Six-Month Open-Label Follow-Up of Risperidone Long-Acting Injection Use in Pediatric Bipolar Disorder

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ABSTRACT

Background: Recent studies suggest that risperidone long-acting injection (RLAI) may be considered for controlling mood episodes in bipolar disorder patients who have relapsed due to medication nonadherence or failure to respond to standard therapies. Currently, no study has reported the usefulness of RLAI in youths with bipolar disorder. The aim of this study was to evaluate short-term effects of RLAI in the naturalistic treatment of early-onset bipolar disorder and its role in symptomatic remission and adherence to treatment.

Method: Nineteen early-onset bipolar disorder outpatients receiving RLAI were observed in a 6-month naturalistic study at the outpatient clinic of the Child and Adolescent Affective Disorders Program at the Institute of Psychiatry of the University of São Paulo, São Paulo, Brazil. All patients met *DSM-IV* criteria for bipolar disorder. Clinical response to RLAI was evaluated using the Children's Global Assessment Scale (CGAS) and Clinical Global Impressions scale (CGI) across 3 time periods: index time (T_0), 8 weeks after (T_1), and 24 weeks after (T_2). These subjects were recruited from May 2008 to December 2009.

Results: Patients receiving RLAI presented considerable improvement in global functioning (CGAS: $T_0 = 20.6$; $T_1 = 42.9$; and $T_2 = 49.2$) and clinical severity (CGI: $T_0 = 5.9$; $T_1 = 3.9$; and $T_2 = 3.4$). Global CGI mean scores of clinical improvement were 2.2 at T_1 and 2.4 at T_2. There were no significant changes in laboratory measurements and weight throughout follow-up.

Conclusions: RLAI was shown to be an alternative treatment for youths with bipolar disorder failing to respond to prior medication trials or with adherence problems. Further blind, randomized controlled studies are necessary to confirm these initial findings.

Trial registration: Sistema Nacional de Informações Sobre Ética em Pesquisa Envolvendo Seres Humanos-Commisão Nacional de Ética em Pesquisa identifier: CAAE 0709.0.015.000-06

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Recent studies have demonstrated that long-acting formulations of second-generation antipsychotics may be considered for controlling mood episodes in adults with bipolar disorder who have relapsed due to medication nonadherence or failed to respond to standard therapies.[1,2] Researchers suggest that the depot formulation offers the advantages of the atypical antipsychotics as well as stabilization of serum drug level.[3]

Psychiatric misdiagnosis, changeable atypical picture, and adverse pharmacologic response are common situations that render pediatric bipolar disorder more cumbersome to manage. One of the major challenges for practitioners is tracking repeated medication nonadherence of children and adolescents with bipolar disorder; such nonadherence can impede the treatment response and lead to an unsatisfactory outcome.[4]

Risperidone long-acting injection (RLAI) is the first long-acting atypical antipsychotic agent to become available as a treatment option. Its safety and maintenance effectiveness have been demonstrated through clinical trials in adults with stable bipolar disorder,[5,6] and Fu-I and colleagues[7] reported 3 cases of youths with bipolar disorder who had adherence problems that benefited from the use of RLAI. Although the US Food Drug and Administration has approved oral risperidone for use in pediatric bipolar disorder patients,[8] few studies have reported the usefulness of RLAI in youths with bipolar disorder.

The present study aims to describe the effects of RLAI as a short-term treatment agent in patients with severe bipolar disorder symptomatology and nonadherence to prescribed oral medications. The tolerability, side effects, and 6-month mood-stabilization effects of RLAI are also reported.

METHOD

The target population was drawn from an extensive pediatric phenomenology study funded by the São Paulo Research Support Foundation, São Paulo, Brazil. The trial was registered at Sistema Nacional de Informações Sobre Ética em Pesquisa Envolvendo Seres Humanos-Commisão Nacional de Ética em Pesquisa (identifier: CAAE 0709.0.015.000-06). Institutional review boards at the respective institutions approved the data collection as part of a clinical research registry.

The subjects of the present study were children and adolescents with bipolar disorder meeting criteria for nonadherence or therapeutic failure in the Children and Adolescents Affective Disorder Program's outpatient clinic at the Institute of Psychiatry of the University of São Paulo, São Paulo, Brazil. These subjects were recruited from May 2008 to December 2009.

Subjects' current bipolar disorder diagnoses were ascertained by 2 child and adolescent psychiatrists (M.A.B. and A.P.F-M.) in face-to-face clinical interviews and 2 structured interviews: the Child Behavior Check List and the Diagnostic Interview for Children and Adolescents[10] were applied. In addition, all psychiatric comorbidities were assessed,

Clinical Points

- Treatments for childhood- and adolescence-onset bipolar disorder include depot formulations of second-generation antipsychotics.
- The best evidence currently available suggests that risperidone long-acting injection is efficient, well-tolerated, and safe in youths with bipolar disorder.
- Clinicians can help bipolar patients who have relapsed due to medication nonadherence or failed to respond to standard therapies.

and clinical records were routinely reviewed. The final best-estimate diagnosis was reached after a consensus panel meeting between research staff and the senior psychiatrist (L.F.-I.).

The Children's Global Assessment Scale (CGAS)[11,12] and Clinical Global Impressions,[13] both Severity of Illness (CGI-S) and Improvement (CGI-I) scales, were periodically used as guidance to assess global functioning, clinical improvement, and treatment response (eg, change of doses, combination with other medications, or need for suspending RLAI).

Weight gain, extrapyramidal symptoms, and adverse events were closely monitored in each clinical visit, and the Systematic Assessment for Treatment Emergent Effects scale[14] was applied to document the presence and the intensity of side effects of RLAI.

The final sample was composed of children and adolescents who (1) fulfilled *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, criteria for bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified (NOS); (2) were currently presenting severe pediatric bipolar disorder symptomatology (CGI-S > 5) with severe functional impairment (CGAS < 31); and (3) had previously used an oral formulation of risperidone with good tolerability and nonadherence to prescribed oral medications. In this study, nonadherence was defined as the failure to follow the recommended time schedules (eg, missing doses, not taking medication according to the recommended time schedule, and lack of adequate supervision by caregivers).

The exclusion criteria were (1) comorbidity with pervasive developmental disorders, schizophrenia, or mental retardation (IQ < 70); (2) reported past hypersensitivity, intolerance, or clinical worsening with the use of risperidone oral formulation; (3) previous history of severe extrapyramidal symptoms or neuroleptic malignant syndrome; (4) reported past intolerance to intramuscular injection; and (5) current use of depot antipsychotics.

Laboratory workup (blood count and kidney and liver functions, thyroid hormones, blood glucose, lipids, and prolactin), electroencephalogram, and electrocardiogram were routinely performed before starting medication or at baseline. Periodic biochemical tests were repeated each 3 months for monitoring metabolic and hormonal profiles. Patients were evaluated initially every 2 weeks. From the second month of treatment on, the evaluation was performed every 1 or 2 months, depending on the stabilization of the patients' clinical picture. A consultation could be arranged at any time in cases of clinical worsening or side effects of medication.

A subject was considered a dropout when the patient failed to receive 2 consecutive injections of RLAI. Good acceptability of treatment was considered if the patient or family did not hinder the use of RLAI. However, if any resistance to the medication was detected, our RLAI application–trained nurse provided specific orientation about treatment benefits (eg, clinical improvement and not taking medication every day). No refusal occurred after this approach was initiated.

All participants and responsible persons were extensively informed about the proposed treatment and possible side effects and adverse events of RLAI, as well as the similarity of the oral risperidone with depot preparation. Patients were specifically warned about the possibility of new adverse events emerging during the use of RLAI and encouraged to contact emergency medical services and to communicate side effects. The treatment started only after patients and their legal guardians signed informed consent forms. The institutional ethics board authorized the prescription of RLAI for these patients fulfilling conditions described above. The Institute of Psychiatry at the University of Sao Paulo supported the RLAI treatment of all cases.

During the observation period, 20 children and adolescents met the inclusion criteria at the index time. One boy could not complete the protocol due to his parent's inability to attend periodic evaluations. The final sample (N = 19) was composed of 16 boys and 3 girls, with a mean age of 12.1 years (standard deviation [SD] = 2.2). The mean age at onset of the first affective episode was 6.9 years (SD = 3.3), and the mean age at onset of the first manic episode was 8.0 years (SD = 3). Most of the subjects were diagnosed with bipolar I disorder (n = 17, 89.5%) and 2 (10.5%) patients with bipolar disorder NOS. Eighteen participants reported familial history of psychiatric disorders (94.7%).

In this sample, all subjects were severely impaired (initial mean CGAS = 20.6, SD = 9.7; and initial mean CGI-S = 5.9 SD = 1.0), and 6 patients (31.6%) had been previously hospitalized on psychiatric wards. Nine patients (47.4%) presented 1 or more psychiatric comorbidities, and 4 (21.1%) had attention-deficit/hyperactive disorder (ADHD), 2 (10.5%) had Tourette syndrome, 2 (10.5%) were diagnosed with conduct disorder, and 1 had enuresis (5.3%).

All patients had previously tried psychopharmacologic treatments and had used a mean of 8.6 (SD = 4.2) different types of medications throughout their treatments. Among the final sample, 11 patients (57.9%) were included in this study for adherence problems, and the most common reasons for nonadherence were inadequate supervision by caregivers (eg, low parental support and failure of the family in monitoring medical treatment) and difficulties inherent to bipolar disorder (eg, patient's refusal to take medication). Eight patients (42.1%) were included because they failed to respond to other therapeutic regimens.

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Table1. Laboratory and Clinical Workup and Outcome in Pediatric Bipolar Patients Taking Risperidone Long-Acting Injection in 3 Time Periods (T_0, T_1, T_2)

Variable, mean (SD)	T_0 n = 19 (0 Months)	T_1 n = 19 (2 Months)	T_2 n = 14 (6 Months)
Dose, mg	25 (0)	37.5 (13.0)	46.3 (16.5)
Outcome			
CGAS	20.6 (9.7)	42.9 (12.8)*	49.2 (14.4)**
CGI-Severity of illness	5.9 (1.0)	3.9 (1.5)*	3.4 (1.6)
CGI-Improvement	NA	2.2 (1.3)	2.4 (1.3)
Weight, kg	54.6 (18.5)	55.7 (17.9)	60.3 (22.4)
Laboratory examination			
Blood glucose, mg/dL	89.4 (7.0)	88.5 (6.8)	89.4 (6.2)
Triglycerides, mg/dL	119.4 (140.9)[a]	98.6 (114.3)	98.8 (76.8)
Cholesterol, mg/dL	150.5 (33.6)	147.3 (36.0)	136.9 (46.0)
HDL, mg/dL	52.3 (14.7)	52.1 (15.0)	56.7 (26.0)
LDL, mg/dL	78.8 (26.5)	77.8 (30.0)	78.4 (29.0)
Prolactin, ng/dL	17.7 (16.2)	26.8 (17.3)	24.2 (13.3)

[a]There were 2 outlier patients with high triglyceride levels (472 mg/dL and 545 mg/dL) at T_0.
*$P < .0001$ from T_0 to T_1.
**$P < .0001$ from T_1 to T_2.
Abbreviations: CGAS = Children's Global Assessment Scale, CGI = Clinical Global Impressions, HDL = high-density lipoproteins, LDL = low-density lipoproteins, NA = not applicable.

Table 2. Acceptability and Side Effects in Children and Adolescents With Bipolar Disorder Taking Risperidone Long-Acting Injection

Variable	n	%
Acceptability[a]	12	63.2
Dropout[b]	5	26.3
Simultaneous medication	6	31.6
Side effect	13	68.4
Increased appetite	6	31.6
Weight gain	7	36.8
Decreased appetite	2	10.5
Sleepiness	2	10.5
Mild tremors	2	10.5
Oculogyric crisis	1	5.3
Drooling	1	5.3
Increased prolactin	11	57.9
Galactorrhea	1	5.3
Dizziness	3	15.8
Nausea	2	10.5

[a]Acceptability was considered good when the patient or family did not hinder the use of medication of injectable formulation.
[b]A patient who failed to receive the risperidone long-acting injection for more than 1 month (2 consecutive injections).

Only 3 patients (15.8%) simultaneously took another medication while taking RLAI. One patient used carbamazepine as a mood stabilizer and chlorpromazine for adjunctive anxiety control, 1 took chlorpromazine as an adjunctive to address sleep complaints, and 1 took divalproex as a mood stabilizer and methylphenidate for ADHD when starting RLAI. The subjects continued using these drugs after initiation of RLAI. No other drugs were associated with controlling mood symptoms or adverse effects during the period of observation for any other patients.

Data Analysis

Three time periods were considered for the data analysis.

- Time 0 (T_0) or baseline was the occasion of the first RLAI injection. On this occasion, most patients were still using oral risperidone and/or other medications. At T_0, patients were evaluated and laboratory tests were performed.
- Time 1 (T_1) or the short-term treatment endpoint, ie, 2 months after the beginning of treatment. At this point, patients who had significant global functioning improvement (CGAS > 31) or clinical severity improvement (CGI-S < 3) and preferred to return to the oral formulation treatment could leave the protocol. The patients who did not improve significantly could also change their therapeutic regimen.
- Time 2 (T_2) or the long-term treatment endpoint, ie, 6 months after beginning treatment, was the point to observe the maintenance of improvement and tolerability of RLAI for a long-term period.

The initial dose of RLAI was 25 mg (1 ampoule) every 15 days. The patients continued to take the oral dose for 3 weeks after beginning the RLAI. At T_1, the mean dose administered was 37.5 mg and at T_2 the mean dose administered was 46.3 mg per injection (Table 1).

Statistical Methods

Descriptive analyses of means, SDs, frequencies, and percentages were derived from data. Paired-sample *t* test within-subject measure of time (T_0, T_1, and T_2) was used to examine response status, main effects, and interactions between factors. Associations were examined between several demographic and clinical factors in the 3 different periods using Fisher exact tests. Analysis was performed using SPSS for Windows, version 17.0 (IBM, Armonk, New York).[15]

RESULTS

Short-Term Treatment

All 19 patients completed the short-term treatment (T_0 to T_1). During this period, global functioning and symptom severity improvement were shown by the significant changes in CGAS (20.6 vs 42.9, $P < .0001$) and CGI-S scores (5.9 vs 3.9, $P < .0001$). The mean CGI-I score was 2.2 at this endpoint (Table 1).

After completing the short-term treatment, 5 patients left the protocol. Three patients left the study after deciding to return to the oral formulation, 1 moved away and was referred to another treatment center, and 1 patient stopped RLAI due to the lack of significant improvement. No one demonstrated worsening of clinical symptoms (Table 2).

Long-Term Treatment Endpoint

Fourteen patients completed the long-term treatment, from T_1 to T_2 or 6 months after T_0. The trend of sustained improvement is reflected in the change in the CGAS mean

score from T_1 to T_2 (42.9 vs 49.2, $P < .0001$). The steady improvement from T_1 to T_2 was shown in similar mean scores of the CGI-S (3.9 vs 3.4, $P = .21$) and CGI-I (2.2 vs 2.4, $P = .834$) (Table 1).

Tolerability and Side Effects

The mean weight gain was 1.1 kg (SD = 0.6) at T_1 and 5.7 kg (SD = 4.1) at T_2. Since most patients had been taking oral antipsychotic medications before starting RLAI, the mean level of prolactin was high at T_0 (see Table 1). However, there was no significant change in the measurement of prolactin throughout the treatment with RLAI. Also, no significant change in lipids (cholesterol and triglycerides) and blood glucose was recorded during the treatment period (Table 1).

During the treatment period (T_0 to T_2), 13 patients (68.4%) presented some other laboratory measurements and symptoms attributable as direct side effects of RLAI. The most significant were high prolactin levels (11 or 57.9%), weight gain (7 or 36.8%), and increased appetite (6 or 31.6%).

Two patients reported mild transient tremors in the T_0 to T_1 periods, and 1 reported a single transient episode of an oculogyric crisis in the T_1 to T_2 period. None presented neuroleptic malignant syndrome, severe extrapyramidal symptoms, or hypersensitivity to RLAI (Table 2).

Some children and adolescents who initially resisted the injectable formulation changed their minds after being provided psychoeducation and guidelines.

DISCUSSION

In this study, we describe the safety and efficacy of RLAI in pediatric bipolar disorder, evaluating its effectiveness in real-world practice. The findings for this 6-month naturalistic follow-up indicate that RLAI in children and adolescents is generally well tolerated and efficacious and that RLAI enhanced adherence of pediatric bipolar disorder patients who had previously used multiple drug treatments with no significant improvement and poor adherence.

Several studies have pointed out the safety and efficacy of risperidone oral formulation for pediatric bipolar disorder,[16,17] and recent trials in adults with bipolar disorder suggested that RLAI is a good treatment option.[6] However, as RLAI is a medication whose vehicle (intramuscular depot) has unprecedented use in children and adolescents, evaluating its safety and efficacy in real-life conditions is essential for obtaining useful results in routine clinical situations.[18]

The severe and dysfunctional conditions of patients at T_0 positively changed at the first endpoint (T_1) of response analysis, and clinical severity, measured by the CGI-S score, passed from the state of *severely ill* at T_0 to *moderately ill* at T_1 (see Table 1). These results are consistent with those found in similar studies of adults with bipolar disorder treated with RLAI[2,19–21] and encourage the use of a depot regimen as a possible treatment option for severely impaired pediatric bipolar disorder patients with poor adherence to oral medication.

The nature of mood instability and the prolonged course of the disease in young bipolar disorder patients may make adherence to any treatment difficult.[4] In this sample, the positive evolution observed at T_1 was maintained at T_2 (see Table 1), indicating that the improvement in overall functioning of these children and adolescents observed in the short-term also remained in the long-term treatment. These findings are consistent with a report of pediatric bipolar disorder patients who benefited from long-term use of RLAI with satisfactory clinical response and tolerability over time.[7]

Regarding safety and tolerability, the results of this naturalistic observation suggest that RLAI may be well tolerated for both short- and long-term use, with low metabolic changes (eg, glucose and lipid profile), and patients with previous use of oral formulation risperidone reported no difference in side effects with RLAI. In our sample, the most important side effects were increased appetite, weight gain, and high plasma levels of prolactin (see Table 1), which are typical concerns when using atypical antipsychotics.

In this study, the weight gain with RLAI was similar to that found in trials with risperidone oral formulation in youths with bipolar disorder.[22] This result is also consistent with results found in recent studies with RLAI in adolescents and young adults with schizophrenia and schizoaffective disorder.[23,24] The increase of prolactin level was also similar to that found in trials with risperidone oral formulation.[25] Galactorrhea was not observed in short-term (2 months) treatment, and only 1 female adolescent presented this side effect at endpoint T_2.

Taking into account the profile of the population (children and adolescents) who generally fear injectable medications, the relatively low dose that was applied allowed for a good acceptability of the vehicle of administration (intramuscular), indicating that intramuscular injection formulation may not be a problem for continued use.

Different factors may lead to noncompliance with treatment, and previous studies have shown that the incidence of nonadherence in adults and young patients with bipolar disorder is highly significant, increasing the incidence of hospitalizations, cycling, and financial costs.[4,26,27] For youths with bipolar disorder, there are several types of nonadherence to a prescribed treatment in a clinical setting. In this sample, the main component of nonadherence was that the family failed to supervise the treatment, possibly due to chaotic family conditions (ie, relatives with psychiatric illness). Taken together, inadequate family functioning, in addition to the characteristics of the disorder itself, may exert negative influence on pediatric bipolar disorder patients' treatment adherence[27,28]; therefore, the alliance between the care provider and the young bipolar disorder patient should be continuously monitored even though a new resource is available.

There are several limitations to our study, and the results should be read with caution and not hastily extrapolated to larger populations. First, our study was limited by the small sample of children with specific characteristics (eg, nonadherence, severely impaired). Secondly, as this was a naturalistic observational study, as opposed to a controlled study, it had a small sample and broad inclusion criteria.

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However, these limitations and the lack of a blind control group or wash-out of previous medication before RLAI application were due to the severity of cases and reflect the real-world practice that was the focus of this follow-up observational study.

Since this clinical subject sample was recruited in a university-based teaching hospital, the selected patients might be more clinically impaired than the general population, but, otherwise, this selection bias might ensure the homogeneity of the sample. Nevertheless, the present study indicates the need for further randomized controlled studies in order to better quantify and qualify the results obtained here.

CONCLUSION

In summary, this study demonstrated that RLAI may be an efficacious and relatively well-tolerated alternative for the treatment of pediatric bipolar disorder. This long-acting antipsychotic could help clinicians to manage the compliance status of patients, preventing the occurrence of more severe complications (eg, suicide attempts or hospitalizations) and dramatically reversing the therapeutic failure of patients who did not follow the recommended oral medication treatment.

Drug names: carbamazepine (Carbatrol, Equetro, and others), divalproex (Depakote and others), methylphenidate (Focalin, Daytrana, and others), risperidone (Risperdal and others).

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