



ORIGINAL ARTICLE

Efficacy of Long-acting, Injectable Antipsychotics in the Treatment of Bipolar Disorders

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Objective: Long-acting injectable (LAI) antipsychotic drugs have been used to treat bipolar disorders, especially in patients with poor medication adherence. We used copies of a questionnaire and chart reviews to investigate the outcome of long-term use of LAI antipsychotic drugs in bipolar patients.

Methods: In this study, the use of LAI antipsychotics, including first-generation LAI (FLAI) antipsychotic drugs and second-generation LAI (SLAI) antipsychotic drugs were studied, to determine their efficacy and side effects. The study group comprised patients with bipolar disorder who were recruited from outpatient clinics at Taipei City Psychiatric Center: 27 patients who received FLAI antipsychotics and 14 patients who received risperidone one of the SLAI antipsychotics. Self-report copies of the questionnaire were gathered, and information from patients' medical records was reviewed and analyzed ($n = 41$).

Results: The frequencies (number of times per year) of mood episodes were found to be significantly different before and after the administration of LAI antipsychotic drugs (0.71 ± 0.65 and 0.23 ± 0.43 , respectively, $p < 0.001$). The frequency of hospitalizations was also significantly different (0.57 ± 0.69 and 0.11 ± 0.26 , respectively, $p < 0.001$).

Conclusion: LAI treatment may decrease the frequency of mood episodes and number of hospitalizations in patients with bipolar disorder.

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1. Introduction

Bipolar disorder is a chronic psychiatric illness with a high relapse rate. Nonadherence or partial adherence of medications is generally considered to be the major cause for repeated relapses of mood episodes,^{1–3} and many ways exist to improve patients' adherence.⁴ Antipsychotic drugs are almost routinely used in treating acute mania, either as monotherapy or in combination with mood stabilizers.⁵ Even during maintenance therapy, antipsychotic drugs are continuously used around 60–90% of the time in outpatient settings.^{6,7}

Long acting-injectable (LAI) antipsychotic drugs were developed to improve patients' adherence. The use of LAI antipsychotics, especially first-generation LAI (FLAI) antipsychotic drugs, is unpopular in clinical practice due to considerable side effects such as extrapyramidal syndromes.⁸

Risperidone, a second-generation LAI (SLAI) antipsychotic drug, which was introduced for the indication for maintenance therapy in bipolar I disorder patients in Taiwan in 2011, has been in extensive use here for this purpose. In a prospective, controlled, randomized study in patients with bipolar I disorder, risperidone LAI antipsychotic monotherapy was found to delay the time to recurrence of mood episodes.⁹ In another randomized, double-blind, placebo-controlled study of maintenance treatment in patients with bipolar I disorder, LAI risperidone adjunctive therapy can delay the time to relapse.¹⁰ All study patients have tolerated its side effects.^{9,10} In this study, the efficacy and side effects in patients with bipolar disorder treated with LAI antipsychotics at Taipei City Psychiatric Center was investigated.

2. Methods

2.1. Study group, tools, and procedures

This study took place in the outpatient clinics at Taipei City Psychiatric Center. Forty-one patients with bipolar disorder were treated with FLAI antipsychotics (1 fluphenazine, 10 haloperidol, 14 flupenthixol, and 2 clopenthixol) or SLAI antipsychotics

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(14 risperidone). They were administered the Chinese Health Questionnaire (CHQ-12),¹¹ brief version of World Health Organization Quality of Life (WHOQOL) questionnaire,¹² Personal and Social Performance scale (PSP),¹³ Clinical Global Impression of Severity (CGI-S) and Drug-induced Extrapyramidal Symptom Scale (DIEPSS).¹⁴ The medical records to determine the number of mood episodes and hospitalizations before and after the administration of LAI antipsychotics were reviewed. This study was approved by the IRB at the Taipei City Hospital in 2013 without the need of obtaining signatures from the patients (TCHIRB-1010810).

2.2. Statistical analysis

The descriptive study data were presented as means and standard deviation. The *t*-test was used to compare the differences between groups with continuous variables. The Statistical Package of Social Science software version 20 for Windows (SPSS, Inc., Chicago, IL, USA) was used to compute the study data. The differences between groups were considered significant if *p* values were less than 0.05.

3. Results

Table 1 shows the patients' demographic information and comparison of the results between FLAI and SLAI antipsychotics groups. No difference was found between the FLAI and SLAI antipsychotic drugs groups in terms of the efficacy, quality of life, and side effects (data not shown).

Extracting from Table 1, Table 2 compares the frequencies (times/year) before and after LAI antipsychotic treatment in both groups. The frequencies were significantly decreased in both FLAI

Table 1 Demographic data of patients who received FLAI and SLAI antipsychotics (mean ± SD)

	FLAI antipsychotic drugs (n = 27)	SLAI antipsychotic drugs (n = 14)
	Mean ± SD	Mean ± SD
Age (y)	45.8 ± 10.5	45.7 ± 9.4
Illness duration (y)	22.2 ± 9.3	19.1 ± 10.3
Duration of LAI treatment (y)	7.70 ± 8.2	1.61 ± 1.44
Frequency of mood episode (times/y) before LAI	0.72 ± 0.76	0.69 ± 0.39
Frequency of mood episode (times/y) after LAI	0.23 ± 0.47	0.24 ± 0.38
Frequencies of hospitalization (times/y) before LAI	0.6 ± 0.8	0.52 ± 0.41
Frequencies of hospitalization (times/y) after LAI	0.13 ± 0.28	0.08 ± 0.21
Number of concomitant use of mood stabilizer (%)	20 (74.1)	9 (64.3)
Number of concomitant use of antipsychotic (%)	17 (63.0)	7 (50.0)
CHQ	3.11 ± 1.93	3.86 ± 2.28
WHOQOL		
Overall score before psychiatric illness	76.1 ± 21.8	73.2 ± 23.4
Current overall score	69.7 ± 23.9	67.5 ± 18.8
Physical	14.0 ± 3.6	13.3 ± 2.5
Psychological	11.6 ± 2.9	11.3 ± 3.0
Social	12.96 ± 2.5	12.5 ± 1.9
Environment	13.1 ± 1.9	12.4 ± 2.7
PSP	73.9 ± 5.9	75.5 ± 5.9
CGI-S	3.0 ± 0.7	2.9 ± 0.9
DIEPSS	2.1 ± 2.3	1.4 ± 1.9

CGI-S = Clinical Global Impression of Severity; CHQ = Chinese Health questionnaire; DIEPSS = Drug-induced Extrapyramidal Symptom Scale; FLAI antipsychotics = first-generation long-acting injectable antipsychotics; PSP = Personal and Social Performance scale; SD = standard deviation; SLAI antipsychotic = second-generation long-acting injectable antipsychotic; WHOQOL = World Health Organization Quality of Life.

Table 2 Comparison of frequency (times/year) before and after LAI antipsychotic treatment in first-generation, second generation, and total antipsychotic groups

	Before the treatment	After the treatment
	Mean ± SD	Mean ± SD
FLAI antipsychotic treatment (n = 27)		
Frequency of mood episodes*	0.72 ± 0.76	0.23 ± 0.47
Frequency of hospitalizations*	0.60 ± 0.80	0.13 ± 0.28
SLAI antipsychotic treatment (n = 14)		
Frequency of mood episodes**	0.69 ± 0.39	0.24 ± 0.38
Frequency of hospitalizations*	0.52 ± 0.41	0.08 ± 0.21
Total patients (n = 41)		
Frequency of mood episodes***	0.71 ± 0.65	0.23 ± 0.43
Frequency of hospitalizations***	0.57 ± 0.69	0.11 ± 0.26

* Statistical significance between before and after LAI antipsychotic treatment groups is: *p* < 0.10.

** Statistical significance between before and after LAI antipsychotic treatment groups is: *p* < 0.05.

*** Statistical significance between before and after LAI antipsychotic treatment groups is: *p* < 0.001.

SD = standard deviation; SLAI = risperidone; FLAI = haloperidol, flupenthixol, clopenthixol, fluphenazine.

and SLAI antipsychotic treatment groups, and also in total LAI antipsychotic treatment patients, both regarding the frequency of mood episodes or hospitalizations.

Table 3 lists the mean dose of each LAI antipsychotic used every 4 weeks. Most of the patients still had concomitant use of mood stabilizers (70.7%) and oral antipsychotics (58.5%).

4. Discussion

Most patients with bipolar disorder received LAI antipsychotics are due to poor adherence to medications and have repeated mood episodes or hospitalizations during the course of their illness. More than 90% of bipolar patients relapse during an 18-month follow-up period following a manic episode,¹⁵ and around 70% of them relapse in the 18 months following a depressive episode.¹⁶ Even under prophylactic lithium therapy, the likelihood of at least one recurrence exceeded 70% within 5 years of recovery.¹⁷ In this study, both the frequency of mood episodes and that of hospitalizations were significantly decreased after receiving all kind of LAI antipsychotics treatment (Table 2). After dividing the data of frequencies into the FLAI and SLAI antipsychotic treatments, the differences of those separate groups were found to remain significant (Table 2). FLAI antipsychotics have been on the market in Taiwan for a much longer period of time than SLAI antipsychotics. At present, the only available SLAI antipsychotic is risperidone, which became available a decade ago, and its indication for bipolar disorder has been approved in Taiwan since 2011.

Table 3 Mean dose of each long-acting injectable antipsychotic drug used every 4 weeks

	Injection dose (mg)	
	Mean ± SD	Min–max dosage
Fluphenazine (n = 1)	100	100–100
Haloperidol (n = 10)	59.2 ± 23.7	25–100
Flupenthixol (n = 14)	23.3 ± 7.3	20–40
Clopenthixol (n = 2)	220	200–240
Risperidone* (n = 14)	48.2 ± 16.6	25–75

* The only second-generation LAI antipsychotic drug used in this study. min–max dosage = minimal to maximal dosage; SD = standard deviation.

In this study, the mean interval of FLAI antipsychotic treatment was 24.5 ± 5.6 days and of SLAI antipsychotic was 21.0 ± 5.4 days (data not shown). In this study, the duration of each injection of risperidone was longer than once every 2 weeks as recommended in the package insert of LAI risperidone. This might be because patients were also taking concomitant mood stabilizers (lithium, carbamazepine, or valproate) or oral antipsychotic drugs. As shown in Table 3, the mean doses of various FLAI antipsychotic drugs and LAI risperidone used for the bipolar disorder study patients were compatible with those used for schizophrenic patients.

In the context of self-reporting on general health, quality of life, and functioning, these study patients rated themselves in a fair to good condition. For the CHQ, the mean score was 3.4 ± 2.0 , with 21 patients (51.2%) scoring less than 3 (a cutoff-point of 3 and above might be a possible case with current difficulties). In four domains of the WHOQOL, the results were compatible with the healthy controls¹⁸ and better in the physical domain than those a group of pulmonary tuberculosis patients in Taiwan, in which the four domain scores were 12.7 ± 2.79 , 12.41 ± 3.05 , 13.28 ± 2.52 , and 12.71 ± 2.51 .¹⁸ As shown in Table 1, the PSP had a mean score of 73.9 ± 5.9 . This finding is also compatible with that in a report from Spain.¹⁹ In their measurement of a group a bipolar patients ($n = 57$), the mean score is 73.0 ± 14.6 ; while in a group of schizophrenic patients ($n = 139$) it is 61.9 ± 19.6 . The mean score of CGI-S of our study patients who received FLAI antipsychotics was 3.0 ± 0.7 , meaning that these patients were in the mildly ill range. The extrapyramidal side effect as measured by DIEPSS (Table 1) revealed illness to a very mild degree (1.9 ± 2.2), in SLAI antipsychotic group, indicating that the tolerance of LAI antipsychotics is good and patients did not suffer from these types of adverse effects. However, the extrapyramidal side effects were not significantly different between patients receiving FLAI and SLAI antipsychotic drugs (Table 1).

4.1. Limitations of the study

The readers are cautioned against over-interpreting the study findings because this study has three major limitations. First, the size of the study group was small ($n = 41$). The number may not reflect the observation for patients receiving LAI antipsychotic treatments. Second, this study was not randomized, placebo-controlled, and double-blind in design. Thus, the study validity was compromised. Third, the study was carried out only at one hospital. Therefore, the generalization of the study data to other patients in Taiwan is doubtful.

4.2. Summary of the study

Taken together, bipolar patients with LAI treatment can have fewer rates of relapse and hospitalization, and a good quality of life with fair functioning and very mild side effects. Recognizing the limitations of the study data, it can be summarized that LAI treatment could decrease the frequency of mood episode and hospitalization, as well as restore their normal lives in patients with bipolar disorder.

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