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Usefulness of long-acting injectable risperidone during 12-month maintenance therapy of bipolar disorder

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Abstract

This study aimed to assess the safety, tolerability, efficacy, and compliance of a risperidone long-acting injection (RLAI) formulation for the maintenance treatment of stabilized bipolar patients. A prospective, open-label trial of RLAI was conducted for 12 months. Stable bipolar patients ($n=11$) were switched from their existing oral antipsychotic agents to RLAI, and injections were given every 2 weeks. The assessments were performed at baseline and at 6 and 12 months of treatment by using the Young Mania Rating Scale (YMRS), Clinical Global Impressions—Severity of Illness (CGI-S) scale, 17-item Hamilton Rating Scale for Depression (HAM-D), Brief Psychiatric Rating Scale (BPRS), and Extrapyramidal Symptom Rating Scale (ESRS). The satisfaction levels of subjects were evaluated at the end of the study period using a 10-point visual analog scale. Ten patients (90.9%) completed the trial, and no significant changes were seen in the YMRS, HAM-D, and BPRS scores throughout the study. CGI-S and ESRS scores were significantly decreased from the baseline to the post-12-month treatment score. Relapses were not reported by any of the participants. This result indicates that RLAI may be beneficial in the maintenance therapy of stable bipolar patients; however, an adequately powered, randomized, placebo-controlled trial is necessary to draw a definite conclusion about the role of RLAI in the maintenance treatment of bipolar patients.

Keywords: Bipolar disorder; Long-acting injections; Maintenance; Risperidone

1. Introduction

Clinicians have been prescribing antipsychotics to relieve the patients' psychotic and behavioral symptoms during acute manic phase. And, some patients continue their antipsychotic medication even after discharge (Keck et al., 1996; Kusumakar, 2002; Sernyak et al., 1997, 1994; Verdoux et al., 1996). Recently, growing bodies of evidences have established that atypical antipsychotics (AAs) such as risperidone, olanzapine, quetiapine, and ziprasidone are efficacious in the treatment of mania. These AAs appear to have mood-stabilizing properties in bipolar disorder (BD) patients regardless of the presence of psychotic symptoms (Fleurence et al., 2006; Sachs et al., 2002; Yatham, 2005).

The emerging evidences for the efficacy and safety of AAs are mainly centered around the acute treatment of BD, while data on maintenance therapy are scarce with the exception of olanzapine and aripiprazole. Olanzapine has received U.S. Food and Drug Administration (FDA) approval as a monotherapy for the maintenance phase of BD (Fountoulakis et al., 2004; Yatham, 2005). Aripiprazole has also been approved as a maintenance drug of BD at 2005 (Chou, 2007; Keck et al., 2003, 2006 Vieta et al., 2005).

Abbreviations: AAs, Atypical antipsychotics; BD, Bipolar disorder; BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impressions—Severity of Illness; ESRS, Extrapyramidal Symptom Rating Scale; HAM-D, Hamilton Rating Scale for Depression; RCT, Randomized, controlled trial; RLAI, risperidone long-acting injection; YMRS, Young Mania Rating Scale; VAS, Visual analog scale.

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Among the currently available AAs, risperidone has been approved for bipolar I disorder and acute manic or mixed episodes associated with bipolar mania in 2003 by the FDA. A number of RCTs have established the efficacy and safety of risperidone as a monotherapy or adjunct therapy in combination with mood-stabilizers (Pavuluri et al., 2006; Perlis et al., 2006; Rendell and Geddes, 2006; Schreiner, 2006; Smulevich et al., 2005). Risperidone was founded to effective and tolerable in a 6-month maintenance treatment for bipolar manic patients as well in a multicenter, open-label trial (Vieta et al., 2004), while placebo-controlled trials for maintenance treatment have been lacked.

Meanwhile, the compliance of BD patients with their medications is unsatisfactory and is linked to poor clinical outcomes and other mental health-related problems (Bonin, 1999; Colom et al., 2003; El-Mallakh, 2007; Keck et al., 1997; Weiss et al., 1998). Data from the VA National Psychosis Registry (n=73,964) showed that only approximately 52% of patients appeared to be fully compliant to antipsychotic medications, indicating a need for better pharmacological options for the treatment of BD (Sajatovic et al., 2005).

Depot antipsychotics may be useful in the maintenance treatment of bipolar disorder. However, only a few case series with flupenthixol, haloperidol, and fluphenazine supported the usefulness not by well-designed, placebo-controlled, clinical trials yet (El-Mallakh, 2007; Esparon et al., 1986; Gelenberg and Hopkins, 1996; Littlejohn et al., 1994; Naylor and Scott, 1980). The complaints of injection pain and the possible long-term side effects of the 1st generation antipsychotics have been reported to be problematic.

In this context, risperidone now comes in various forms including the risperidone long-acting injection (RLAI) formulation, which is frequently used in chronically psychotic patients who are in stable condition (Lee et al., 2006). In addition, most clinical trials favored depot formulations over oral preparations on relapse rates (Davis et al., 1994; Hogarty et al., 1979). Moreover, RLAI was found to be more beneficial in terms of injection pain and patients' satisfaction comparing with 1st generation depot antipsychotics (Han et al., 2005; Lindenmayer et al., 2005).

To our knowledge, only one retrospective study related to the treatment of BD with RLAI has been reported (Savas et al., 2006). The purpose of the present 12-month study was to assess the safety, tolerability, efficacy in preventing relapse, and the compliance of RLAI monotherapy in stabilized bipolar patients, beyond the acute treatment.

2. Methods

2.1. Study design

This was an open-label trial conducted in two university-based teaching hospitals for 12 months. The trial strictly followed the guidelines of the International Conference on Harmonization for Good Clinical Practice, as contained in the Declaration of Helsinki. In addition, the study protocol was approved by the Institutional Review Board. After hearing the objectives and methodology of this study, all subjects provided written informed consent before enrollment in the study.

2.2. Subjects

The subjects considered for the study were aged 18 years or older and had bipolar I disorder with a manic or mixed episode according to the DSM-IV-TR. Patients who were under maintenance treatment with oral atypical antipsychotics only and met the criteria for enrollment, defined as a YMRS score of 12 or lower maintained for at least 4 continuous weeks, were eligible to enroll in the study. They were regarded as being in stable remission states under maintenance therapy using only oral atypical antipsychotics with no other mood-stabilizing Drugs (6 received risperidone, 3 received olanzapine, and 1 received amisulpride). Patients were excluded from the trial if they were treated with clozapine within 3 months or if they had significant physical problems, tardive dyskinesia, or a history of neuroleptic malignant syndrome. Patients treated with a conventional depot antipsychotic within one treatment cycle of screening were also ineligible. Patients were excluded if they had a history of severe drug sensitivity or allergy, including sensitivity to risperidone, or had a history of being unresponsive to risperidone. Pregnant or breast-feeding patients were also ineligible, and all other female subjects of childbearing potential were required to use adequate contraception and to have a negative urine pregnancy test at the screening visit. Clinical visits were scheduled bi-weekly (or as necessary to ensure appropriate patient care) during the study phase.

2.3. Study medication

RLAI was administered into a gluteal muscle every 2 weeks for 12 months. The flexible dosing schedule of 25 to 37.5 mg was used according to the clinical status of each patient. Patients were switched from their previous oral antipsychotic agents to RLAI without an oral risperidone run-in. Patients who were treated previously with an oral antipsychotic drug continued to receive that agent at the same dose for 21 days after the first injection of RLAI, after which it was stopped or tapered off over 7 days.

2.4. Assessments

Clinical interviews were conducted by psychiatrists for all participants every 2 weeks during the study period to spot early signs of relapse. Assessments were performed a total of 3 times, at baseline and after 6 and 12 months of treatment with RLAI, using the following tools.

The primary efficacy measure was the change from open-label baseline to endpoint in mean Young Mania Rating Scale (YMRS) total scores (Young et al., 1978). Other measures of efficacy included the Clinical Global Impressions—Severity of Illness scale (CGI-S) (Guy, 1976), 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), and Brief Psychiatric Rating Scale (BPRS) (Andersen et al., 1989). Each scale was measured at baseline, 6 months, and 12 months.

The Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese, 2005) was administered at baseline and all subsequent time points for evaluating the severity of extrapyramidal symptoms (EPS).

Table 1
Characteristics of the bipolar patients in this study

	Sex	Age	Dosage (mg)	Oral medication before injection	Duration of illness (months)	Reasons for medication change into risperidone, long-acting injectable
1	F	42	25	Risperidone 1 mg	112	Weight gain
2	F	36	25	Risperidone 1 mg	51	Weight gain
3	M	26	25	Amisulpride 100 mg	39	Chronic depressive symptoms
4	F	31	25	Risperidone 1 mg	183	Chronic depressive symptoms
5	F	43	37.5	Olanzapine 10 mg	48	Weight gain
6	F	48	25	Risperidone 1 mg	63	Having difficulty in concentration
7	F	31	25	Amisulpride 100 mg	132	Weight gain
8	M	27	25	Risperidone 1 mg	102	Non-compliance
9	F	39	25	Risperidone 1 mg	65	Chronic depressive symptoms
10	F	22	25	Amisulpride 100 mg	48	Non-compliance

Patients and their caregivers were asked to indicate their satisfaction level on a 10-point visual analog scale (VAS; 1–10, where 1 is the lowest level, and 10 is the highest) (Han et al., 2005).

2.5. Statistical analysis

The Friedman test with two-tailed probability was employed for non-normally distributed variables (YMRS, CGI-S, HAM-D, BPRS, ESRS, and body weight). If the Friedman test revealed significant changes, *post hoc* analyses by Wilcoxon signed-ranks tests with Bonferroni correction were performed, comparing baseline values to post-treatment values ($p<0.05$ was considered statistically significant). All data analyses were performed using SPSS version 10.0.

3. Results

3.1. Patient demographics and baseline medications

A total of 11 outpatients (3 men, 8 women) were enrolled in this study. One patient was excluded in the second week because of his inability to attend the regular 2-week interval visits due to his work. The remaining 10 patients fulfilled the clinical trial. The average age was 34.50±8.45 years and ranged from 22 to 48. The average duration of illness was 84.30±46.81 months. The oral medications that were taken before enrollment were as follows: risperidone ($n=6$), olanzapine ($n=3$), and amisulpride ($n=1$). Details of the 10 patients included in the trial are given in Table 1. Mean body weight was 62.14±12.12 kg at enrollment and 61.31±12.30 kg post-12-month treatment. There was no significant change (Friedman; $p>0.05$).

3.2. Efficacy — relapse prevention

YMRS scores increased from a baseline score of 2.40±3.10 to a post-12-month treatment score of 3.30±3.30, but this was not statistically or clinically significant (Friedman; $p>0.1$). CGI-S scores significantly decreased from a baseline score of 3.10±0.57 to a post-12-month treatment score of 1.70±0.48 (Friedman; $p<0.01$). *Post hoc* analysis with the Bonferroni

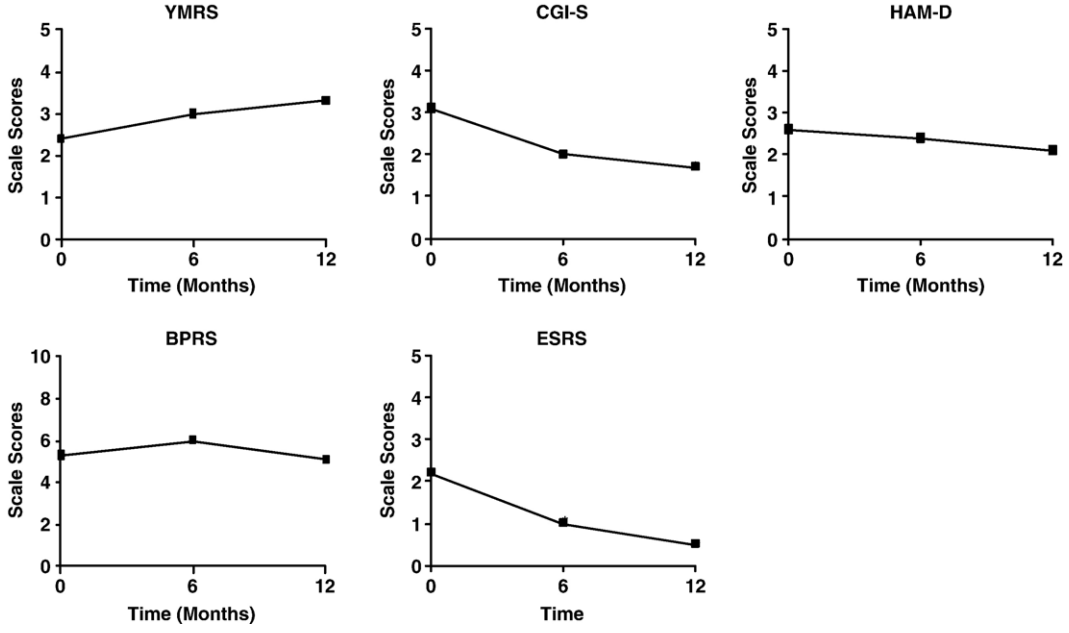

Fig. 1. Changes of each scale score during 12-month treatment in 10 patients. Values are means±standard deviation; *Significantly different from baseline, $p<0.05$ (Friedman test followed by *post hoc* analysis with Bonferroni correction for multiple comparisons). YMRS=Young Mania Rating Scale, CGI-S=Clinical Global Impressions-Severity of Illness scale, HAM-D=Hamilton Rating Scale for Depression, BPRS=Brief Psychiatric Rating Scale, and ESRS=Extrapyramidal Symptom Rating Scale.

correction reached statistical significance after the 12-month treatment (Wilcoxon signed-ranks test with Bonferroni correction; $p<0.01$). HAM-D scores decreased from a baseline score of 2.60±2.72 to a post-12-month treatment score of 2.10±1.85, but without significance (Friedman; $p>0.1$). BPRS scores increased from a baseline score of 5.30±3.74 to a post-12-month treatment score of 5.10±5.02, but without significance (Friedman; $p>0.1$; Fig. 1).

3.3. Safety

ESRS scores decreased from a baseline score of 2.20±1.14 to a post-12-month treatment score of 0.50±0.53 (Friedman; $p<0.05$). *Post hoc* analysis with Bonferroni correction reached statistical significance post-6-month treatment (Wilcoxon signed-ranks tests with Bonferroni correction; $p<0.05$). No subject reported any serious adverse events during the study period.

3.4. Subject satisfaction with Drugs

Patients reported high levels of satisfaction in the self-reported assessment questionnaire. According to the VAS, the satisfaction levels of the patients were 8.40±1.43 and the levels of the caregivers were 8.65±1.06 in the final assessment.

4. Discussion

In this study, maintenance of a euthymic mood state was demonstrated by the YMRS scores as primary efficacy measures. The YMRS scores during the 12 months of treatment were maintained at less than 12 points, and these low YMRS scores could be regarded to indicate remission states. Similar patterns were observed in other secondary efficacy measures (HAM-D, BPRS). In addition, the CGI-S showed a significant decrease from the baseline. None of the subjects reported any signs of relapse.

A few explanations are possible for the relapse prevention effects of RLAI observed in this study. RLAI showed advantages in achieving compliance. Non-compliance is often encountered in patients with bipolar disorder (Colom et al., 2000). Medication adherence is associated with longer survival times in bipolar disorder (Altman et al., 2006). As a method for achieving compliance, the use of the injectable form is very useful. First, if a patient becomes noncompliant, the clinician knows immediately because an injection has been missed. One can then initiate efforts to deal effectively with the problem. In addition, if a patient relapses, an accurate evaluation can be made as to whether the patient was taking medication prior to relapse (Kane, 2003). Second, relatively small doses of RLAI were used, and this simple regimen may be easier to follow. The doses were maintained at 25 mg except in one person. A negative and significant correlation with respect to prescribed daily dose and adherence intensity was observed for risperidone in another study (Gianfrancesco et al., 2006). As a result, we can assume that using small doses of RLAI would be a positive aspect for long-term successful management of bipolar I disorder. Finally, treatment with RLAI was generally well tolerated. There were no participants who discontinued the RLAI injection due to adverse effects. This was also evident in the significant decrease of ESRS scores from the baseline. In the *post hoc* analysis, this decrease was already shown from the post-6-month treatment. This finding is in line with another longer maintenance study that used RLAI in other indications (Mohl et al., 2005).

There was no significant body weight change in this study during RLAI treatment, although 4 participants switched to RLAI due to weight gain. Mohl et al. (2005) reported a small but significant body weight shift in their study using RLAI for other psychiatric disorders. Because the diagnosis and characteristics of the patients are different, there could be a limitation in direct comparison with our results.

Nevertheless it would be prudent that clinician should meticulously consider RLAI for patients who are likely to outweigh the medication adverse events such as tardive dyskinesia (Gentile, 2007). In addition we might suggest that stable bipolar patients on small maintenance dose of antipsychotics and without risk factors to extrapyramidal side effects should be relevant for this formulation.

The present study should be considered as an exploratory trial because of open-label design, lack of randomization, control and/or comparator group, small sample size, and limited follow-up visits. We tried to evaluate the effectiveness and tolerability of RLAI for bipolar patients in a naturalistic setting similar to a real clinical practice setting. Hence aforementioned limitations do not warrant our results to be translated into real clinical practice. Besides, although YMRS<12 has been frequently used in other studies, conservative definition of remission (*e.g.*, YMRS<5 or 8) should have be more useful to evaluate the effectiveness of the drug on relapse prevention. Clearly adequately powered randomized, placebo-controlled study will be mandatory.

Despite methodological limitations, our results show that RLAI may be a useful treatment option for the long-term maintenance of already stabilized bipolar patients.

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