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Potential benefits of combining two long-acting injectable antipsychotic: a retrospective study

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Abstract. – OBJECTIVE: The aim of this study was to evaluate the efficacy and tolerability of the combination of two long-acting injectable antipsychotics (LAIA) in psychiatric disorders, especially in schizophrenia.

PATIENTS AND METHODS: Eighty-three patients treated with dual LAIA were included in the study by retrospective screening from the hospital registration system. The present study was designed as an observational, retrospective, naturalistic mirror-image study. The number of hospitalizations before and after switching to dual LAIA was compared in patients who received oral antipsychotics and single LAIA during the study period. In addition, it was analyzed which was the preferred dual antipsychotic combination.

RESULTS: Of the patients, 44.6% had schizophrenia, 41.0% had schizoaffective disorder, and 14.4% had other psychiatric disorders. The number of patients receiving oral treatment prior to dual LAIA use was 80 (96.4%). Data on dual LAIA regimens showed that 31.3% were receiving paliperidone and aripiprazole, 24.1% were receiving paliperidone and flupenthixol, 18.1% were receiving paliperidone and zuclopenthixol, and 26.5% were receiving the other combinations. After dual LAIA treatment, there was a significant decrease in the number of hospitalizations compared to before (from 5.95 to 0.99, $p<0.001$). In addition, while the number of patients who did not require hospitalization in the pre-treatment period was 10.8%, it reached 48.1% in the post-treatment period ($p<0.001$). No significant adverse effect related to the use of dual LAIA was observed in any patient during the treatment period.

CONCLUSIONS: The use of dual LAIA instead of oral antipsychotics or single LAIA in chronic psychotic patients with poor social support and irregular medication use is thought to reduce hospitalization and related treatment costs and regularize medication use.

Key Words:
Dual LAIA, Injection Polypharmacy, Schizophrenia.

Introduction

Antipsychotic agents are the mainstay of treatment in many patients with severe mental illness[1]. These agents are used in various psychiatric disorders, including schizophrenia spectrum, bipolar disorder, and substance-induced disorders. Guidelines[2] recommend avoiding antipsychotic polypharmacy (APP), which can be defined as co-prescribing more than one antipsychotic medication for a particular patient. Exceptions to this may be cases where the APP is required when changing agents or resistant to treatment cases. While high APP rates are expected in patients with schizophrenia and schizoaffective disorder, the observation of APP was of interest in many patients with bipolar disorder and in a few patients with mental illnesses[1].

A significant proportion (20-60%) of patients with schizophrenia are resistant to treatment, and clozapine remains the recommended treatment option despite the increasing variety of antipsychotic drugs. Especially in cases where clozapine cannot be tolerated, combinations of antipsychotics can be used[3]. Although evidence-based treatment guidelines[2] recommend co-treatment with antipsychotics only after unsuccessful attempts of multiple monotherapies, including clozapine, some studies[4] have shown an increasing trend towards the use of polypharmacy in the same treatment. Prevalence of antipsychotic polypharmacy range was reported from 7% to approximately 50%[4].

Concomitant use of antipsychotics in treatment-resistant disease has also been investigated[5] in the literature, but these are predominantly oral formulations. A comprehensive meta-analysis[4] of randomized controlled trials (RCTs) investigating monotherapy *vs.* antipsychotic co-treatment in schizophrenia demonstrates the

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superiority of the antipsychotic co-treatment over the two predefined co-primary outcomes of all-cause cessation and ineffectiveness, as defined in each study.

Multiple drug use can be applied in treatment-resistant patients or when switching from one antipsychotic to another[6]. Schizophrenic patients use 2.0 ± 0.81 antipsychotics and 3.52 ± 2.55 pills per day[7]. The high number of tablets taken daily may be a factor that disrupts the patient's compliance with treatment in the long term.

Treatment nonadherence is indeed recognized[8] as one of the main causes of antipsychotic failure. The advent of long-acting "depot" antipsychotic injections (LAIA) represented a crucial improvement in treatment adherence and clinical benefit, such as emergency room visits and reduced hospitalizations. It is recommended[9] to use a single LAIA when the patient prefers the formulation or to avoid treatment nonadherence. However, whereas recent nationwide cohort studies[10-12] have reported that a combination of two orally administered antipsychotics (other than clozapine supplementation) may be a useful option, concurrent use of two LAIs (dual-LAIs) has not been addressed.

Although there are no treatment guidelines for combining 2 LAIAs, this practice has been used. Overall, the decision to use two LAIAs is difficult, because there is no broad evidence base to support practice or guidance from treatment guidelines. Therefore, most patients do not use dual LAIA therapy[9].

Only a few case reports[3,9,12] have described the successful use of dual LAIs with significant improvements in clinical symptoms without significant side effects. More recently, Mathew et al[13] reported that they observed reductions in hospitalizations and in length of stay after initiation of dual LAIs in a case series of 5 patients with schizophrenia.

Only one study[3] was found to report elevated efficacy and tolerability of dual-LAIs in the literature. In this retrospective study[3], including thirteen patients, it was observed that patients with treatment-resistant schizophrenia and inadequate drug therapy may provide significant clinical benefit from dual LAIs.

The aim of our study was to evaluate the efficacy and tolerability of the combination of two LAIAs in a larger series of 83 patients with schizophrenia, schizoaffective disorder, and other few psychiatric disorders.

Patients and Methods

Study Design

This retrospective study was performed in the Psychosis Clinic of the Psychiatry Hospital, Pamukkale University Faculty of Medicine. Eighty-three patients treated with dual LAI were included in the study by retrospective screening from the hospital registration system. The study was approved by the Pamukkale University Non-interventional Clinical Research Ethics Committee (approval no: 07, date: 30.03.2021) before the study, and it conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000).

The present study was designed as an observational, retrospective, naturalistic mirror-image study. The number of hospitalizations before and after switching to dual long-acting antipsychotics was compared in patients who received oral antipsychotic and single long-acting antipsychotic treatment during the study period. In addition, it was analyzed which is the more preferred dual antipsychotic combination.

Statistical Analysis

The conformity of continuous variables to normal distribution was checked by Shapiro-Wilk's test. Data conforming to normal distribution are shown as mean (mean)± standard deviation (SD). Data not conforming to normal distribution are shown as median (minimum value - maximum value). Data not conforming to normal distribution were compared between two dependent groups using Wilcoxon signed-rank test. Categorical variables are shown as number and percentage. Categorical variables were compared using the Chi-square test. Statistical analysis of the study was performed with Statistical Package for Social Sciences (SPSS) for Windows Version 22.0 (IBM Corp., Armonk, NY, USA).

Results

The mean age of the patients was 34.7±9.5 years. According to the distribution of the patients according to their diagnoses, 37 patients (44.6%) had schizophrenia, 34 patients (41.0%) had schizoaffective disorder, 6 patients (7.2%) had bipolar disorder, 4 patients (4.8%) had mental retardation, and 2 patients (2.4%) had organic mental disorders (Table I).

Table I. Diagnosis distribution of patients.

Diagnosis	%	N
Schizophrenia	44.6%	37
Schizoaffective disorder	41.0%	34
Bipolar disorder	7.2%	6
Mental retardation	4.8%	4
Organic Mental Disorder	2.4%	2
Total	100.0%	83

The number of patients receiving oral treatment prior to dual long-acting injectable drug use was 80 (96.4%). Data on dual long-acting injectable drug treatment regimens showed that 26 patients (31.3%) were receiving paliperidone and aripiprazole, 20 patients (24.1%) were receiving paliperidone and flupenthixol, 15 patients (18.1%) were receiving paliperidone and zuclopenthixol, 5 patients (6.0%) were receiving paliperidone and haloperidol, and 5 patients (6.0%) were receiving flupenthixol and haloperidol and twelve patients (14.4 %) were receiving the other combinations (Table II).

The average number of hospitalizations required after dual long-acting injectable drug use was 5.95 [median: 5 (0-22)] in the pre-treatment period. In the post-treatment period, the mean was 0.99 [median: 1 (0-9)]. This difference was statistically significantly lower ($p<0.001$). In addition, while the number of patients who did not require hospitalization in the pre-treatment period was 9 (10.8%), the number of patients who did not require hospitalization in the post-treatment period was 39 (48.1%). This difference between the groups was statistically significant ($p<0.001$).

No significant adverse effects related to the use of dual long-acting injectable drugs were observed in any patient during the treatment period.

Discussion

In the present study, hospitalization rates in patients with single LAIA use in addition to oral treatment were found to be significantly higher compared to patients with dual LAIA use. These high hospitalization rates observed due to symptom control and nonadherence to oral therapy have decreased with the use of dual LAIA.

In English literature, several case reports and one study[3,9,12,14] involving thirteen patients, have reported the successful use of dual LAIA treatment with significant improvements in clinical symptoms without significant adverse effects. Also, in this study, no serious side effects related to the use of dual LAIA were observed. In addition, in only one study in literature[3], it was reported that the rate of hospitalization decreased from 2.6 to 1.3. Similarly, a significant decrease (5.94 to 0.99) in hospitalization rates was found in this study[3]. It is thought that the use of dual LAIA without oral treatment instead of oral or single long-acting antipsychotic drugs in treatment-resistant schizophrenia patients with poor social support and irregular medication use reduces hospitalizations.

In a meta-regression of RCTs[4], similar dose combinations, second-generation antipsychotic (SGA) + first-generation antipsychotic (FGA), and concomitant onset of polypharmacy were reported to be important. In addition, it has been reported[3,9] that nonclozapine SGAs are mostly combined with each other or with FGAs in clinical practice. The dual LAIA reported in case reports and case series in literature[15] is mostly FGA – SGA combination. In the present study, 89.1% of the patients were treated with the combination of FGA-SGA. In addition to optimized

Table II. Distribution of treatment regimens in patients.

Agents of dual LAIA	Dual LAIA usage rates (%)
Paliperidone-LAIA and AOM	31.3
Paliperidone-LAIA and Flupentixol-LAIA	24.1
Paliperidone-LAIA and Zuclopenthixole-LAIA	18.1
Paliperidone-LAIA and Haloperidol-LAIA	6.0
Flupentixol-LAIA and Haloperidol-LAIA	6.0
Flupentixol-LAIA and Risperidone-LAIA	3.6
Zuclopenthixole-LAIA and Flupentixol-LAIA	3.6
Paliperidone-LAIA Three-Monthly and AOM	2.4
Zuclopenthixole-LAIA and Haloperidol-LAIA	2.4
Risperidone-LAIA and Haloperidol-LAIA	1.2
Zuclopenthixole-LAIA and AOM	1.2

AOM: Long Acting Aripiprazole 400 Mg One-Monthly.

adherence to therapy, the efficacy of dual LAIAs may be associated with an optimal combination of pharmacodynamic profiles resulting in effects on both dopamine receptor 2 (D2) and various non-D2 receptors.

Aripiprazole is the first member of the D2 partial agonizing antipsychotic family, which is also seen[16,17] as a third-generation APs. Therefore, it does not lead to D2 receptor up-regulation and decreased incidence of extrapyramidal side effects side effects. In this study, 34.9% of patients were treated with the combination of SGA-aripiprazole, except only for one patient using combination of FGA-aripiprazole. It was thought that aripiprazole may be safer in combination with antipsychotics because of its partial agonistic effect.

In the present study, 85.6% of the patients were diagnosed with schizophrenia and schizoaffective disorder. In the abovementioned case reports and case series involving dual LAIA, all diagnoses were schizophrenia and schizoaffective disorder, no other psychiatric diagnoses were reported. However, dual LAIA experiences in other psychiatric diagnoses including bipolar disorder, mental retardation and organic mental disorder were also presented in this study. To the best of our knowledge, the use of dual LAIA has not been reported in these diagnoses in English literature.

Limitations

The limitations of the study are as follows: including small number of patients, although this is the largest number of cases in the literature; not evaluating symptom severity; limited follow-up period; single center experience; not including separate groups for each dual LAIA.

Conclusions

It is thought that the use of dual LAIA drugs instead of oral antipsychotics or single LAIA in chronic psychotic patients with poor social support and irregular drug use will reduce hospitalization and related treatment costs and regularize drug use.

Despite the limitations, the findings of this study were considered to provide the highest level of proof up to date for the use of dual LAIs in maladaptive and resistant schizophrenia and schizoaffective disorder. In the absence of higher levels of evidence from larger controlled trials, in cases of treatment-resistant schizophrenia where clozapine is not an option and medication adherence is a concern, it is reasonable to consider this strategy on a case-by-case basis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

The study was conducted in line with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the Faculty of Medicine, Pamukkale University (approval no: 07, date: 30.03.2021).

Informed Consent

All patients included in the study provided written informed consent.

Availability of Data and Materials

The data associated with the paper are available from the corresponding author upon reasonable request.

Authors' Contribution

Concept/Design: Ayse Nur Inci Kenar; Data Collection: Alper Mert, Ayinzeliha Matsar Ay; Data Analysis: Ayse Nur Inci Kenar; Writing and Editing: Gonca Ayse Unal, Ayse Nur Inci Kenar; Final version approval and responsibility with critical revision of the article: Gonca Ayse Unal, Ayse Nur Inci Kenar, Alper Mert, Ayinzeliha Matsar Ay.

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