



## ARAŞTIRMA / RESEARCH

# Clinical use of long-acting antipsychotics for the treatment of bipolar disorder type I patients

Bipolar bozukluk tip I hastalarının tedavisinde uzun etkili antipsikotiklerin klinik kullanımı

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### Abstract

**Purpose:** This study aims to determine the usage frequency of long-acting injectable antipsychotics among bipolar disorder type 1 patients who presented to the Dicle University Faculty of Medicine Psychiatry and Mental Health outpatient clinic, the clinical characteristics of these patients, and the preferences of clinicians about these agents.

**Materials and Methods:** Our study included 111 patients older than 18 years old with bipolar disorder. The data of the patients were retrospectively obtained from electronic data records. The data were recorded in the data collection form prepared by the researchers with the support of the literature.

**Results:** The rate of the patients who used long-acting injectable antipsychotics was 21.6%. Among the patients who used long-acting injectable antipsychotics, the rate of those who used second-generation long-acting injectable antipsychotics was 58.3%, and the most frequently preferred agent was paliperidone palmitate. The patients who were using long-acting injectable antipsychotics had significantly higher rates of not working and numbers of hospitalizations.

**Conclusion:** Our results showed that long-acting injectable antipsychotics are preferred by clinicians in our outpatient clinic in the later stages of bipolar disorders and for patients with poor drug compliance, poor functionality, and more hospitalizations. Starting long-acting injectable antipsychotics in the early stages of bipolar disorders, even following the first attack, may increase treatment compliance, reduce the duration of hospitalization, and contribute to the functionality of patients.

**Keywords:** Antipsychotics, bipolar disorder, long-acting injectable antipsychotics

### Öz

**Amaç:** Bu çalışmada, Dicle Üniversitesi Tıp Fakültesi Psikiyatri polikliniğine başvuran Bipolar Bozukluk Tip 1 hastalarının uzun etkili enjektebl antipsikotik kullanım sıklığı ve hastaların klinik özellikleri ile klinisyenlerin bu ilaca yönelik tercihlerinin belirlenmesi amaçlanmıştır.

**Gereç ve Yöntem:** Çalışmamız, 18 yaş üstü, 111 bipolar bozukluk tanısı almış hastanın katılımı ile gerçekleştirildi. Hasta verileri elektronik veri kayıtlarından retrospektif olarak elde edildi. Veriler araştırmacılar tarafından literatür destekli olarak hazırlanmış veri kayıt formuna kaydedildi.

**Bulgular:** İkinci kuşak uzun etkili enjektebl antipsikotik kullanan hastaların oranı %58,3 olup en çok tercih edilen paliperidon palmitat idi ve hastaların %21,6'sı uzun etkili enjektebl antipsikotik kullanıyordu. Uzun etkili enjektebl antipsikotik kullanan hastalarda çalışmama oranı ve hastanede kalış anlamı olarak daha yüksekti.

**Sonuç:** Bulgularımız uzun etkili enjektebl antipsikotiklerin, Bipolar Bozuklukların ileri evrelerinde, ilaç uyumu ve işlevselliği kötü olan ve poliklinikte klinisyenler tarafından daha fazla yatış endikasyonu olan hastalarda tercih edildiğini göstermiştir. Uzun etkili enjektebl antipsikotiklerin bipolar bozukluğun erken evrelerinde, hatta ilk atakta başlanması, tedaviye uyumu artırılabilir, hastaneye yatış sayısını azaltılabilir ve hastaların işlevselliğine katkıda bulunabilir.

**Anahtar kelimeler:** Antipsikotikler, bipolar bozukluk, uzun etkili enjektebl antipsikotikler

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## INTRODUCTION

Bipolar Disorder (BD) is a chronic and persistent mental illness characterized by states of depression, mania, hypomania, or mixed types. Mood stabilizers and second-generation antipsychotics (SGAs) are used in the main treatment. The use of SGAs in BD has increased over the past 20 years.<sup>1</sup> While SGAs are preferred for acute and preventive treatment in manic episodes, quetiapine is also effective in the acute and preventive treatment of depression. First-generation antipsychotics (FGAs) are recommended only for the acute treatment of mania.<sup>2</sup>

However, non-compliance with treatment in BD is one of the main problems in the treatment of patients. Non-adherence to drug therapy is a common problem in bipolar patients. The rates of non-adherence to drug therapy in bipolar patients vary between 20% and 60%.<sup>3-6</sup> Patients with poor compliance with treatment are at risk of recurrent episodes and hospitalization. Strategies like education about symptoms, identifying triggers, and early warning signs, including family, phone reminders, and motivational interviewing can be used to increase treatment adherence. Switching to long-acting injectable (LAI) antipsychotics (APs) can also be a pharmacological strategy. The use of LAI APs may be an alternative pharmacological treatment in patients with poor compliance with treatment.<sup>7</sup>

Although LAI FGAs may effectively reduce manic relapses, they may increase the risk of worsening depression. Currently, LAI FGAs are not recommended for the maintenance treatment of BD, although they are still frequently used for BD.<sup>8,9</sup> LAI APs such as fluphenazine decanoate, haloperidol decanoate, olanzapine pamoate, paliperidone palmitate, and risperidone are approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia. For the maintenance treatment of BD Type 1, only aripiprazole monohydrate and LAI risperidone are approved, and other LAI antipsychotics are used off-label.<sup>10,11</sup> Risperidone: The most prevalently studied LAI AP in BD in the literature is risperidone, and its effects in the maintenance treatment of BD have been shown in many studies. Compared to oral AP treatment or placebo injection, risperidone has been found associated with decreasing relapse rates, delaying the time to the recurrence of mood episodes, and reducing hospitalization in BD<sup>12-14</sup>.

Aripiprazole monohydrate: In a study conducted at 103 sites in 7 countries as a 52-week, double-blind, placebo-controlled, and randomized study with BD patients, aripiprazole monohydrate increased time to relapse and reduced relapse rates.<sup>15</sup> In a second study with the same sample, aripiprazole monohydrate reduced hospitalization risk for any mood episode by more than 85% for a one-year period<sup>16</sup>.

Paliperidone palmitate (PP): As a metabolite of risperidone, PP has fewer adverse effects than risperidone does<sup>17</sup>. Both oral and LAI PP have been found effective for affective symptoms as well as psychotic symptoms in patients with schizoaffective disorders<sup>18,19</sup>. A few studies and case reports have shown that PP effectively reduces hospitalization rates, relapse rates, and length of inpatient stay<sup>19,20</sup>. A study conducted by Çalışkan et al. in Turkey revealed that PP effectively decreased the number of manic and mixed episodes and hospitalizations<sup>21</sup>. One of the newer antipsychotics, cariprazine was found to be highly effective against manic episodes and effective and safe in the treatment of depressive symptoms at a dose of 2-4 mg/day<sup>22</sup>. Aripiprazole, asenapine, and cariprazine are recommended for the treatment of manic episodes with mixed features<sup>23</sup>. In patients with bipolar disorder, it is of great importance to investigate the drug compliance of patients in terms of reducing treatment and care costs and better patient outcomes. For this, studies examining treatment regimens and patient characteristics are needed.

This study aims to determine the frequency of LAI AP usage among Bipolar Disorder Type 1 patients who presented to the Dicle University Faculty of Medicine Psychiatry and Mental Health Outpatient Clinic, the clinical characteristics of these patients, and the LAI AP preferences of clinicians in the outpatient clinic.

## MATERIALS AND METHODS

We conducted this study to determine the frequency of LAI AP usage among Bipolar Disorder Type 1 patients, the clinical characteristics of these patients, and the LAI AP preferences of clinicians. Ethics committee approval of the study was received from the Non-Interventional Clinical Studies Ethics Committee of the Faculty of Medicine at Dicle University (05.12.2019/06). Our study was conducted in compliance with the ethical principles of the Declaration of Helsinki.

## Design and participants

This study was conducted with a descriptive and cross-sectional design. The G\*Power-3.1.9.2 software was used in our study, and the minimum required sample size was calculated in a 95% confidence interval. According to the results of the analysis, the medium effect size was standardized as  $\alpha=0.05$ . The minimum sample size was calculated as 108 with a theoretical power of 0.80. Our study included 111 patients older than 18 years of age with bipolar disorder who presented to the Psychiatry outpatient clinic of the Faculty of Medicine at Dicle University between September 2018 and September 2019.

We have a separate BD outpatient clinic in our psychiatry unit. Patients diagnosed with BD in the general outpatient clinic and patients with BD who have been hospitalized and discharged after treatment are followed up and treated in our BD outpatient clinic. In this unit, the data of each patient are recorded in their patient file. The data for this study were obtained by retrospectively examining these records.

In our study, the sample inclusion criteria were determined as (i) being diagnosed with BP 1 at least 3 years ago and/or being over 18 years of age, (ii) Using the same drugs for the past year, (iii) Having at least moderate adherence to one's medication in the last 6 months according to the Morisky Treatment Adherence Scale, and (iv) No additional psychiatric comorbidity. Accordingly, the exclusion criteria were (i) being diagnosed with BP 1 less than 3 years ago and/or being under 18 years of age, (ii) using the same drugs for less than 1 year, (iii) adherence to medication treatment below moderate levels in the last 6 months according to the Morisky Treatment Adherence Scale, and (iv) psychiatric comorbidities.

The diagnostic criteria published in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), were used to diagnose patients with BP 1.<sup>24</sup> We divided BP 1 patients who met the inclusion criteria into two groups as LAI AP users and non-users and compared their parameters. Oral treatments mostly included APs, antidepressants, mood stabilizers, and benzodiazepines suitable for the phase of the illness.

## Data collection tools

The data were collected using a Personal Data Form and the Morisky Treatment Compliance Scale.

Information on the data collection tools is shown below.

### Personal data form

The patients' personal data were recorded in the sociodemographic data form created by the researchers.

### Morisky Treatment Compliance Scale

It was developed by Donald E. Morisky and validated by Morisky, Gren, and Levine in 1986. The Cronbach's alpha coefficient of the original scale was found to be 0.61.<sup>25</sup> The scale evaluates drug compliance and consists of four yes/no questions answered by the patient. If the answers to all the questions are "no", drug compliance is high. If one or two questions are answered "yes", drug compliance is considered moderate, and if three or four questions are answered "yes", drug compliance is considered low. The validity and reliability study of the scale in Turkey was conducted by Güven in 2013, and the Cronbach's alpha reliability coefficient of the scale was reported as 0.625.<sup>26</sup> In our study, the Cronbach's alpha coefficient of the scale was found to be 0.71.

### Statistical analysis

After data entry by the researchers, data analysis was performed using the Statistical Package for the Social Sciences (SPSS) 25.0 IBM statistical program. Descriptive statistical methods (frequency, percentage, mean, and standard deviation) were used in data analysis regarding the sociodemographic and clinical characteristics of the patients. Homogeneity tests between the groups were conducted with one-way analysis of variance (ANOVA) and Chi-squared test. The conformity of the data to normal distribution was evaluated with the Shapiro-Wilk test. The Mann-Whitney U test was used to determine the relationships between variables. In the evaluation of the results that were obtained, a 95% confidence interval and an error level of  $p<0.05$  were taken into account.

## RESULTS

The sociodemographic and clinical characteristics of the BP 1 patients who participated in this study are shown in Table 1. The mean age of patients was  $39.55\pm 12.08$  (min: 19, max: 75). The mean age of the group using LAI APs was  $37.67\pm 10.75$  (min: 24, max: 64), the mean age of the group not using these agents

was  $40.07 \pm 12.43$  (min: 19, max: 75), and there was no statistically significant difference between the two groups. 48.6% of the patients were women, and 51.4% were men. 47.7% of the patients were single, and 52.3% were married. There was no significant difference between the group that used LAI APs and the group that did not use LAI APs in terms of their sex, marital status, education, smoking status,

substance abuse status, and family history of psychiatric illness. However, the patients in the group using LAI APs had significantly higher rates of not working and numbers of hospitalizations. The information of the education levels, working statuses, smoking statuses, substance abuse rates, and mean numbers of hospitalizations among the patients is presented in Table 1.

**Table 1. Sociodemographic and Clinical Characteristics of Patients (n=111)**

Items	Using LAI AP (n=24) n (%)	Not using LAI AP (n=87) n (%)	Total (n=111) n (%)	Homogeneity test between groups Test and sig.
Sex				
Female	9 (37.5)	45 (51.1)	54 (48.6)	$\chi^2=1.098$
Male	15 (62.5)	42 (48.9)	57 (51.4)	$p=0.219$
Marital Status				
Single	13 (51.2)	37 (42.5)	50 (45.0)	$\chi^2=0.721$
Married	11 (48.8)	50 (57.5)	61 (55.0)	$p=0.313$
Working status				
Working	2 (8.3)	33 (37.9)	35 (31.5)	$\chi^2=.329$
Not working	22 (91.7)	54 (62.1)	76 (68.5)	$p=0.006^{**}$
Smoking				
Yes	7 (29.2)	41 (47.1)	48 (43.2)	$\chi^2=1.654$
No	17 (70.8)	46 (52.9)	63 (56.8)	$p=0.118$
Substance abuse <sup>a</sup>				
Yes	4 (1.7)	12 (13.8)	16 (14.4)	$\chi^2=1.897$
No	20 (98.3)	75 (86.2)	95 (85.6)	$p=0.724$
Family history of psychiatric illness				
Yes	15 (62.5)	47 (54.0)	62 (55.9)	$\chi^2=2.321$
No	9 (37.5)	40 (46.0)	49 (44.1)	$p=0.461$
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
Age	37.67 $\pm$ 10.75	40.07 $\pm$ 12.43	39.55 $\pm$ 12.08	$F=0.213, p=0.422$
Education (Years)	8.08 $\pm$ 3.12	9.17 $\pm$ 4.21	8.94 $\pm$ 4.01	$F=1.006, p=0.408$
Number of hospitalizations	3.46 $\pm$ 4.26	2.06 $\pm$ 1.86	2.36 $\pm$ 2.61	$F=0.321, p=0.019^*$

N, sample size; %, frequency; SD, standard deviation; LAI, Long-Acting Injectable; AP, Antipsychotic; F=ANOVA, One-way analysis of variance;  $\chi^2$ =Chi-squared test; \* $p<0.05$ ; \*\* $p<0.01$   
<sup>a</sup>Stimulant substances such as cannabis, heroin, bonzai.

There was no significant difference in the illness durations between the two groups. Information on the duration of oral AP use before LAI AP, the duration of oral AP use in non-LAI AP users, and the duration of LAI AP use in LAI AP users is given in Table 2.

Table 3 shows some clinical characteristics of the patients. The rate of adherence to oral treatments before adding LAI or switching to LAI was

significantly lower in the LAI users compared to those using only oral treatments. Table 4 presents information about the usage of oral treatments or LAI APs by the patients. 21.6% of the patients were using LAI APs, 2.7% were using LAI APs alone, and the others were using LAI APs combined with oral treatments (Table 4). Table 5 shows the LAI AP usage statistics of the patients. Among the patients who were using LAI APs, 58.3% were using LAI SGAs, and 41.7% were using LAI FGAs (Table 5).

**Table 2. Clinical characteristics of patients (n=111)**

Items	Using LAI AP (n=24)	Not using LAI AP (n=87)	Total (n=111)	Test and sig.
	Mean±SD	Mean±SD	Mean±SD	
Illness duration	14.42±7.48	13.62±8.32	13.79±8.12	U=0.956, p=0.385
Duration of oral treatment use before LAI AP	9.17±6.33			
Duration of oral treatment use in non-LAI AP users		11.97±7.92		
Duration of LAI AP use in LAI AP users	3.58±4.10			

n, sample size; SD, standard deviation; LAI, Long-Acting Injectable; AP, Antipsychotic; U, Mann-Whitney U

**Table 3. Comparison of treatment adherence levels (n=111)**

Adherence to oral treatments	Using LAI AP (n=24)	Not using LAI AP (n=87)	Test and Sig.
	Adherence before LAI AP treatment n (%)	Current treatment n (%)	
High	12 (50)	63 (72.4)	U=1.231
Moderate	12 (50)	24 (27.6)	p=0.038*

n, sample size; %, frequency; SD, standard deviation; LAI, Long-Acting Injectable; AP, Antipsychotic; U, Mann-Whitney U

**Table 4. Patient Usage of Oral Treatment or LAI AP (n=24)**

Items	n	%
Oral treatment	87	78.4
LAI AP	3	2.7
Oral treatment+LAI AP	21	18.9

n, sample size; % frequency; SD, standard deviation; LAI, Long-Acting Injectable; AP, Antipsychotic

**Table 5. LAI APs Used by Patients (N=24)**

Items	n	%
SGAs	14	58.3
Paliperidone palmitate	9	37.5
Aripiprazole monohydrate	3	12.5
Risperidone	2	8.3
Items	n	%
FGAs	10	41.7
Zuclopenthixol decanoate	6	25
Haloperidol decanoate	4	16.7

n, sample size; %, frequency; SD, standard deviation; LAI, Long-Acting Injectable; AP, Antipsychotic; SGAs, Second-Generation Antipsychotics; FGAs, Second-Generation Antipsychotics

## DISCUSSION

We conducted this study to determine the frequency of LAI AP use in patients with Bipolar Disorder Type 1, the clinical characteristics of the patients, and the preferences of clinicians for these drugs. Non-compliance with drug therapy in psychiatric patients may not be caused by drug side effects. Patients often do not comply with the use of their drugs because they do not accept that they are sick. Therefore, we

included patients with high adherence to treatment in our study, and then, we examined their durations of drug use and compared some variables. Additionally, we examined clinician preferences.

Our study included patients with moderate or high levels of compliance with their current treatment. The LAI AP users in this study had longer disease durations than the non-users. In BD, non-adherence to treatment is one of the main problems among

patients, and it is observed in varying proportions of patients. Patients with poor compliance with treatment are at risk of recurrent episodes and hospitalization. The use of long-acting APs is an alternative pharmacological treatment method in patients with poor compliance with treatment<sup>2,7</sup>.

There was no significant difference in terms of age, sex, marital status, education, smoking status, substance abuse rates, family history of psychiatric illness, or illness duration between the group using LAI APs and the group not using these agents. However, the patients in the group using LAI APs had significantly higher rates of not working and numbers of hospitalizations compared to those in the group using only oral treatments. The rate of adherence to oral medication therapy before adding LAI or switching to LAI was significantly lower in the LAI users compared to those using only oral treatments. The duration of oral medication treatment use before LAI APs was  $9.17 \pm 6.33$  years. These results showed that LAI APs are preferred in the later stages of BD and for patients with poor drug compliance and functionality and more hospitalizations in our outpatient clinic. These findings were consistent with the literature<sup>27,28</sup>. The initiation of LAI APs within one year has been found associated with a significant reduction in hospitalization rates and healthcare costs<sup>29</sup>. Of course, this may also apply to BD, and the first episode may even be a rational time for LAI AP use.

21.6% of the patients who participated in this study were using LAI APs. According to an online survey on psychiatrist.com, the rate of psychiatrists using LAI in BD 1 patients was quite low. Only 20% of psychiatrists treated more than 5% of their patients with LAI agents<sup>30</sup>. Similar to our study, in a study conducted in Turkey, the rate of using LAI agents in patients with BD was 20%<sup>31</sup>. The results of our study were similar to those in the literature. Furthermore, 58.3% of the patients were using second-generation LAI APs, and 41.7% were using first-generation LAI APs. PP, aripiprazole monohydrate, and risperidone were preferred among SGAs, while zuclopenthixol decanoate and haloperidol decanoate were preferred among FGAs. The SGA preferences of the clinicians that were determined in our study were similar to those in the literature<sup>28</sup>. The rates of LAI FGA use were high. The effects of LAI FGAs in the treatment of BD have not been researched enough. LAI FGAs are not currently recommended for BD treatment due to the lack of evidence, and they are not

approved by the FDA for BD treatment<sup>9</sup>. However, their use in the treatment of BD is not rare. Even so, LAI FGAs are still frequently used for treating BD. The effectiveness and therapeutic profiles of LAI FGAs for the maintenance treatment of BD remain unclear.

The social cost of BD is quite high. In previous studies, LAI antipsychotics have been associated with lower costs by improving treatment adherence, reducing hospital admissions, and increasing functionality<sup>29,32</sup>. The reason for this is that we cannot access separate information about the hospitalizations before and after the depot patients. We think that it was before the use of Hospitalizations LAI-AP. the majority of the treatment period already includes the pre-LAI-AP period. In our study, contrary to the literature, the number of hospitalizations among the LAI AP users was found to be significantly higher than that among those not using LAI APs ( $p=0.019$ ). In our study, the small number of cases, cross-sectional and retrospective design, and single-center settings were considered limitations. Prospective and longitudinal studies with LAI SGAs should be conducted with more cases.

In this study, we examined the frequency of LAI AP use in BD Type 1 patients, the clinical characteristics of these patients, and the preferences of clinicians for these drugs. The results of our study showed that LAI APs are preferred in patients with poor drug compliance and functionality and those who have more indications for hospitalization in the outpatient clinic. In this context, starting the use of LAI APs in the early stages of bipolar disorder, even following the first attack, may increase adherence to treatment and reduce the number of hospitalizations. This way, patients will be more functional, they will become more social, and the quality of life of patients will increase.

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**Yazar Katkıları:** Çalışma konsepti/Tasarımı: AA, BU, DGB; Veri toplama: AA, BU, DGB; Veri analizi ve yorumlama: BU, AA; Yazı taslağı: BU, AA; İçeriğin eleştirilme incelenmesi: BU, AA, DGB; Son onay ve sorumluluk: BU, AA, DGB; Teknik ve malzeme desteği: AA, BU, DGB; Süpervizyon: AA, BU, DGB; Fon sağlama (mevcut ise): yok.

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**Conflict of Interest:** Authors declared no conflict of interest.

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