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ORIGINAL RESEARCH ARTICLE

Effectiveness, Adverse Effects and Drug Compliance of Long-Acting Injectable Risperidone in Children and Adolescents

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Abstract

Background and Objectives Although the use of oral risperidone in children and adolescents has been well studied, there is little information on the intramuscular use of long-acting injectable risperidone (LAIR). The aims of this study were to investigate the effectiveness and adverse effects of LAIR in children and adolescents with conduct disorder, bipolar disorder, and schizophrenia.

Methods In total, 42 patients (age range 12–17 years) who were non-adherent to oral antipsychotic drugs, received 25 mg of LAIR intramuscularly every 2 weeks. The drug was administered at least four times and up to 66 times (median drug use: 9.50 times). The effectiveness and adverse effects of the treatment were examined.

Results There was an improvement in 13 (92.8%) of the 14 patients diagnosed with bipolar disorder, in 25 (78.1%) of 32 patients diagnosed with conduct disorder and in one (50%) of two patients diagnosed with schizophrenia. Six patients had comorbid conduct disorder and bipolar disorder. Totally, 81% of the patients improved with LAIR. Weight-gain, daytime somnolence, muscle stiffness and spasms, impaired concentration, and fatigue were the most common side effects through the whole sample. Menstrual problems were common in girls. In the study, 57.1% of the patients continued to receive their injections regularly until the end of the treatment, under physician control. A total of 16.7% discontinued the treatment due to non-adherence. The LAIR treatment was terminated in 26.2% of the patients, due to weight-gain, dystonia, and galactorrhea.

Conclusions In children and adolescents with conduct disorder, bipolar disorder and schizophrenia who show noncompliance with oral drugs, LAIR may improve treatment compliance. LAIR is a reliable treatment in terms of its effectiveness. Weight-gain, dystonia, and galactorrhea were the adverse effects that were responsible for LAIR treatment cessation.

Key Points

In children and adolescents who show noncompliance with oral drugs, LAIR may improve treatment compliance.

The LAIR treatment was effective in children and adolescents with conduct disorder with aggression and bipolar disorder.

Weight-gain, daytime somnolence, muscle stiffness and spasms, impaired concentration, fatigue, and menstrual problems in girls were the most common side effects. The LAIR treatment was terminated in 26.2% of patients, due to weight-gain, dystonia, and galactorrhea.

The text under the methods section was incorrectly published in the original publication. The correct value is now updated in the original article.

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1 Introduction

The clinical use of first-generation neuroleptic agents became widespread after the 1950s. Clozapine, the first atypical antipsychotic agent, was introduced in 1960. Although it was effective in the management of treatment-resistant schizophrenia, its initial promise diminished after a report documenting its association with fatal agranulocytosis in a case series in Europe [1]. Risperidone, another atypical antipsychotic, was introduced to the market in the USA [2]. Risperidone is a benzisoxazole derivative. Although it shares some pharmacological features with clozapine, it has not been associated with agranulocytosis.

Following the introduction of atypical antipsychotics, reports of acute adverse effects related to the extrapyramidal system and the anticholinergic system decreased [1]. Drug compliance and use increased due to the tolerability of atypical antipsychotics [3]. To further improve treatment regimens and reduce treatment noncompliance; long-acting injectable antipsychotics were introduced. Conventional long-acting depot antipsychotics, developed in the 1960s, and long-acting injectable risperidone (LAIR), a well-established oral atypical antipsychotic, became available in Europe from August 2002 [4]. The long-acting injectable formulation was launched in Turkey in April 2005.

To date, risperidone is the best studied antipsychotic agent in pediatric populations. Risperidone has been used to treat various symptoms and disorders in children and adolescents, including bipolar disorder [5, 6], serious behavioral problems in autism [7], severe disruptive and aggressive behavior, conduct disorder (CD) [8], and Tourette syndrome [9]. Although the use of oral risperidone in children and adolescents has been well studied [1], there is little information on the intramuscular use of LAIR [10–12]. One study of 19 pediatric bipolar disorder cases showed that it was effective in this population [12]. However, to the best of our knowledge, there have been no studies of the effectiveness and adverse effects of the injectable formulation in children and adolescents with CD, bipolar disorder, and schizophrenia.

The present study consisted of children and adolescents with CD, bipolar disorder, and schizophrenia who attended the Child and Adolescent Psychiatry Department of Yildirim Beyazit University Faculty of Medicine, the unique child and adolescent in-patient clinic in Ankara, Turkey, and were treated with LAIR because of noncompliance. The aims of this study were to investigate the effectiveness and adverse effects of LAIR in children and adolescents with CD, bipolar disorder, and schizophrenia.

2 Methods

2.1 Participants

Patients were recruited from those receiving treatment in the inpatient clinic of the Child and Adolescent Psychiatry Department of Ankara Yildirim Beyazit University Yenimahalle Education and Research Hospital between 01.01.2013 and 31.08.2016. The patients aged between 12–17 years, who had been selected for treatment with LAIR instead of oral antipsychotics, because of noncompliance to oral drugs, were included in the study and received minimally four LAIR injections. All the selected patients were monitored at monthly follow-up visits after discharge.

The study group consisted of hospitalized patients with serious clinical disorders and noncompliance with oral drugs. The dose of LAIR was 25 mg every 2 weeks. No other antipsychotic drugs were given during the study period because the sample consisted of orally noncompliant patients. The patients were evaluated during their hospitalization and then monthly at the outpatient clinic, after discharge. The patient and his/her parents were informed about LAIR and its potential side effects prior to starting the treatment, and informed consent was obtained from all parents. The study was approved by Ankara Yildirim Beyazit University Yenimahalle Education and Research Hospital Ethics Board.

The diagnoses were based on the Kiddie schedule for affective disorders and schizophrenia for school-age children (K-SADS-PL) [13], and cognitive functions were evaluated using the Wechsler Intelligence Scale for Children-Revised (WISC-R) (12–16 years) [14] and Wechsler Adult Intelligence Scale-Revised (WAIS-R) (used for 17-year-old patients) [15]. To determine the severity of the disorder, the Clinical Global Impression-severity (CGI-S) index was completed after the patient was hospitalized and at a 2-month follow-up. The Clinical Global Impression improvement (CGI-I) scale was also completed at the 2-month follow-up. The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) was used to identify side effects of LAIR treatment after the administration of the final dose. The body weight of each patient was recorded when the patient attended the center to receive treatment.

2.2 Data Collection Tools

2.2.1 K-SADS-PL

All the participants were screened for psychiatric disorders using the K-SADS-PL, which is based on DSM-IV criteria

[13]. The K-SADS-PL is a semi-structured interview scale, which is widely used to evaluate 20 different diagnostic domains. The Turkish version of the form was adapted and validated previously [16]. A physician administered this scale to all patients and their parents.

2.2.2 WISC-R

The WISC-R is applicable to children aged 6–16 years [14]. It consists of six verbal subtests (information, vocabulary, arithmetic, comprehension, similarities, and digit span) and six performance subtests (picture completion, block design, object assembly, picture arrangement, coding, and mazes), with supplementary subtests. In addition to these subtests, standard scores and verbal, performance, and total IQ score coefficients were obtained. The Turkish version of this form was validated earlier [17].

2.2.3 WAIS-R

The WAIS-R assesses three general areas of IQ (verbal IQ, performance IQ, and full-scale IQ) using six verbal subtests and five performance subtests: information, digit span, vocabulary, arithmetic, comprehension, similarities, picture completion, picture arrangement, block design, object assembly, and digit symbol [15]. In the present study, the WAIS-R was administered to adolescents aged 17 years.

2.2.4 CGI Index

The CGI index is a widely used three-item observer-rated scale in psychiatry that measures the severity of the illness (CGI-S), global improvement or change in symptoms (CGI-I), and therapeutic response (or efficacy) [18]. In the present study, only CGI-S and CGI-I items were used. The CGI-S is a 7-point scale. Based on responses to a range of questions, it grades the severity of the illness as (1) normal, not at all ill; (2) borderline mentally ill; (3) mildly ill; (4) moderately ill; (5) markedly ill; (6) severely ill; or (7) extremely ill.

The CGI-I index is a 7-point scale. On the scale, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = slightly worse, 6 = much worse, and 7 = very much worse [18]. Based on these CGI-I scores, the clinician assesses how much a patient's illness has improved or worsened relative to a baseline state. The CGI-I index was used to assess the improvement in the present study after 2 months of treatment. Each component of the CGI scale is rated separately. Thus, the instrument does not yield a global score.

2.2.5 LUNSERS

The LUNSERS instrument was developed to determine the adverse effects of antipsychotic drugs [19], and Yilmaz and Buzlu confirmed its reliability and validity in a Turkish population [20]. According to their reliability analysis, the Cronbach alpha reliability coefficient was 0.89. LUNSERS is a 5-point Likert-type self-administered scale, which is scored as follows: 0 = none, 1 = very low, 2 = low, 3 = fair, and 4 = very high). The scale assesses the intensity of a list of side effects experienced in the previous month. The scale includes side effects [extrapyramidal, anticholinergic, autonomic, general, psychological, allergic, hormonal (41 items)]. In calculating the total side effect scores, items that attract attention in another direction can be calculated separately or together. The total scores denote the severity of the various side effects. When analyzing the scores, 0 points and 1 point signify no side effects, and 2, 3, and 4 points signify the presence of side effect(s).

2.3 Statistical Analyses

The diagnostic distributions of the cases according to the K-SADS instrument and frequency of side effects listed according to the LUNSERS instrument are given as numbers (n) and percentages (%). The primary outcome measure was the change in the CGI-S scores. In this study, the CGI-S index was administered twice.

The relationship between the number of doses administered and the total score for antipsychotic side effects according to the LUNSERS instrument was examined using Spearman's correlation analysis. Statistical significance was defined as $p < 0.05$.

3 Results

3.1 Patients' Demographic and Clinical Characteristics

In the study, 42 patients were used minimally four LAIR injections. The age range of the patients was 12–17 years (average age 15.6 ± 1.5 years). Twenty-eight (66.7%) were female, and 14 (33.3%) were male. Among the patients, 76.5% (n = 32) were diagnosed with CD, 33.3% (n = 14) with bipolar affective disorder, and 4.8% (n = 2) with schizophrenia. There were 42 patients in our study. Six patients had comorbid CD and bipolar disorder. All patients who were diagnosed with CD exhibited aggressive behaviors, such as self-harming or harming people and property. Among the cases, 30 (71.4%) were diagnosed with two comorbid disorders, 6 (14.3%) with 3 comorbid disorders, and 6 (14.3%) with one disorder. The diagnoses

of the patients are given in Table 1. The drug was administered at least 4 times and up to 66 times (median drug use = 9.50 times) (Table 1).

3.2 Clinical Severity

In the first evaluation of the 42 patients,10 were classified as extremely ill (CGI = 7), 19 were classified as severely ill (CGI = 6), and 13 were classified markedly ill (CGI = 5). At the 2-month follow-up, when the CGI-S was re-administered, one patient was classified as severely ill (CGI = 6), two were classified as markedly ill (CGI = 5), five were classified as moderately ill (CGI = 4), 12 were classified as mildly ill (CGI = 3), and 16 were classified as borderline mentally ill (CGI = 2). Six patients were classified as normal, not at all ill (CGI = 1).

3.3 Effectiveness of the LAIR Treatment

In the second evaluation of the patients using the CGI, the CGI-I scale was also administered. Thirty-four (81%) patients were classified as improved; 9 (21.4%) of whom were very much improved, and 25 (59.5%) much improved. Seven patients (16.6%) were classified as minimally improved. One patient (2.3%) showed no change. The improvements observed in the patients are shown in Fig. 1.

There was an improvement in 13 (92.8%) of the 14 patients diagnosed with bipolar affective disorder. There was also an improvement in 25 (78.1%) of 32 patients diagnosed with CD and in one (50%) of two patients diagnosed with schizophrenia. Of eight patients who showed minimal or no improvement, four had comorbid mental retardation.

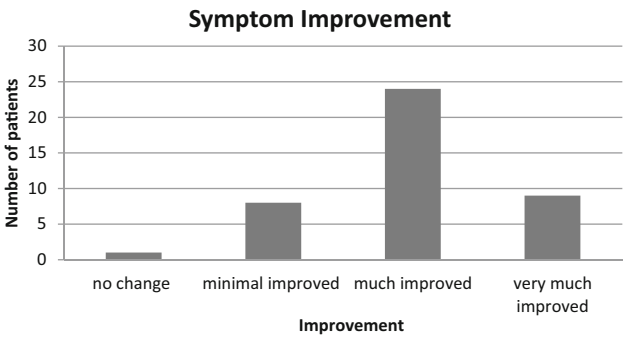

Fig. 1 Graph showing improvements according to CGI-I, 2 months after commencing the LAIR treatment. *CGI-I* the clinical global impression improvement scale, *LAIR* long-acting injectable risperidone

3.4 Adverse Effects

Weight gain, difficulty staying awake during the day, and muscle stiffness were the most common adverse effects in both sexes. Menstrual problems and swollen or tender breasts were the most common adverse effects among girls. The LAIR-related side effects are detailed in Table 2.

There was no significant correlation between the number of LAIR doses and the LUNSERS score ($p = 0.284$; $r = -0.169$). Furthermore, there was no significant correlation between the total number of doses and side effects according to the LUNSERS in the correlation analysis, which was applied separately for males and females (girls: $p = 0.432$; $r = -0.155$; boys: $p = 0.330$; $r = -0.281$).

Marked weight gain occurred in 10 (23.8%) patients (2, 3 or 4 points from LUNSERS weight-gain item), and

Table 1 Psychiatric diagnoses of the subjects

	Conduct disorder	Bipolar affective disorder	Schizophrenia
No comorbidity	1	4	1
Mental retardation	13	1	1
ADHD	6	3	
PTSD	4	–	
OCD	2	1	
Depression	2	–	
Autism	1	–	
Substance abuse	1	–	
Conduct disorder		6	

Six patients had one disorder, 30 patients had two disorders, and six patients had three disorders

ADHD attention deficit hyperactivity disorder, *PTSD* post-traumatic stress disorder, *OCD* obsessive compulsive disorder

Table 2 Frequency of adverse effects reported by the participants

	n	%
Menstrual problems	11[a]	39.2[a]
Swollen or tender breasts	12[b]	28.6[b]
Weight gain	10	23.8
Difficulty staying awake during the day	10	23.8
Muscle stiffness	9	21.4
Sleeping too much	7	16.7
Muscle spasms	7	16.7
Difficulty remembering things	7	16.7
Tiredness	6	14.3
Slowing of movements	6	14.3
Nausea	6	14.3
Increased dreaming	6	14.3
Dizziness	6	14.3
Periods less frequent	4[a]	14.2[a]
Dry mouth	5	11.9
Difficulty concentrating	5	11.9
Tension	5	11.9
Increased urination	4	9.5
Headache	4	9.5
Depression	4	9.5
Blurred vision	4	9.5
Increased sweating	4	9.5
Shakiness	4	9.5
Itchy skin	4	9.5
Difficulty getting to sleep	3	7.1
Apathy	3	7.1
Restlessness	3	7.1
Sensitivity to sun	3	7.1
Constipation	2	4.8
Increased saliva or drooling	2	4.8
Increased sex drive	2	4.8
Parts of body moving of their own accord (e.g. foot tapping)	2	4.8
Rash	2	4.8
Difficulty achieving climax	2	4.8
New or unusual skin marks	2	4.8
Difficulty urinating	1	2.4
Palpitations	1	2.4
Pins and needles	1	2.4
Diarrhea	1	2.4
Weight loss	1	2.4
Reduced sex drive	1	2.4

[a] Male cases were not included in the calculation

[b] One male and 11 females

minimal weight gain occurred in 12 (28.6%) patients (one point from LUNSERS weight-gain item). In total, 52.4% of the patients complained of weight gain. The median of weight gain per dose was 0.41 kg (weight gain/per dose range 0–1.33 kg). In 6 (14.3%) patients, LAIR was terminated due to weight gain, although the patients had benefited from the medication.

Dystonia was seen in seven (16.7%) patients in our study, three of whom discontinued LAIR treatment (Table 2).

3.5 Drug Compliance

Of the 42 study group participants, 24 (57.1%) completed the LAIR treatment plan, and 18 (42.8%) withdrew from treatment. Among these 18 patients, 7 (16.7%) discontinued the treatment due to non-adherence. Reasons for non-adherence were injection fear and lack of family support for LAIR. From the total 42 patients, 83.3% adhered to LAIR treatment. The other 11 patients discontinued the treatment due to the following adverse effects: weight gain (n = 4, 9.5%) dystonia (n = 3, 7.1%), galactorrhea (n = 2, 4.8%), and weight gain and galactorrhea (n = 2, 4.8%) (Fig. 2).

3.6 Concomitant Oral Psychotropic Agent Use

All 42 hospitalized patients showed non-adherence to oral psychotropic agents. Due to the severity of their disorders or comorbid psychiatric disorders, 14 patients (33%) continued to take mood stabilizers (lithium or sodium valproate), 9 (21.4%) continued to take psychostimulant agents, and 7 (16.7%) continued to take selective serotonin reuptake blockers, irregularly.

4 Discussion

Risperidone is the most commonly used and studied atypical antipsychotic agent in children and adolescents. However, there are insufficient data on the use of LAIR in children and adolescents. A previous study investigated the effectiveness of LAIR in adolescents with bipolar disorder [12]. The present research is the first study to evaluate the effectiveness and side effects of LAIR in children and adolescents with CD and/or bipolar disorder or schizophrenia.

The first finding of the present study was that LAIR was effective in children and adolescents with CD. This finding was consistent with studies of children and adolescents who were treated with oral risperidone, with the drug found to be effective for severe disruptive behavior [21] and CD [22]. In an open-label study of patients aged 5–14 years with disruptive behaviors and sub-average intelligence, Croonenberghs et al showed that risperidone was a well-tolerated and effective long-term treatment for disruptive behavior disorders. In the present study, 78.1% of the patients with CD and aggression showed an improvement [23]. This is the first study to show the effectiveness of LAIR for CD. It was noteworthy that four of seven patients with no obvious improvement had comorbid mental retardation, and this decreased the response rate to the antipsychotic medication.

Pharmacological intervention was not the first-line treatment for our patients with CD. Children and adolescents with conduct disorder are treated with psychological, behavioral, psychosocial (targeting the child and the family) and pharmacological approaches, alone or in combination in clinical practice [24]. In our study, patients who were hospitalized underwent psychological, behavioral, and psychosocial therapy, as well as drug treatment. This approach may also have contributed to the improvement of our patients with CD.

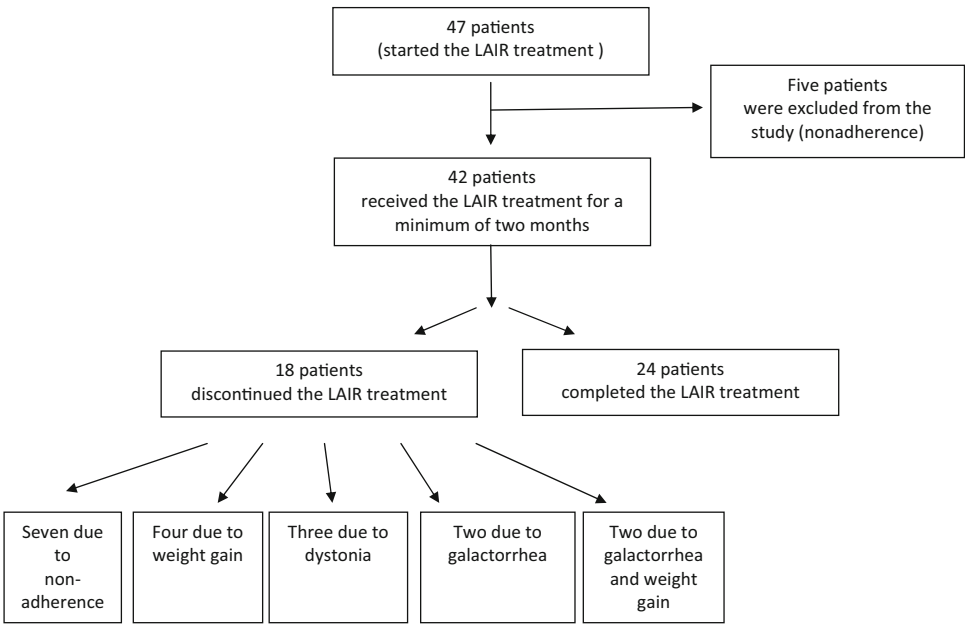

Fig. 2 Study flow. *LAIR* long-acting injectable risperidone

In the present study, all patients with CD exhibited aggressive behavior, and this was the target symptom to treat. Many patients with psychiatric disorders present to the clinic with aggressive behaviors, which are a major complication of numerous psychiatric disorders. In patients with psychiatric disorders, distorted or deficient cognitive processes and impaired impulse control can lead to extreme alarm in response to environmental events [25]. Thus, someone with CD may exhibit aggression rather than other emotions. In the present study, mental retardation and associated cognitive deficits may have explained the resistance to treatment in some cases.

The second finding of this study was that LAIR and mood stabilizers were effective in children and adolescents with bipolar disorder, with 13 (92.8%) of 14 patients showing an improvement. This finding was consistent with the results of a study of adults by Wu et al. [26]. Adolescents with bipolar disorder can be treated with oral risperidone. A previous study of adolescents with bipolar disorder treated with a mood stabilizer (lithium or valproic acid) and oral risperidone reported an improvement in 80–82% of patients [5, 6]. Studies reported that the injectable formulation of risperidone enabled more predictable and consistent plasma drug concentrations than the oral form of the drug [27, 28]. The use of the injectable formulation may explain the higher rate of recovery in the present study.

In the current study, two adolescent patients had schizophrenia, one of whom benefited from LAIR. Given the low number of patients with schizophrenia in the study, it is difficult to draw any conclusions in terms of effectiveness. Most previous studies of adults treated with LAIR had schizophrenia spectrum disorder. As schizophrenia patients are poorly insightful about their illness, many are unsuitable candidates for treatment with oral drugs [29, 30]. A previous study found that 40% of outpatients with schizophrenia did not respond well to antipsychotic treatment [4]. The long-term consequences of drug adherence in schizophrenia have been studied [31]. Exacerbations in psychopathology were reported to be more common in noncompliant patients, and hospitalization rates were reported to be higher [31, 32]. It places a greater financial burden on the healthcare system. Earlier studies showed that treatment compliance increased in patients with schizophrenia treated with LAIR and that the effective blood concentration of the drug exceeded that of oral risperidone, resulting in increased recovery rates and decreased hospitalization rates [28, 29, 33]. A study of Australian patients with schizophrenia treated with LAIR reported that symptom severity, suicidal and homicidal thoughts, and self-injury behavior decreased in the first 3 months after treatment [34].

The third finding of the present study is related to the frequency of adverse effects. Although these were assessed subjectively, each potential adverse effect was listed separately on LUNSERS, which was completed by the family and adolescent. Table 2 shows the most common adverse effects among males and females. Among the 42 patients, 52.4% experienced weight gain (28.6% mild weight gain and 23.8% experienced marked weight gain). Weight gain was responsible for 6 (14.3%) withdrawals from the study, although they had benefited from the treatment. Weight gain among patients using LAIR should be closely monitored, as it places patients at risk of developing metabolic syndrome in the future. In a large, prospective study conducted with patients using oral atypical antipsychotics, 64.4% of patients receiving risperidone showed a weight gain $\geq$7% [35].

A review of randomized controlled studies of oral risperidone reported that risperidone-induced extrapyramidal effects varied from 8 to 26%. The number-needed-to-harm for tremor, dyskinesia, and other extrapyramidal symptoms varied from 6–33 according to the dose and duration of oral risperidone [36]. Sedation is a frequent adverse side effect of risperidone that appears at the initiation of the treatment and time of dose titrations. Previous research demonstrated that serum prolactin levels seemed to increase in response to risperidone treatment. Other side effects, such as menstrual irregularities, breast tenderness, and sexual dysfunction, have also been reported in other studies. Differences in the frequency of adverse effects seem to be linked mainly to differences in drug doses, patients' ages, and metabolism [35].

Many aspects of pharmacokinetics are similar among adults, children, and adolescents. However, metabolic differences and hormonal changes during childhood and adolescence can affect the drug plasma concentration [37]. A previous study suggested that the pediatric population may be more vulnerable to metabolic, endocrine, and extrapyramidal adverse effects of atypical antipsychotics than adults [35]. There are insufficient data on LAIR-induced side effects in children and adolescents. A study of adult patients treated with LAIR reported rates of sedation, weight gain, headaches, and tremor of 10, 8.7, 7.1, and 6.5%, respectively [34]. In a placebo-controlled study, Kane et al, found rates of headache, sleepiness, and anxiety disorder of 18, 11, and of 11%, respectively in adults [38]. In a study that examined the oral use of risperidone in autistic children, the adverse effects were increased appetite [11% ($n = 9$)]; increased weight and vomiting [9% ($n = 7$) each]; sedation, pyrexia, and upper respiratory tract infection [8% ($n = 6$) each]; nasopharyngitis [6% ($n = 5$)]; and somnolence and fatigue [5% ($n = 4$) each] [39]. The same study reported extrapyramidal adverse effects in 6 (8%) patients.

The fourth finding of the present study was that LAIR treatment is increasing drug compliance of patients with non-adherence. The study was conducted with 42 patients with the irregular oral intake. In this study, the compliance to LAIR was 83.3%. Seven patients discontinued to injections due to their family's non-supportive attitude. When treating children and adolescents with oral antipsychotic drugs, noncompliance is a common problem due to familial non-collaboration, lack of insight of the patient, and obstinacy. Thus, the LAIR regimen, which is administered twice a month, is more practical than the twice daily oral regimen in adolescent patients.

Another finding of this study was the continuity rate of LAIR use. In 42.8% (n = 18) of cases, the drug treatment was discontinued due to various side effects and non-adherence. In the total study group, 16.7% ceased the treatment due to drug non-adherence, 9.5% due to weight-gain, 7.1% due to dystonia, 4.8% due to galactorrhea, and 4.8% due to both weight gain and galactorrhea. Our study consisted of patients who were non-adherent to oral drug use. A high percentage of patients ceased LAIR treatment because of side effects. Thus, if the patient is coherent to oral use, then oral use of the drug should be tried first.

Among 42 patients, 57.1% (n = 24) continued to receive regular injections until the treatment was terminated by the doctor. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study of adults with chronic schizophrenia, 74% of patients underwent antipsychotic drug treatment due to a lack of response and intolerability during 18 months of treatment [40]. In the present study, the severity score of the patients was high, and these patients lacked insight with regard to their illness.

Recently, atypical antipsychotics are increasingly used in children and adolescent patients. Metabolic syndrome and extra pyramidal system side effects are not rare with atypical antipsychotics in children and adolescents [41]. To reduce side effects and optimize treatment, it is important to perform accurate monitoring of drug blood levels in these patients [42]. Therapeutic drug monitoring (TDM) is aimed at minimizing the risk of possible drug toxicity as well as optimizing the efficacy of treatment, by keeping the drug concentrations in the therapeutic range. TDM should not be considered as just measuring the blood concentration of the drug and comparing it to the concentration range that it should be. TDM can be used to individualize the drug to the clinical status of the patient (such as age, weight, kidney function) and is considered one of the best ways to to deliver so-called "personalized psychiatry". In the future, the aim should be to obtain more effectiveness and fewer side effects from risperidone treatment by monitoring the blood levels of risperidone and its active metabolites [43, 44].

5 Limitations

The present study had a number of limitations. The number of patients is low and this may impair the study's statistical power. It was a clinical follow-up study, and there was no control group. More rigorous studies including randomized control groups in children and adolescents are needed in the future. The side effects were subjectively assessed and not compared with those of a placebo group. A randomized, placebo-controlled trial with LAIR may be conducted in the future. Biochemical data, such as serum prolactin levels, lipid profiles, and liver function, were not regularly monitored in the assessment of the side effects.

The focused therapeutic and psychoeducation interventions at an inpatient unit potentially improved compliance along with a tendency to increase compliance after discharge. Another limitation was the concomitant use of additional medications because of patients benefit. CD or bipolar disorder frequently have other comorbid psychiatric diagnoses, thus comorbidities should be treated together in these disorders. These factors may also contribute to the improvement of our patients.

6 Conclusion

The LAIR treatment was effective in children and adolescents with CD with aggression and bipolar disorder. Of two adolescent patients with schizophrenia, the treatment alleviated the symptoms of one of the patients. Given the small number of patients with schizophrenia in the study, a definitive conclusion cannot be reached on the effectiveness of LAIR. In children and adolescents who show noncompliance with oral drugs, LAIR may improve treatment compliance. LAIR is a reliable treatment in terms of its effectiveness. Weight gain, daytime somnolence, muscle stiffness and spasms, impaired concentration, fatigue, and menstrual problems in girls were the most common side effects. The LAIR treatment was terminated early in 26.2% of the patients, due to weight gain, dystonia, and galactorrhea. In the study, 57.1% of the patients continued to receive their injections regularly until the end of the treatment, under physician control.

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Compliance with Ethical Standards

Funding This study was not supported by any pharmaceutical company.

Conflict of interest The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval The study was approved by Ankara Yildirim Beyazit University Yenimahalle Education and Research Hospital Ethics Board. All procedures performed were in accordance with the 1964 Helsinki Declaration and its later amendments.

Informed consent Written informed consent was obtained from all individual participants and their families included in the study.

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