosis groups as the number of patients in the subgroups was limited.

In conclusion, polypharmacy may be a choice for patients who have a poor prognosis. However, the rate of polypharmacy is higher than severe cases as seen in our study and as such it is not possible to say it is used only for severe cases. Atypical antipsychotics are frequently used in high doses and in combination with both other atypicals and with typical ones. Reasons for changing and combining drugs are usually stated as lack of efficacy and side effects while polypharmacy itself increases side effect risk. As polypharmacy use is rarely suggested in good clinical practices, studies about this issue are limited. However, further studies to compose treatment and monitor algorithms in treatment resistant patients to guide clinicians are required.

Clozapine use, which is suggested by all treatment algorithms for treatment-resistant patients, was quite low in our study group. While the use of clopazine is limited due to its known side effects, more research is needed for the unknown side effects of polypharmacy. Another method suggested to improve adherence to treatment is use of long-acting antipsychotics. More data about the use of the long-acting antipsychotics are necessary and it should considered in guidelines, as well.

The change between the monotherapy and polypharmacy groups of the study indicates the instability during the course of the disorder. Treatment noncompliance is related with polypharmacy use both in treatment type (in/out-patients) and time dimensions. Treatment noncompliance is not peculiar to the patient but changes with time. In the light of the data above, it can be stated that polypharmacy might increase the efficacy of the treatment, but also likely results in more side effects and treatment noncompliance.

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