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Safety of Atypical Antipsychotics in a Child and Adolescent Inpatient Setting: A Naturalistic Study

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ABSTRACT

Background: This study's objective was to investigate the adverse effects of atypical antipsychotics (AAPs) on the metabolic, hematological, and endocrinological systems in the inpatient environment for children and adolescents with diverse psychiatric disorders.

Methods: A retrospective assessment of 208 children's and adolescents' medical records was conducted. All patients were on AAP monotherapy. At baseline and after treatment, measurements of body weight, height, body mass index (BMI), BMI z-score, fasting blood glucose (FBG), total cholesterol, low-density lipoprotein cholesterol, triglycerides, high-density lipoprotein cholesterol, complete blood count, liver functions, thyroid functions, and prolactin levels were made. Scores from the Children's Global Assessment Scale (CGAS) and the Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA) were preserved.

Results: The overall patient population had a mean age of 14.50 ± 2.32 years, 139 girls, and 69 boys. Of the patients, 63 (30.29%) were on risperidone (RIS), 69(33.17%) were on aripiprazole (ARI), 32 (15.39%) were on quetiapine (QUE), 42 (20.19%) were on olanzapine (OLA), and 2 (0.96%) were on clozapine (CLO). In the OLA group, the BMI and BMI z-score increased more than in the RIS, QUE, and ARI groups ($P=.030$, $P=.014$, and $P=.001$, respectively) ($P=.001$). The mean difference in CGAS and HoNOSCA between the start of antipsychotic medication and hospital discharge was statistically different for all four groups ($P=.001$ for all). The mean FBG levels in the OLA group increased statistically significantly ($P=.013$, $P=.021$) in contrast to the RIS group. In addition, a statistically significant difference in triglycerides across the groups was found ($P=.003$).

Conclusion: According to the findings of our study, children and adolescents appear to be at a significant risk for psychotropic-induced PRL increase, weight gain, metabolic, and hematological consequences. To prevent serious health problems, a meticulous risk–benefit assessment for AAPs treatment should be done between clinicians and patients and their families.

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INTRODUCTION

Among adults diagnosed with schizophrenia and psychosis, atypical antipsychotics (AAPs) represent a major advance due to their a cut above efficacy and side effect profile compared to typical antipsychotics (TAs). However, in prescribing practices for children and adolescents, antipsychotics were prescribed adolescent schizophrenic patients without specific approval for many years. Clinicians usually prescribed these agents to young patients on the basis of their clinical experience with adults. It was not uncommon using both TAs and AAPs (including clozapine [CLO], aripiprazole [ARI], olanzapine [OLA], risperidone [RIS], paliperidone, ziprasidone, quetiapine [QUE]) as off-label drugs for other pediatric psychiatric disorders such as obsessive-compulsive disorder, bipolar disorder, severe attention deficit/hyperactivity disorder, tic disorders such as Tourette's disorder, eating disorders, and disorders with the features of disruptive behaviors and aggression. According to randomized-controlled research, the majority of antipsychotics are only taken when they are indicated as the first-line treatment for particular child and adolescent psychiatric illnesses.[1] These agents are primarily used for the treatment of autism spectrum

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disorders, disruptive behavior disorders (e.g., conduct disorder, oppositional-defiant disorder), mood disorders or intellectual disabilities, and schizophrenia and other psychotic disorders.[2] The AAPs have also shown promise in the treatment of violence, self-harm, and extremely irritable in young people who suffer from a variety of psychiatric problems. In children and adolescents, the AAP prescription rate has been increasingly all around the world.[2] The increased rates of prescribing AAPs have been shown to be associated with the use of AAPs not only for psychotic disorders, but also for non-psychotic disorders and their use for long term.

For off-label indications, several studies have demonstrated that AAPs are usually preferred as the sole antipsychotic rather than as a part of a combination therapy with other AAPs, and switching one AAP to another is not common during the first year of the treatment.[3] Tendencies to prescribe particular antipsychotics appear to vary, and there is no absolute data supporting the relative supremacy of one agent over another for any psychiatric disorder.[4] The other reasons for the dramatic increase in the AAP prescription rate are the expectation of larger safety and tolerability features, particularly for extrapyramidal symptoms (EPSs) compared to TAs. However, the data is still limited and inconclusive in children and adolescents to compare the tolerability and efficacy of various antipsychotics.[5]

Atypical antipsychotics have a low risk for both chronic and acute neuromotor side effects. In general, adverse effect profiles of AAPs were similar both in children/adolescents and adults.[6,7] For psychotropic medications, irrespective of the patient age, the most concerning side effects are endocrine and metabolic side effects, due to their short and long-term consequences.[8] Despite the paucity of data on the safety of AAPs, it appears that children and adolescents are more susceptible than adults to antipsychotic-induced hyperprolactinemia and weight gain, which may result in additional metabolic abnormalities. In consequence of the unique effects of AAPs on dopaminergic, serotonergic, noradrenergic, cholinergic, and histaminergic receptors, both therapeutic and adverse effects are exerted. In the pediatric population, due to the different pharmacokinetic features of these agents, higher doses per kilogram of body weight and more frequent dosing per day are required to achieve the expected efficacy.[7]

Over the last decades, the widespread use of AAPs in a variety of diagnoses among young individuals treated in the inpatient setting has been the focus of increasing attention, due to both their effectiveness and their side effects. The number of studies involving children and adolescents are still rather modest, and those examining the metabolic and endocrinological side effects of AAPs have very small sample sizes and generally brief follow-up periods. Determining the metabolic, hematological, and endocrinological side effects of AAPs over a 12-year naturalistic follow-up period in pediatric and adolescent inpatient settings with a variety of psychiatric diseases was the goal of the current study.

MAIN POINTS

- Prescription rates for atypical antipsychotics (AAPs) in children and adolescents have been rising everywhere.
- Few studies have been conducted on children and adolescents, and those that have looked into the metabolic and endocrinological side effects of AAPs have very small sample sizes and relatively short follow-up periods.
- During a 12-year naturalistic follow-up period, the aim of this study is to investigate the deleterious metabolic, hematological, and endocrinological consequences of AAPs in the inpatient setting for children and adolescents with various psychiatric diseases.
- Our study indicates that children and adolescents appear to be at a greater risk for psychotropic-induced PRL increase, weight gain, metabolic, and hematological side effects.

MATERIAL AND METHODS

Study Population and Sample

Between January 2005 and December 2017, this retrospective, single-center investigation was carried out at the university hospital's inpatient section for child and adolescent psychiatry. Inclusion criteria were as follows: being aged eighteen or younger; being diagnosed with psychiatric disorders based on diagnosis criteria in the Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR, American Psychiatric Association, 2000) and the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013); using AAPs medication; taking clozapine, quetiapine, olanzapine, aripiprazole, or risperidone parenterally or orally; being an inpatient in the child and adolescent psychiatry clinic. Medical charts of a total of 208 children and adolescents were reviewed. All patients were on AAP monotherapy. BMI (body mass index) at baseline and after treatment, body weight, height, triglyceride, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), complete blood count (CBC), liver functions, thyroid functions, and prolactin (PRL) levels were all recorded. The Children's Global Assessment Scale (CGAS) and Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCAs) scores were recorded.

Assessment of Metabolic, Endocrine, and Hematologic Parameters

The patient's weight in kilograms was divided by the square of the body's height in meters to determine the BMI. Anthropometric data, including weight, height, and BMI measured in the baseline and after treatment, was converted into z-scores using national guidelines for boys and girls, as appropriate.[9] Blood is routinely taken from all patients who are planned to start antipsychotic

drug treatment in our inpatient unit to evaluate baseline triglyceride, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), complete blood count (CBC), liver functions, thyroid functions, and prolactin (PRL) levels at 9 am on the day after admission to the unit on an empty stomach. In patients receiving antipsychotic drug treatment, blood is routinely collected at 9 am on the day before the planned discharge from the unit to evaluate the above-mentioned parameters for control purposes. The waist circumference measurements, gamma-glutamyl transferase (GGT), alanine transaminase (ALT), aspartate transaminase (AST), triglycerides, TC, LDL-C, HDL-C, fasting glucose blood levels, CBC, thyroid-stimulating hormone (TSH), and free thyroxine (FT_4), PRL, hemoglobin levels, leucocytes, and thrombocytes counts results of the children and adolescents were extracted. All assessments were made based on the hospitalization duration, irrespective of the prior antipsychotic use due to the lack of conclusive data.

Assessment Tools

The Global Assessment Scale (GAS) was originally created to measure the degree of functioning over a predetermined time period. The CGAS is the GAS's modification for children and adolescents. It is used to evaluate the child's functionality with values ranging from 1 to 100. Higher ratings denote improved overall functionality.[10]

The HoNOSCA is a clinical outcome measure designed for use in inpatient mental health treatment for children and adolescents (3-18 years old). The behaviors, problem areas, symptoms, and social functioning of children and adolescents with mental health issues are assessed using this frequently used measurement tool. The HoNOSCA rating by a clinician is independent from the type of psychiatric diagnosis. The clinician assessed the patient's condition at admission and discharge using a 5-point Likert-type score, which is a numerical record with 13 items (0=no problem, 1=minor problem that does not require intervention, 2=a mild but definitely present problem, 3=a moderately serious problem, and 4=serious or very serious problem). Reduced scores signify a better clinical outcome after treatment.[11] A scale for clinician ratings and a self-rated patient version were provided by Gowers et al.[12] The HoNOSCA rating by a clinician is independent from the type of psychiatric diagnosis. The Turkish validity and reliability of the HoNOSCA was performed by Halfon et al in 2020.[13] The Turkish version of HoNOSCA has an adequate level of internal consistency (Cronbach's alpha=0.46) according to reliability studies.[13]

Statistical Analysis

The statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). Where appropriate, descriptive statistics were presented as mean with standard deviation (SD), number and frequency with percentages, or other appropriate units. Chi-square tests were used to compare the distribution of frequencies. Fisher correction was used, if applicable. Continuous variables were tested using *t*-tests. Paired *t*-tests were used to examine the significance of changes from the initiation of antipsychotic treatment during the admission to discharge from the hospital for metabolic, hematological, and endocrinological parameters. Statistical significance was defined as a *P* value of .05. The retrospective chart review approach precluded the use of a priori power estimations. The effect sizes were presented to aid in establishing the context of noteworthy findings.

Ethical Procedure

The participants' parents or legal guardians provided signed consent after being fully briefed. The Dokuz Eylül University Non-Invasive Clinical Research Ethics Committee approved the study protocol (Date: November 20, 2014, No: 2014/35-31). The Declaration of Helsinki's guiding principles were followed in conducting the study.

RESULTS

The mean age of all patients was 14.50 ± 2.32 (6-18) years, with 69 boys and 139 girls constituting the patient population. The average length of stay in the hospital was 11.10 ± 3.85 (4-40) weeks. The participants consisted of children and adolescents with depressive spectrum disorders (n=85), bipolar spectrum disorders (n=37), conduct disorder (n=23), psychotic spectrum disorder (n=21), eating disorder (n=13), attention deficiency/hype ractivity disorder (n=10), disruptive mood dysregulation disorder (n=8), obsessive compulsive disorder (n=9), and anxiety spectrum disorders (n=2), respectively. Some of the patients had multiple psychiatric diagnoses. None of the patients had any other comorbid medical conditions.

The Cronbach's alpha internal consistency coefficients and item-total correlations for each three factors of the Turkish version of HoNOSCA which we used in our study were looked at. Item-total correlations for "behavioral externalizing problems" ranged from 0.33 to 0.48, and internal consistency coefficient (Cronbach's alpha=0.55); item-total correlations for "perceptual-physical impairments" ranged from 0.34 to 0.46, and internal consistency coefficient (Cronbach's alpha=0.55); and item-total correlations for "emotional-relational problems" ranged from 0.27 to 0.31, and internal consistency coefficient (Cronbach's alpha=0.51) was calculated.

All children and adolescents were on an AAP medication. Among all children and adolescents who were on AAP monotherapy, 69 (33.17%) were on ARI, 63 (30.29%) were on RIS, 42 (20.19%) were on OLA, 32 (15.39%) were on QUE, and 2 (0.96%) were on CLO. The mean follow-up duration was 9.96 ± 2.61 weeks for RIS, 9.63 ± 3.22 weeks for ARI,

9.94 ± 4.14 weeks for OLA, 10.39 ± 2.47 weeks for QUE. There was no statistically significant difference ($F=4.27$, $df=3$; $P=.734$) in the duration of follow-up between all four atypical antipsychotic groups. Weight gain, height increase, BMI increase, BMI z-scores, and waist circumferences of all patients according to the treatment are summarized in Tables 1-4.

Comparing the OLA group to the RIS and ARI groups, it was discovered that the gain in body weight in the OLA group was considerably greater ($P=.001$, across the board). The OLA group and QUE group, however, showed no statistically significant difference ($P = .498$). The effect of sex on weight gain was not statistically significant ($F=0.80$, $P=.778$, $\omega^2=0.00$). Thus, there was a significant interaction between antipsychotic use and the sex of the patient ($F=2.991$, $P=.030$, $\omega^2=0.44$). Weight gain was similar among the RIS (2.96 ± 3.54 kg for boys and 2.08 ± 4.41 kg for girls), QUE (5.58 ± 3.76 kg for boys and 3.99 ± 2.78 kg for girls), and OLA (5.32 ± 4.05 kg for boys and 5.88 ± 3.52 kg for girls) groups between male and female patients, while weight gain was found statistically significant difference between two sexes in the ARI group (−0.71 ± 2.95 for boys and 1.83 ± 3.37 for girls).

For RIS, OLA, and QUE groups, there was a statistically significant difference in BMI between initiation of antipsychotic treatment to discharge from the hospital ($P=.001$ for all) (Table 1, Tables 3, and Table 4). There was a greater increase in BMI in the OLA group than in both RIS and ARI groups ($P=.001$; $P=.001$, respectively) but not the QUE group ($P=.136$). Also, in terms of an increase in BMI, there was a statistically significant difference between QUE and ARI groups ($P=.011$). The effect of sex on BMI was not statistically significant ($F = 0.15$, $P=.699$, $\omega^2=0.477$). However, there was a significant interaction between antipsychotic use and the sex of the patient on BMI ($F=2.887$, $P=.040$, $\omega^2=0.48$). The increase in BMI was similar in the RIS (0.90 ± 0.42 for boys and 0.95 ± 0.32 for girls) and QUE (1.88 ± 0.54 for boys and 1.32 ± 0.43 for

Table 1. Differences in the Weight Gain, Height, BMI, BMI z-score, Waist Circumferences, CGAS, HoNOSCA, PRL, TSH, FT4 levels, FBG levels, the Liver Function Tests (i.e., ALT, AST, and GGT), Lipid Panel Parameters (i.e., TC, LDL-C, HDL-C, and triglycerides), Hemoglobin, Leukocyte, and Thrombocyte Counts Between the Initiation of Risperidone Treatment During the Admission and Discharge from the Hospital

	During the Admission to the Hospital (n=63)	Discharge from the Hospital (n=63)	Mean Difference	95% CI of Difference	*P**
	Mean ± SD	Mean ± SD			
Weight (kg)	60.77 ± 16.84	63.37 ± 16.55	−2.59	−3.63-(−1.55)	**.001**
Height (cm)	162.18 ± 9.04	162.46 ± 8.95	−0.28	−0.47-(−0.08)	**.007**
BMI	22.96 ± 5.40	23.94 ± 5.48	−0.98	−1.35- (−0.60)	**.001**
BMI z-score	0.72 ± 1.43	1.00 ± 1.31	−0.28	−0.39- (−0.18)	**<.001**
Waist circumference (cm)	74.58 ± 13.62	77.93 ± 13.90	−3.34	−4.72-(−1.96)	**.001**
CGAS	40.57 ± 9.47	57.66 ± 9.38	−17.09	−19.74-(−14.44)	**.001**
HoNOSCA	27.92 ± 4.83	16.75 ± 5.19	11.16	9.11-13.22	**.001**
PRL	49.38 ± 33.36	51.05 ± 35.45	−1.67	−12.82-9.47	.765
TSH	2.38 ± 1.49	2.09 ± *0*.98	0.28	−0.06-0.64	.106
FT4	1.12 ± 0.29	1.12 ± 0.32	−0.003	−0.07-0.07	.928
FBG (mg/dL)	82.89 ± 8.69	82.16 ± 10.75	0.72	−1.92-3.38	.584
ALT(IU/L)	14.68 ± 12.40	14.75 ± 9.06	−0.06	−2.94-2.80	.963
AST (IU/L)	18.95 ± 7.34	18.35 ± 6.35	0.60	−1.06-2.26	.474
GGT(IU/L)	16.50 ± 5.19	16.95 ± 7.72	−0.45	−3.63-2.71	.768
TC (mg/dL)	170.34 ± 32.32	160.19 ± 33.35	10.15	2.14-18.16	**.014**
HDL (mg/dL)	51.45 ± 11.37	48.84 ± 10.79	2.61	0.58-4.63	**.012**
LDL (mg/dL)	94.95 ± 22.65	91.12 ± 23.77	3.83	−1.90-9.57	.186
TG (mg/dL)	111.67 ± 65.86	115.94 ± 68.31	−4.27	−20.32--11.78	.596
Hemoglobin (g/dL)	13.53 ± 1.13	13.35 ± 0.96	0.17	0.00-0.35	**.043**
Leucocytes (K/mm^3)	7.71 ± 1.83	7.34 ± 1.53	0.37	−0.13-0.88	.147
Thrombocytes (K/mm^3)	271.8 ± 66.88	267.98 ± 59.57	3.30	−5.61-12.22	.461

*Paired sample *t*-test. Values in bold indicate statistical significance.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CGAS, Children's Global Assessment Scale, FT4, free thyroxine; FBG, fasting blood glucose levels; GGT, gamma-glutamyl transferase; HONOSCA, Health of the Nation Outcome Scales—Children and Adolescents; PRL, prolactin; TSH, thyroid-stimulating hormone; TC, total cholesterol; TG, triglyceride.

Table 2. Differences in the Weight Gain, Height, BMI, BMI z-Score, Waist Circumferences, CGAS, HoNOSCA, PRL, TSH, FT4 levels, FBG levels, the Liver Function Tests (i.e., ALT, AST, and GGT), Lipid Panel Parameters (i.e., TC, LDL-C, HDL-C, and Triglycerides), Hemoglobin, Leucocyte, and Thrombocyte Counts Between the Initiation of Aripiprazole Treatment during the Admission and Discharge from the Hospital

	During the Admission to the Hospital (n=69)	Discharge from the Hospital (n=69)	Mean difference	95% CI of Difference	*P**
	Mean ± SD	Mean ± SD			
Weight (kg)	61.06 ± 18.61	62.15 ± 18.63	−1.08	−1.91-(−0.26)	**.010**
Height (cm)	157.95 ± 10.79	158.45 ± 10.47	−0.50	−0.82-(−0.17)	**.003**
BMI	23.81 ± 6.63	24.07 ± 6.61	−0.26	−0.64-0.12	.180
BMI z-score	0.24 ± 1.21	0.27 ± 1.23	−0.04	−0.01-0.07	.104
Waist circumference (cm)	80.94 ± 16.59	81.89 ± 16.70	−0.94	−2.08-0.18	.100
CGAS	35.95 ± 8.01	55.31 ± 9.59	−19.35	−22.15-(−16.56)	**.001**
HoNOSCA	29.03 ± 6.70	17.58 ± 7.21	11.44	9.43-13.46	**.001**
PRL	27.82 ± 28.74	14.42 ± 19.11	13.40	7.38-19.42	**.001**
TSH	2.33 ± 1.58	1.98 ± 1.17	0.34	−0.01-0.70	.058
FT4	1.02 ± 0.22	1.09 ± 0.34	−0.07	−0.15-(−0.00)	**.047**
FBG (mg/dL)	83.04 ± 15.21	83.89 ± 9.43	−0.84	−4.10-2.40	.605
ALT(IU/L)	15.83 ± 8.08	15.29 ± 7.72	0.53	−1.32-2.40	.567
AST (IU/L)	19.68 ± 5.31	19.22 ± 6.74	0.46	−1.11-2.04	.560
GGT(IU/L)	15.82 ± 7.32	17.24 ± 8.24	−1.41	−3.52-0.70	.182
TC (mg/dL)	166.93 ± 35.69	164.12 ± 38.72	2.80	−2.71-8.31	.314
HDL (mg/dL)	48.76 ± 13.60	48.75 ± 14.22	0.01	−2.16-2.19	.989
LDL (mg/dL)	99.84 ± 30.07	97.65 ± 32.91	2.19	−2.00-6.38	.300
TG (mg/dL)	106.38 ± 49.35	104.36 ± 51.81	2.01	−6.35-10.38	.632
Hemoglobin (g/dL)	13.06 ± 1.26	12.86 ± 1.30	0.20	0.01-0.39	**.032**
Leucocytes(K/mm^3)	7.52 ± 1.81	7.11 ± 1.54	0.40	−0.02-0.84	.064
Thrombocytes (K/mm^3)	261.20 ± 72.22	253.69 ± 58.83	7.50	−4.46-19.47	.215

*Paired sample *t*-test.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CGAS, Children's Global Assessment Scale, FT4, free thyroxine; FBG, fasting blood glucose levels; GGT, gamma-glutamyl transferase; HONOSCA, Health of the Nation Outcome Scales—Children and Adolescents; PRL, prolactin; TSH, thyroid-stimulating hormone; TC, total cholesterol; TG, triglyceride.

girls) groups between boys and girls; however, there was a statistically significant difference in BMI between boys and girls in both in the ARI (-0.57 ± 0.45 for boys and 0.57 ± 0.27 for girls) and OLA (3.25 ± 0.51 for boys and 2.17 ± 0.33 for girls) groups.

In addition, for RIS, OLA, and QUE groups, there was a statistically significant difference in BMI z-scores between initiation of antipsychotic treatment and discharge from the hospital (Table 1, Table 3, and Table 4). There was a greater increase in BMI z-scores in the OLA group than in both RIS, QUE, and ARI groups (P=.030; P=.014; P=.001, respectively). Also, in terms of an increase in BMI z-scores, there was a statistically significant difference between ARI and RIS and QUE groups (P=.015; P=.008, respectively). The effect of sex on BMI z-scores was not statistically significant (F=0.52, P=.472, ω^2=0.03). However, on BMI z-scores, there was a significant interaction between antipsychotic use and the sex of the patient (F=19.41, P =0.020, ω^2=0.54). The increase in BMI z-scores was similar in the QUE group (8.91 ± 3.60 for boys and 7.80 ± 2.90 for girls) between boys and girls, while there was a statistically significant difference in the BMI z-scores of the RIS (9.60 ± 2.80 for boys and 5.70 ± 2.10 for girls), ARI (−4.40 ± 2.95 for boys and 3.10 ± 1.80 for girls), and OLA (23.70 ± 3.40 for boys and 15.60 ± 2.20 for girls) groups between both sexes.

For RIS, QUE and OLA groups there was a statistically significant difference in waist circumference between initiation of antipsychotic treatment to discharge from the hospital (Table 1, Tables 3 and 4). Both QUE and OLA groups showed statistically significant increase in waist circumference comparing with ARI group (P=.001 for both) but there were no statistically significant difference between OLA, QUE, and RIS groups (OLA vs. QUE: P=.950; OLA vs. RIS: P=; QUE vs. RIS: P=.710). Also in terms of increasing waist circumference there was no statistically significant difference between ARI and RIS groups (P=.060). There was no significant interaction between antipsychotic use and the sex of the patient in terms of an increase in waist circumference (F=1.23, P=.300, ω^2=0.220).

Table 3. Differences in the Weight Gain, Height, BMI, BMI z-Score, Waist Circumferences, CGAS, HoNOSCA, PRL, TSH, FT4 levels, FBG levels, the Liver Function Tests (i.e., ALT, AST, and GGT), Lipid Panel Parameters (i.e., TC, LDL-C, HDL-C, and Triglycerides), Hemoglobin, Leukocyte, and Thrombocyte Counts Between the Initiation of OLANZAPINE Treatment during the Admission and Discharge from the Hospital

	During the Admission to the Hospital (n=42)	Discharge from the Hospital (n=42)	Mean difference	95% CI of Difference	*P**
	Mean ± SD	Mean ± SD			
Weight (kg)	49.62 ± 13.78	55.35 ± 13.38	−5.72	−6.85-(−4.58)	**.001**
Height (cm)	158.40 ± 12.10	158.90 ± 11.95	−0.50	−0.83-(−0.16)	**.004**
BMI	19.46 ± 3.81	21.59 ± 3.48	−2.13	−2.59-(−1.67)	**.001**
BMI z-score	0.67 ± 0.51	1.00 ± 1.42	−0.33	−0.50-(−0.17)	**<.001**
Waist circumference (cm)	66.88 ± 11.24	71.93 ± 10.98	−5.05	−6.53-(−3.57)	**.001**
CGAS	37.66 ± 9.28	55.52 ± 9.19	−17.85	−20.89-(−14.81)	**.001**
HoNOSCA	25.57 ± 6.29	16.75 ± 6.45	8.82	6.96-10.68	**.001**
PRL	32.27 ± 22.42	52.58 ± 36.13	−20.30	−32.63-(−7.98)	**.002**
TSH	1.83 ± 1.09	2.05 ± 1.36	−0.21	−0.81-0.38	.469
FT4	1.13 ± 0.29	1.15 ± 0.34	−0.02	−0.15-0.09	.660
FBG (mg/dl)	76.66 ± 10.57	82.30 ± 10.76	−5.64	−9.23-2.05	**.003**
ALT(IU/L)	17.53 ± 11.43	18.43 ± 10.79	−0.90	−4.75-2.95	.639
AST (IU/L)	20.65 ± 7.01	20.14 ± 5.97	0.51	−1.63-2.66	.633
GGT(IU/L)	15.22 ± 4.60	16.68 ± 7.18	−1.45	−3.13-0.22	.086
TC (mg/dL)	173.68 ± 39.49	176.85 ± 36.34	−3.17	−12.74-6.40	.507
HDL (mg/dL)	54.78 ± 15.49	54.92 ± 14.72	−0.14	−3.93-3.64	.938
LDL (mg/dL)	100.41 ± 32.49	100.48 ± 31.34	−0.06	−8.22-8.09	.987
TG (mg/dL)	95.46 ± 39.16	120.92 ± 68.18	−25.46	−43.08-(−7.85)	**.006**
Hemoglobin (g/dL)	12.93 ± 1.55	12.92 ± 1.05	0.01	−0.36-0.37	.968
Leucocytes (K/mm^3)	6.83 ± 1.87	6.89 ± 1.58	−0.06	−0.54-0.42	.798
Thrombocytes (K/mm^3)	267.95 ± 76.14	272.75 ± 80.95	−4.81	−24.73-15.13	.629

*Paired sample *t*-test.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CGAS, Children's Global Assessment Scale, FT4, free thyroxine; FBG, fasting blood glucose levels; GGT, gamma-glutamyl transferase; HONOSCA, Health of the Nation Outcome Scales—Children and Adolescents; PRL, prolactin; TSH, thyroid-stimulating hormone; TC, total cholesterol; TG, triglyceride

For ARI and OLA groups there was a statistically significant difference in the average difference of PRL levels between initiation of antipsychotic treatment to discharge from the hospital ($P=.001$; $P=.002$ respectively). The effect of sex on PRL levels was not statistically significant ($F=0.239$, $P=.626$, $\omega^2=0.001$). Additionally, there was no significant interaction between antipsychotic use and the sex of the patient in terms of PRL levels ($F=1.84$, $P=.140$, $\omega^2=0.028$). Between the start of antipsychotic medication and hospital discharge for any AAP groups, there were no appreciable variations in TSH and FT4 levels. The effect of sex on TSH levels was not statistically significant ($F=0.453$, $P=.502$, $\omega^2=0.020$). Thus, there was no significant interaction between antipsychotic use and the sex of the patient in terms of TSH levels ($F=1.21$, $P=.310$, $\omega^2=0.020$).

Changes in the FBG levels, the liver function tests (i.e., GGT, ALT, AST), lipid panel parameters (*i.e.*, triglycerides, LDL-C, TC, HDL-C), hemoglobin levels, leucocyte and thrombocyte counts at the time of discharge compared to baseline were also summarized in Tables 1-4. There was a statistically significant increase in the mean FBG levels in the OLA group ($P=.003$). For all treatment groups, there were no statistically significant difference in the liver function tests (i.e., GGT, ALT, AST) between initiation of antipsychotic treatment to discharge from the hospital. There was a statistically significant difference in the TC and HDL-C levels in the RIS group ($P=.014$, $P=.012$, respectively). There was a statistically significant difference in triglyceride levels in the OLA group ($P=.006$). For RIS, ARI, and QUE groups there was a statistically significant difference in the hemoglobin levels between the initiation of antipsychotic treatment to discharge from the hospital ($P=.043$; $P=.032$; $P=.012$, respectively). There was a statistically significant difference in thrombocyte counts in the QUE group ($P=.031$).

DISCUSSION

We examined the changes in body weight, height, BMI, BMI z-scores, FBG, triglycerides, LDL-C, HDL-C, and TC,

Table 4. Differences in the Weight Gain, Height, BMI, BMI z-Score, Waist Circumferences, CGAS, HoNOSCA, PRL, TSH, FT4 levels, FBG levels, the Liver Function Tests (i.e., ALT, AST, and GGT), Lipid Panel Parameters (i.e., TC, LDL-C, HDL-C, and Triglycerides), Hemoglobin, Leukocyte, and Thrombocyte Counts between the Initiation ofQuetiapine Treatment During the Admission and Discharge from the Hospital

	During the Admission to the Hospital (n=32)	Discharge from the Hospital (n=32)	Mean Difference	95% CI of Difference	*P**
	Mean ± SD	Mean ± SD			
Weight (kg)	64.42 ± 16.72	68.85 ± 16.75	−4.43	−5.59-(−3.26)	**.001**
Height (cm)	165.52 ± 9.56	165.78 ± 9.45	−0.25	−0.49-(−0.24)	**.032**
BMI	24.19 ± 5.25	25.66 ± 5.06	−1.47	−2.02-(-0.92)	**.001**
BMI z-score	0.72 ± 1.34	1.43 ± 1.80	−0.71	−1.08-(−0.33)	**<.001**
Waist circumference (cm)	78.02 ± 16.38	82.32 ± 16.05	−4.30	−6.21-(−2.39)	**.001**
CGAS	40.52 ± 8.40	59.13 ± 7.52	−18.61	−21.99-(−15.23)	**.001**
HoNOSCA	27.04 ± 5.42	16.61 ± 4.65	10.42	7.86-12.99	**.001**
PRL	27.27 ± 32.73	19.80 ± 13.95	7.47	−5.69-20.64	.255
TSH	2.41 ± 1.54	1.95 ± 1.10	0.46	−0.14-1.06	.130
FT4	4.18 ± 16.70	0.99 ± 0.18	3.18	−3.18-9.54	.315
FBG (mg/dL)	79.13 ± 9.38	80.71 ± 6.65	−1.58	−6.12-2.96	.483
ALT(IU/L)	17.42 ± 9.69	21.19 ± 17.05	−3.77	−8.67-1.12	.126
AST (IU/L)	19.58 ± 6.76	20.90 ± 9.23	−1.32	−4.51-1.87	.404
GGT(IU/L)	17.92 ± 9.55	19.54 ± 10.07	−1.61	−3.67-0.44	.113
TC (mg/dL)	166.43 ± 27.99	166.80 ± 36.32	−0.37	−8.73-8.00	.929
HDL (mg/dL)	48.77 ± 9.96	47.57 ± 10.35	1.20	−1.23-3.62	.320
LDL (mg/dL)	94.32 ± 25.95	96.71 ± 28.94	−2.39	−10.91-6.12	.570
TG (mg/dL)	111.63 ± 61.49	111.37 ± 56.46	0.26	−12.52-13.05	.967
Hemoglobin (g/dL)	13.41 ± 1.64	13.01 ± 1.21	0.40	0.09-0.72	**.012**
Leucocytes (K/mm^3)	7.25 ± 2.04	6.76 ± 1.67	0.49	−0.27-1.26	.197
Thrombocytes (K/mm^3)	260.84 ± 73.82	237.29 ± 64.36	23.54	2.33-44.77	**.031**

*Paired sample *t*-test.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CGAS, Children's Global Assessment Scale, FT4, free thyroxine; FBG, fasting blood glucose levels; GGT, gamma-glutamyl transferase; HONOSCA, Health of the Nation Outcome Scales—Children and Adolescents; PRL, prolactin; TSH, thyroid-stimulating hormone; TC, total cholesterol; TG, triglyceride

CBC, liver functions, thyroid functions, and PRL levels from baseline during the AAP treatment in children and adolescents admitted to the pediatric psychiatry clinic in the current study. The findings of our investigation revealed statistically significant disparities in the weight gain with cardiometabolic adverse effects among the AAP groups. Additionally, the RIS, QUE, and OLA groups' waist circumference during hospitalization varied in a statistically significant way. Children and adolescents reported weight increase associated with AAP usage more frequently than adults did, notably with RIS, OLA, QUE, and CLO.[2] Guber et al looked at the likelihood of obesity in young children using an AAP for six months or longer. They discovered that AAPs were linked to an increased risk of obesity, and that in the first year, the risk of obesity was 34% higher with ARI than RIS.[14] In some studies, ARI and ziprasidone were not found to be associated with obesity.[7] The FBG associated with diabetes mellitus (DM), which is another significant metabolic parameter, has been previously shown to increase in children and adolescents receiving AAPs.[2,6] While on AAP medication, the undesirable and fearful result of weight gain and obesity is associated with DM. Increased adipose tissue with weight gain may potentially cause insulin resistance, glucose intolerance, and eventually DM. Also, it has been proposed that AAPs exert their direct effects on insulin secretion.[2,7] High levels of fatty acids also have also effects on glucose metabolism and, in some cases, an insufficient pancreatic β-cell response to blood glucose levels may occur. Diabetes mellitus caused by the AAP use may be both reversible and irreversible, and its mechanism still remains to be elucidated. In our study, only the OLA group's FBG levels were statistically different from baseline, and their BMI and BMI z-scores increased more than the RIS and ARI groups' did. The mean increase in TC in the RIS group differed statistically significantly from baseline, but the mean increase in triglycerides was found to differ statistically significantly in the OLA group. Dyslipidemia is also another concern regarding treatment with AAPs.[2] Patel et al. found that increased BMI was correlated with high levels of TC, triglycerides, LDL-C, and

HDL-C. Children and adolescents taking AAPs need to be monitored often because dyslipidemia is a separate risk factor for cardiovascular diseases (CVD).[15]

Cardiometabolic, endocrine, and hematological side effects of AAPs can be seen in young patients with lifelong implications on physical health. Excessive weight gain resulting in an increased BMI and waist circumference, hypertension, blood lipid and glucose alterations may lead to adulthood obesity, sleep apnea, cardiovascular morbidity, metabolic syndrome, osteoarthritis, and malignancies.[2] However, the exact biological mechanisms of AAPs which cause weight gain and other undesirable metabolic side effects have not been fully understood, yet.[2] The weight gain in the ARI group, the BMI in the ARI and OLA groups, and the BMI z-scores in the RIS, ARI, and OLA groups between male and female patients were all statistically different in the current study. Female adolescents have an increased susceptibility to AAP-induced obesity compared with male peers.[2] The literature consistently demonstrates that female patients are more likely to gain weight while on a long-term pharmaceutical treatment with RIS.[16,17] However, it is still unclear for both CLO and OLA; the only available study on QUE has suggested no effects of sex on being overweight.[18] We believe that further prospective studies investigating the relation of AAPs with cardiometabolic side effects and sex are needed.

The mean PRL levels among the groups also showed a statistically significant difference. Another well-known adverse effect due to blockade of the nigrostriatal pathway of AAPs is serum PRL alteration. By blocking dopamine D2 receptors, most of the AAPs cause hyperprolactinemia. Nearly half of patients who are on an AAP medication suffer from elevated PRL levels. Younger individuals, women, and patients with previous antipsychotic use are usually at a higher risk for hyperprolactinemia. In addition to the type, dose, and duration of AAP use, genetic factors are implicated in the etiology of hyperprolactinemia. In particular, D2 receptor gene polymorphism is thought to be responsible for higher serum PRL levels.[19] High PRL levels may cause sexual dysfunction, particularly erectile dysfunction, gynecomastia, galactorrhea, fertility and menstrual cycle problems along with osteopenia and osteoporosis. Among AAPs, while RIS, paliperidone, sulpiride and amisulpride cause moderate to severe elevation in PRL; CLO, OLA, sertindole, ziprasidone and asenapine are associated with mild or transient elevation.[19,20] During ARI monotherapy, different from other AAPs, hypoprolactinemia may occur; the PRL levels reduce to below baseline measurements due to its partial dopaminergic effect.[21] Since the effects of AAPs on PRL may vary, PRL levels should be followed before the initiation of the AAP and on a regular basis thereafter.

When the literature is evaluated, there are few studies on thyroid functions following antipsychotic treatment in both children/adolescents and adults. Atypical antipsychotic drugs have both central and peripheral effects on thyroid function. Thyroid-releasing hormone (TRH)-stimulated TSH levels may be affected by AAPs due to their D2 receptor blockage. Several studies have demonstrated increased TRH-stimulated TSH levels by using amisulpride compared to either placebo or flupentixol.[22,23] In general, AAPs have moderate effects on thyroid functions due to dopamine antagonism, by interfering TSH response to TRH without causing major endocrine problems. Among AAPs, QUE has been shown to reduce total T4 levels without any significant effect on thyroxin and TSH levels.[14,22] This can be attributed to the competitive metabolism of thyroid hormones and QUE mediated by UDP glucuronyl transferase. Other AAPs seem not to have significant effects on thyroid functions. Although QUE reduces total T4 levels, routine follow-up for thyroid functions is not recommended.[22] In line with earlier findings, we found that there was no discernible change in TSH and FT4 levels among the AAP groups.

Blood dyscrasias have also reported with TAs and AAPs.[24] Over the past two decades, CLO-related agranulocytosis has been shown in several studies along with other blood dyscrasias such as leukocytosis, leucopenia, neutropenia, eosinophilia, and thrombocytopenia.[25] When compared to CLO and TAs, patients receiving AAPs had greater rates of transient anemia and neutrophilia. While transient eosinophilia and anemia were reported in female patients, transient neutrophilia was reported in male patients who were on AAP treatment.[26] Transient thrombocytosis and thrombocytopenia were most commonly seen in patients treated with CLO.[25-27] CLO has been extensively used to study the mechanism of drug-induced blood dyscrasias. It is asserted that a variety of genetic variables and CLO metabolites, which mostly target peripheral blood cells, are involved in the exact mechanism, even if this is unknown.[26] Both OLA and QUE have been previously reported to cause agranulocytosis.[28,29] Given their structural similarity, it is possible that these drugs and CLO share the same mechanism that causes agranulocytosis. Chemically, ARI and CLO are different from one another, suggesting that the neutropenic impact may entail additional factors. ARI-induced neutropenia has only ever been reported once, according to the literature.[30] In our study, there was a significant difference in the hemoglobin levels among ARI, RIS, and OLA groups, while no significant difference was discovered in the QUE group. Based on these data, clinicians are considering routine blood testing for children and adolescents starting any AAP.

Abnormalities in liver enzymes have been shown to occur not only with TAs but also with AAPs in recent studies. Antipsychotics typically elevate liver enzymes in adult patients without any apparent symptoms.[31] Even though they are uncommon, both child and adult populations have reported cases of severe hepatotoxicity.[32,33] Clozapine is the most accused AAP agent that causes asymptomatic liver enzyme elevation. Studies with OLA have also shown

elevated liver enzymes, whereas RIS and QUE studies have shown such elevations in child and adolescent populations.[14,34] In the study by Erdogan et al., asymptomatic abnormalities of the liver enzymes were discovered in 38.2% of the patients, and in 0.8% of the cases treated with RIS, a significant rise in the liver enzymes AST and ALT was discovered.[34] Long-term RIS therapy frequently results in changes in liver function; however, at therapeutic doses in children and adolescents, it infrequently results in significant liver damage. The concurrent use of RIS, antidepressants, and methylphenidate in this trial was, however, the primary drawback. In contrast to these findings, we did not discover any proof that the AAP groups' ALT, AST, or GGT levels differed significantly from one another. The possible relationship between AAP treatment and liver enzymes should be further examined in future studies.

The present research has several limitations. First, the sample size for this study is quite modest due to its retrospective methodology and single-center setting. Second, data including DM, dyslipidemia, hypertension, and smoking habits in the family history of the patients were unable to be examined. Third, hospitalization is a sedentary process that may cause an increase in body weight, but a separate assessment or measurement could not be implemented to delineate the main causes of potential increase in weight. Finally, there was no control group consisting of cases who were not using AAP medications.

In conclusion, obesity, metabolic and hematological effects caused by AAPs, as well as their elevation of PRL, appear to be serious risks for children and adolescents. To prevent serious health problems, a meticulous risk-benefit assessment for antipsychotic treatment should be done between clinicians and patients and their families. Any start or continuation of antipsychotic medication should include a side effect evaluation as well as food and lifestyle recommendations. Optimizing physical and psychological outcomes requires regular, proactive monitoring of side effects. It is important to weigh the potential benefits of treating very severe manic, tic, psychotic, and/or aggressive symptoms against the potential risks of specific antipsychotic side effects, especially in the vulnerable group of patients who are children and adolescents.

Ethics Committee Approval: This study was approved by the Ethics Committee of Dokuz Eylül University (Approval Number:2014/35-31; Date: November 20, 2014).

Informed Consent: Informed consent was obtained from all participants and their parents who agreed to take part in the study.

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