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Does Combined Antipsychotic Treatment Provide Better Control on Symptoms in Patients with Schizophrenia than the Monotherapy?

Ersin Hatice Karslioglu[1], Elvan Ozalp[2], Ismail Volkan Sahiner[1], Mehmet Ozturk[1], Melike Nur Albayrak[1], Serap Aydin[1], Sadik Aydin[1], Ozgur Ahmet Yuncu[1], Ali Caykoylu[3]

ABSTRACT:

Does combined antipsychotic treatment provide better control on symptoms in patients with schizophrenia than the monotherapy?

Objective: Combined antipsychotic treatment is frequently used in clinical practice either to improve the symptom control or to reduce the severity of side effects. The expected benefits by combining different antipsychotics include active cross-titration and co-utilization of different administration routes of the therapeutic agents. However, except the add-on therapies to clozapine, there is no objective evidence implying the superiority of combined therapy over monotherapy. Furthermore, there are a number of published case reports of significant side effects accompanying combined antipsychotic usage such as extrapyramidal and metabolic symptoms, seizures, and electrocardiographic abnormalities. It is also argued that switching into a new therapeutic agent might be more beneficial than augmenting the ongoing medication by polypharmacy. Here, we studied on a group of hospitalized schizophrenia patients in a training and research hospital in Turkey whether the Positive and Negative Symptom Scale (PANSS) scores differ between the patients under monotherapy and combined therapy.

Methods: Hospital records belonging patients with schizophrenia who were followed up between the years of 2003 and 2013 were retrieved. Schizophrenia diagnoses were re-evaluated and confirmed according to the DSM-IV-TR criteria. All the patients who met the diagnostic criteria and having PANSS subscale scores (n=158) were included in the study. PANSS scores at the time of hospitalization are represented by adding "-before" suffixes, while the ones at the time of discharge by adding "-after".

Results: Our series composed of 158 schizophrenia patients (54 women and 104 men). When the medications were reviewed, we found that 66 patients (41.8%) were treated with a single drug and the atypical antipsychotics were the most commonly used group. Multiple drugs were combined on 92 patients (58.2%) and the most common combination was the "atypical + typical" antipsychotics. PANSS subscales and their comparisons among the groups of monotherapy and combined therapy revealed a slight statistical difference in PANSS negative scores at the time of hospitalization, although we found no significant changes in terms of PANSS scales, in general.

Conclusion: In this study, we presented the overall frequency and patterns of our combined antipsychotic therapy in our daily routine work. We only used severity of symptoms in our study, and observed no differences between mono and combined therapy groups in terms of the PANSS evaluation. Further clinical studies with clinical, metabolic, and laboratory data as well as the long follow-ups are needed to uncover if combined therapy proves to be beneficial over monotherapy.

Keywords: schizophrenia, antipsychotic, monotherapy, polypharmacy, positive symptoms, negative symptoms

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[1]M.D., [2]Assoc. Prof., [3]Prof., Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Psychiatry, Ankara - Turkey

Corresponding author:
Dr. Ersin Hatice Karslıoğlu,
Mahmut Esat Bozkurt Caddesi, No: 2,
Kolej, Ankara - Türkiye

E-mail address:
ehkarslioglu@gmail.com

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INTRODUCTION

The perception about the devastating clinical course and the disturbing social consequences of schizophrenia has been changing in the recent past with the introduction of the new antipsychotics. There is a consensus, however, on the potentially chronic course of the disease and the risk of exacerbation or recurrence, as the most worrisome clinical problems. Thus, preemptive strategies that might reduce inadequate response to treatment or some serious side effects are continually being explored. Combined antpsychotics use in schizophrenia patients is probably the most widely seen example of such strategies. Despite the expected benefits, multiple medication use would result in increased cost[1], side effects[2], reduced compliance of the patients[3], and other medical conditions, such as metabolic syndrome[4]. Nonetheless, having a poor response to the treatment, resistance to the selected agents, impaired functionality of the patients, naturally drive the clinicians into multiple medication use. Furthermore, treatment-resistant schizophrenia cases can also make psychiatrists more inclined to seek other new generation agents, which can be used as stand-alone or add-on to clozapine. Yet, the efficacy of such new strategies is either unproved or conflicting.

Antipsychotic combination therapy, or antipsychotic polypharmacy, is one of the most common methods used by physicians, in selected cases. A previous meta-analysis reported the prevalence of antipsychotic polypharmacy to vary from 7% to 50% in the United States[5]. Antipsychotic combination therapy is depend on various factors such as disease severity, resistance to treatment, duration of disease, length of hospital stay, and geographical region[10-12]. Although monotherapy is recommended by most of the treatment guidelines for schizophrenia, there are studies reporting that combined antipsychotics may reduce the length of hospital stay and also has a positive effect on the course of the disease[9]. Antipsychotic combination therapy is also a common practice in the majority of psychiatric treatment centers in Turkey[10-12]. There are randomized controlled trials for combination therapies with clozapine. However, there are only a limited number of studies, despite increased use of non-clozapine combination therapies in clinical practice. Among the literature related to the psychopharmacological therapy modalities in schizophrenia, one study reported that the frequency of using a second antipsychotic drug during the course of treatment was 64.7%; whereas the rate of multiple drug use was found as 38.2%, in another one[10,11]. Similarly, a study exploring antipsychotic treatment habits revealed that the rate of adding a depot antipsychotic to the ongoing plan was about 40.2% in general, and this rate was especially higher (63.8%) with typical antipsychotics[12].

The main driving force behind the use of the antipsychotic combinations might be the feeling provided by the relatively safer side effect profiles of atypical antipsychotics to the physicians. The clinicians' choice for the combination therapy rather than initiating a single drug at a high dose may be explained by the fact that the high-dose antipsychotic administration may result in severe and acute adverse effects, such as cardiac problems and conduction disturbances[13]. Paradoxically, the combination therapies may also lead to a significantly increased incidence of side effects, in contrast to their expected clinical benefits. Some trials even reported that mortality rates were not low in the combination therapies[13]. In general, the expectation for an early response to the treatment, although there is no such a proven effect of the combined antipsychotic medication, and the probability of getting worse in clinically more severe patients, the clinicians may unconsciously feel obligated to try higher doses and/ or combine atypical antipsychotic medications[14]. Data revealed that there is a three- to fourfold increase in the use of double and even triple combinations within the past 10 years[15]. Yet, it is still controversial whether the combination therapy is preferential or the most effective if it is used in this way. According to the conclusions of a previous meta-analysis, combination therapy was superior to the

monotherapy in terms of efficacy in 12 out of 18 studies. Although, such superiority was observed to be lost when compared each drug's overall doses equivalent to chlorpromazine[5].

From the point of view the advantages and disadvantages of antipsychotic combinations, one study, which dealt with the patients who discontinued antipsychotic polypharmacy and shifted to monotherapy, reported a reduced body mass index upon the shift to monotherapy[16]. Again, the same study revealed an improved compliance of the patients when combination therapy was introduced[16]. Contrary to this, however, there are some reports claiming weight gain in the patients under monotherapy[17]. Another study reported that antidepressant use was lower in patients receiving antipsychotic combination therapies when compared to those receiving monotherapy. Furthermore, there were a lower number of suicide attempts resulting death[18]. Given the variety of atypical and typical antipsychotics, currently it is likely to have more than 200 types of combinations, and it is impossible to make a conclusion, which can be generalized, to each one of such polypharmacy options. Therefore, there might be dramatically variable outcomes among the different patients, as well as in the same patient with different combinations. In one study, probable harms and benefits of antipsychotic combinations were discussed and the general risks were reported as the elevated incidence of side effects such as weight gain, dry mouth, and sexual dysfunction, as well as increased overall antipsychotic doses or need for using anticholinergic agents, all of which may impair the cost effectiveness of the treatment. The general benefits, on the other hand, were listed as better and sustainable symptom management[19].

The present study aimed to explore the preferred types of antipsychotic combinations in routine daily practice of a busy training and research hospital's psychiatry clinics in Turkey, and to compare such combination therapies with monotherapy in terms of their effectiveness on symptom management.

MATERIALS AND METHODS

The study has been carried out by using the archival data of the schizophrenia patients, who were treated in the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Psychiatry Clinic with a diagnosis of schizophrenia based on DSM IV-TR, between the years of 2003 and 2013. A total of 158 patients, whose PANSS scores both at the time of hospitalization and discharge were available, have been included to our series. Patients with incomplete or missing PANSS subscale scores were excluded. Approval was obtained for the study from the Ethical Committee of our hospital. All the patients had been given the PANSS scale at least twice: Firstly at the time of hospitalization and secondly at the time of discharge. We divided our series into two main groups as combination and monotherapy, based on the medications given, which were ascertained from a thorough review of their hospital records. The monotherapy group was divided into subgroups as "atypical antipsychotic", "typical antipsychotic", "clozapine", and "depot atypical antipsychotic". The combination group was subdivided into the groups of "atypical + typical", "atypical + atypical", "typical + typical", "clozapine + atypical", "clozapine + typical", "clozapine + depot typical", and "clozapine + depot atypical".

Sociodemographic data sheet: For all patients, a sociodemographic data sheet was used, which was developed by the researchers and included the variables of age, gender, place and date of birth, educational status, alcohol/substance use and smoking, age of disorder onset, family history, and personal disease history.

Positive and Negative Symptom Scale (PANSS): PANSS was developed by Kay et al.[20]. It is a semi-structured interview scale involving a thirty items and a seven-point severity rating. Out of thirty psychiatric parameters assessed by the interviewer, seven parameters are included in the positive syndrome subscale, seven parameters are included in the negative syndrome subscale, and the remaining sixteen parameters are included in the

general psychopathology subscale. Its validity for Turkish language was assessed and published by Kostakoglu et al. in 1999[21].

Continuous variables are represented by Mean±Std.Dev and the discrete ones are shown using Count and Percent (n and %) notations. Student t test, Mann Whitney U test and Chi-square test have been performed to make comparisons between monotherapy and combined therapy groups. The P value was set as 0.05 for the statistical significance. All statistical analyses have been performed by using SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Out of 158 patients, 104 were men and 54 were women. Table 1 summarizes the gender, age, length of education, and the duration of disease among the monotherapy and combined therapy groups. Table 2 shows the sociodemographic data including education and marital status as well as smoking habits and the frequency of alcohol or substance use disorder. When the patients were evaluated for smoking between the monotherapy and combined therapy groups, no difference has been observed. However, we noticed a significantly

Table 1: Summary of demographic and some clinical characteristics in patients on monotherapy and combined antipsychotic therapy groups

	Monotherapy		Combined Therapy		Statistic	Significance (p)
	n (66)	%	n (92)	%	Chi-square	
Gender						
Female	23	34.8	31	33.7	0.23	0.880
Male	43	65.2	61	66.3		
	Mean	**Std. Dev.**	**Mean**	**Std. Dev.**	**t**	
Patients' age	40.05	10.63	40.22	12.55	- 0.90	0.928
Length of education (years)	9.98	3.81	8.46	4.14	2.364	0.019
Duration of disease (years)	16.42	7.61	14.13	8.28	1.777	0.078

Std. Dev.: Standard Deviation, n: Total Number of Patients in the Corresponding Columns

Table 2: Summary of the sociodemographic data in patients on monotherapy and combined antipsychotic therapy groups

	Monotherapy		Combined Therapy		Statistic	Significance (p)
	n (66)	%	n (92)	%	Chi-square	
Educational Status (n - %)						
Unschooler	-	-	6	6.5	7.799	0.099
Elemenraty School	16	24.2	27	29.3		
Middle School	9	13.6	18	19.6		
High School	25	37.9	26	28.3		
College	16	24.2	15	16.3		
Above College	-	-	-	-		
Marital Status (n - %)						
Single	41	62.1	44	47.8	5.740	0.125
Married	14	21.2	36	39.1		
Divorced	6	9.1	7	7.6		
Widowed	5	7.6	5	5.4		
Separate	-	-	-	-		
Smoking (n - %)						
No	19	28.8	40	43.5	3.545	0.060
Yes	47	71.2	52	56.5		
Alcohol or substance use (n - %)						
disorder No	54	81.8	81	88.0	1.197	0.274
Yes	12	18.2	11	12.0		

n: Total Number of Patients in the Corresponding Columns

higher incidence of smoking in males than female patients (p=0.003, not shown in the table). Although alcohol and substance use disorder did not differ between the two groups, we have to say that only one female patient was using alcohol in contrast to 22 males with some degree of alcohol exposure, which produces a statistically significant difference (p=0.001, not shown in the table). Overall assessment of the sociodemographic data, including the duration of disease revealed that there were no significant and clinically relevant differences between the monotherapy and combination therapy groups in terms of age, gender, educational status, marital status, duration of disease, smoking habits, and alcohol use, except a relatively longer length of education in monotherapy group (p=0.019).

Table 3 summarizes the schizophrenia types as paranoid versus non-paranoid and the medications given to the patients. According to the reliably documented and available patient data from our series, 66 of the patients (41.8%) were treated with a single medication and the atypical antipsychotics were the most commonly used group (56%). Multiple medications were combined on 92 patients (58.2%) and the most common combination was the "atypical + typical" antipsycotics (67%).

Table 3: Summary of clinical data in patients on monotherapy and combined antipsychotic therapy groups

	Monotherapy		Combined Therapy		Statistics	Significance (p)
	n (66)	%	n (92)	%	Chi-square	
Type of Schizophrenia (n – %)						
Paranoid	52	78.8	78	49.4	0.947	0.330
Non-paranoid	14	21.2	14	8.9		
Monotherapy agents (n - %)						
Atypical Antipsychotic	37	56	-	-		NC*
Typical Antipsychotic	16	24	-	-		
Clozapin	4	6	-	-		
Atypical Depot	6	9	-	-		
Typical Depot	3	5	-	-		
Combined Agents (n - %)						
Atypical + Typical	-	-	62	67		NC*
Atypical + Atypical	-	-	1	1		
Typical + Typical	-	-	11	12		
Clozapin + Atypical	-	-	9	10		
Clozapin + Typical	-	-	6	7		
Clozapin + Atypical Depot	-	-	2	2		
Clozapin + Typical Depot	-	-	1	1		

*NC: Not compared. Monotherapy and combined therapy groups are mutually exclusive and not comparable. The number of patients and the overall percentages are given to make the data visually appreciated more easily.

Table 4: PANSS subscale values compared in between the monotherapy and combined therapy groups

	Monotherapy			Combined Therapy			Z statistics	p
	Median	25%	75%	Median	25%	75%		
PANSS Subscales								
PANSS Positive - Before	23	18	27	21	17.5	25.5	-0.560	0.576
PANSS Positive - After	15	12	20	15	12	18.5	-0.198	0.843
PANSS Negative - Before	20	17	27	21	16.5	26	-2.057	0.040
PANSS Negative - After	16	12	21	16	12	20	-1.407	0.159
PANSS General - Before	43.5	35	50	39.5	30.5	47.5	-0.163	0.871
PANSS General - After	33	27	40	30	25	37	-0.166	0.868
PANSS Total - Before	85.5	77	100	82.5	71	95.5	-1.464	0.143
PANSS Total - After	65	57	76	61.5	51.5	74.5	-1.047	0.295

25%: 1st quantile, 75%: 3rd quantile, Z statistics from Mann-Whitney U test, p: Statistical Significance at alpha level <0.05

When compared the PANSS scores measured at the time of hospitalization and at the time of discharge between the monotherapy and combined therapy groups, we did not notice any dramatic differences among the subscales, except for a slightly elevated PANSS Negative scores in the combined therapy group at the time of hospitalization, although it did not reach clinical significance (p=0.04). However, one can hypothesize that the combined therapy might more frequently be preferred in patients having predominantly negative symptoms, in the first place. Table 4 summarizes the comparison of the groups on account of the PANSS scores.

DISCUSSION

Although antipsychotic monotherapy is the primarily recommended way in the treatment of schizophrenia, there are many studies reporting antipsychotic combination therapies are very common, especially in inpatient psychiatry services. As revealed in one of such study, 42.5% of the patients with schizophrenia and 50% of the institutions, in which inpatient services are available, have been using at least two antipsychotics, and the rate of other psychotropics combined with antipsychotics can be raised up to 70%[22]. Another study revealed that 90% of the treatment-resistant patients with schizophrenia received some forms of antipsychotic combination therapy, during the course of the illness[23]. Similar studies from Turkey reported that the multiple antipsychotic medications use varied from 38.2% to 64.7%[10,11,24]. In the present study, we have reported that 58.2% of our patients (n=92), who were admitted to the psychiatry inpatient service, were actually treated with antipsychotic combination therapy. The data from this study showed that our daily practice is no different with the contemporary trends of combination therapy and consistent with the current literature and treatment guidelines.

Our data revealed that the combination therapy is relatively frequent in the patients who have a little higher, yet statistically significant, PANSS Negative scores at the time of hospitalization. It is a well known and accepted practice using low-dose antipsychotics in patients with apparent negative symptoms. At the same time, the need to control of prominent positive symptoms, which generally require the patient to be hospitalized, may warrant higher doses of medications. We think that psychiatrists unconsciously, somehow, tend to formulate a mix of combined low-dose agents, rather than using only one high-dose antipsychotic, both for tailoring an individualized, more symptom control-based therapies and lowering the probability of unwanted adverse effects.

Another observation from our study is the slightly consistent co-occurrence of monotherapy on the patients with relatively longer education periods (Table 1). Based on this finding, one can speculate that the longer education might provide a better cooperation and compliance of patients to therapy, which may allow a sustainable and/or adjustable monotherapy to be continued as long as needed.

The patients receiving either combined or single clozapine treatment accounted about 14% of all our subjects. The addition of other antipsychotics to clozapine was reported to be approximately 60% in the clinical practice[25]. In the present study, the ratio of patients who were taking clozapine only versus clozapine plus another agent was about 1/4.5 and the majority of such patients were preferentially given typical or atypical depot antipsychotics. So, the pattern of our approach to the patients seemed very similar to those in the recent studies. However, the use of single or combined clozapine was lower in our service than the rates reported from most of the previous studies. Such a difference may have resulted from the clinicians' choice for non-clozapine therapies and combinations over using clozapine in recent years[3,4,26]. Given that the one-third of the patients with schizophrenia are resistant to treatment[27] and despite the known therapeutic efficacy of clozapine in treatment resistant cases[28], such a low rate might be emerged from the concerns of the clinicians about the known side effects of clozapine, like metabolic derangements.

To our opinion, the majority of the clinicians preferring combination therapy may unconsciously expect to achieve a satisfactory and quick response, especially in the hospitalized patients[29], although there is no such a recommendation or proven effect in the established guidelines for schizophrenia treatment. Actually, all treatment guidelines and major textbooks still recommend a time period varying from 4 to 6 weeks for the assessment of the antipsychotic efficacy. However, we think that most of the psychiatrists are not so much inclined to wait for such a relatively long time, according to our observations. In practice, most psychiatrists either try to combine some other antipsychotics to the one already started, or shift to another agent, to establish a swift and sustainable clinical improvement, particularly in patients with severe symptoms.

The relatively higher rates of our antipsychotic combination habit over monotherapy can be attributable to the rapid circulation of our inpatient service, with a roughly three to four week hospital stay for any given patients. Besides, mean PANSS scores of the hospitalized patients in our clinic are generally above the 80, which might affect our pattern of pharmacological intervention planning by making us more prone to start with a combination instead of using monotherapy, in the first place. Nonetheless, we found no significant differences in symptom management between monotherapy and the combination therapy groups, in general.

Among the recent articles we reviewed on the issue of combination therapy, we have encountered many conclusions, which were essentially opposite to one another. A Hungarian group, for example, claimed that the treatment compliance of the patients in monotherapy was better, while the combination therapy was far more superior both in terms of the shortening the hospital stay and decreasing the overall mortality rate[30]. Another article, which reviews the trials of high-dose monotherapy and combination therapy on the aggressive patients with schizophrenia, suggested that the combination therapies were more effective on the preventing the increased severity of the illness. It also reported that the clinicians tended to favor classical antipsychotics more and more, as the aggression level increased[31]. Another study argued that the quality of patients' life was considerably better with the combination therapy despite the increased risk for their side effects[32].

There are some limitations to our study. First of all, the data have been retrieved from our hospital's archives between the years of 2003 and 2013. Ten years is a long period of time and one cannot guarantee the consistency of protocols and evaluations, especially for obtaining PANSS scales, which are being administered by different healthcare professionals. So, there might be some observer biases, which we do not have a chance to eliminate in the first place. Secondly, we know that the practice of antipsychotic medication use has changed over the time between these years, and the algorithms of decision making on combined therapy might be affected by such changes, especially by the introduction of new generation antipsychotic agents. That might also affect the contents of our dataset. And lastly, although we would like to analyze the frequency of comorbidities as well as the possible adverse effects of the medications we use, our series did not allow it because of the missing laboratory data from most of the subjects.

In conclusion, we have found no statistically significant differences between monotherapy and combination therapy groups, in terms of the symptom management of the hospitalized patients with schizophrenia. We think that the desire to achieve a more sustainable response with a low adverse effects profile, especially in the inpatient services, makes the physicians more inclined to use combination therapies, even a reasonable response can also be obtained with monotherapy. Studies with larger sample sizes exploring drug compliance, cost effectiveness, equivalent doses, comorbid systemic diseases, and mortality along with the side effect profiles are required with long-term follow-ups in this regard.

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