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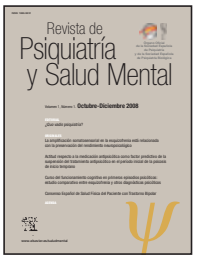

ORIGINAL ARTICLES

Attitude Toward Antipsychotic Medication as a Predictor of Antipsychotic Treatment Discontinuation in First-Episode Early-Onset Psychosis

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KEY WORDS
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Abstract

Background: Antipsychotic drug discontinuation is a key risk factor in psychosis relapses. Clinical relapse is related to poor outcome, especially in the earlier stages of psychotic illness. The attitude toward treatment during the acute phase of a first episode of psychosis has been proposed as one of the main determinants of treatment discontinuation. However, the relationship between attitude toward antipsychotic medication and treatment discontinuation in the adolescent population has not been properly assessed.

Methods: Adolescents, aged 12-18 years old, consecutively admitted to an adolescent unit with a first lifetime admission for a first episode of psychosis were asked to participate in a randomized, flexible-dose, 6-month controlled trial of olanzapine versus quetiapine. Attitude toward antipsychotic medication was assessed using the 10-item Drug Attitude Inventory (DAI). The outcome variable was all-cause treatment discontinuation over the 6-month follow-up. The study sample was composed of 42 patients (34 boys [82.9%], 8 girls [17.1%]; mean age [SD], 16.1 [1.3]).

Results: Of the 42 patients, only 29 (69%) continued the medication throught the entire 6-month follow-up, while 13 (31%) discontinued the medication. DAI scores were greater than zero at all assessments, indicating that the general attitude of the patients toward medication was positive. Higher DAI scores at baseline were related to lower all-cause treatment discontinuation (adjusted hazard ratio [HR] = 0.81 [95%CI, 0.68-0.96], $P = .016$), while DAI scores at 15 days were unrelated to treatment discontinuation (adjusted HR = 1.0 [95%CI, 0.82-1.23], $P = .998$).

Conclusions: A better attitude toward antipsychotic medication at a first lifetime psychiatric admission for a first early-onset psychotic episode was significantly related to lower all-cause antipsychotic treatment discontinuation.

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PALABRAS CLAVE
Psicosis.
Adolescente.
Primer episodio.
Antipsicótico.
Suspensión.
Actitud respecto
a medicación.

Actitud respecto a la medicación antipsicótica como factor predictivo de la suspensión del tratamiento antipsicótico en el período inicial de la psicosis de inicio temprano

Resumen
Antecedentes: La suspensión de la medicación antipsicótica constituye un factor de riesgo clave para las recurrencias en la psicosis. La recurrencia clínica está relacionada con una mala evolución, en especial en las fases más tempranas de la enfermedad psicótica. Se ha propuesto que la actitud respecto al tratamiento durante la fase aguda de un primer episodio de psicosis es uno de los principales factores determinantes de la suspensión del tratamiento. Sin embargo, la relación entre la actitud respecto a la medicación antipsicótica y la suspensión del tratamiento no se ha evaluado adecuadamente en una población adolescente.
Métodos: Se propuso a adolescentes, de entre 12 y 18 años, ingresados de forma consecutiva en una unidad de adolescentes en lo que constituía su primer ingreso como consecuencia del primer episodio de psicosis, la participación en un ensayo controlado, aleatorizado, de 6 meses, con dosis flexibles de olanzapina frente a quetiapina. Se evaluó la actitud respecto a la medicación antipsicótica utilizando el instrumento de 10 ítems Drug Attitude Inventory (DAI). La variable de valoración fue la suspensión del tratamiento por cualquier causa durante el seguimiento de 6 meses. La muestra de estudio la formaron 42 pacientes (34 varones [82,9%], 8 mujeres [17,1%]; edad media ± DE, 16,1 ± 1,3).
Resultados: De los 42 pacientes, tan sólo 29 (69%) continuaron con la medicación durante todo el período de 6 meses de seguimiento, mientras que 13 (31%) suspendieron la medicación. Las puntuaciones del DAI fueron superiores a 0 en todas las valoraciones realizadas, lo que significa que la actitud general de los pacientes respecto a la medicación era positiva. La mayor puntuación del DAI en la situación basal estaba relacionada con una menor suspensión del tratamiento por cualquier causa (razón de riesgos [HR] ajustada = 0,81 [IC del 95% 0,68-0,96], p = 0,016), mientras que las puntuaciones del DAI a los 15 días no estaban relacionadas con la suspensión del tratamiento (HR ajustada = 1,0 [IC del 95% 0,82-1,23], p = 0,998).
Conclusiones: Una mejor actitud respecto a la medicación antipsicótica en el momento del primer ingreso psiquiátrico en la vida del paciente por un primer episodio psicótico de inicio temprano presentaba una relación significativa con una menor suspensión del tratamiento antipsicótico por cualquier causa.

Introduction

Antipsychotic medications have proven effective in reducing rates of relapse among patients with first-episode schizophrenia.[1] However, up to 30%-50% patients with a first-episode psychosis do have a relapse during the first year of illness.[1,2] Time to medication discontinuation has been recognized as an important index of antipsychotic effectiveness, independent of cause.[3] In fact, the most relevant risk factor for relapse is treatment discontinuation, which has been associated with higher rates of readmission, longer hospitalizations, and slower recovery from psychotic symptoms.[1,4] Notwithstanding, up to 40% of patients with first-episode schizophrenia were estimated to discontinue medication, and 20% were estimated to be inadequately compliant.[2]

In general terms, risk factors for antipsychotic treatment discontinuation in schizophrenia patients include: drug side effects,[5-9] poor level of insight,[10-17] and presence of severe psychotic symptoms.[2,17,18] Second generation antipsychotics (SGA) have been reported to produce fewer extrapyramidal symptoms (EPS) and to be better tolerated than first generation antipsychotics (FGA). However, no differences have been found between FGA and SGA users in either attitude toward medication or compliance.[13,14,19,20]

In early-onset psychosis (EOP), SGA discontinuation rates after 1 year of treatment have been found to be about 70%,[21] similar to those found in an adult schizophrenia population.[3] In contrast, other studies have described how discontinuation tends to be more prominent among patients in the earlier phases of schizophrenia.[2,6,15,20,22] In this sense, patients early in the course of the illness could be more willing to take the risk of finding out whether they might remain stable without medication, especially before suffering repeated episodes of relapse.[15]

Antipsychotic drug continuation is an important predictor of clinical outcome, especially at early stages of the illness.[8,23-25]

Medication discontinuation may be influenced by clinical factors, such as duration of illness and severity of symptoms,[26] and patients' initial negative perceptions of medications.[11,27] In this sense, attitude toward treatment during the acute phase of a first episode of psychosis has been proposed as one of the main determinants of the patient's treatment continuation.[6,16] However, data on the relationship between attitude toward antipsychotic medication and treatment discontinuation in an adolescent population has not been properly assessed.

Hence, to evaluate the relationship between treatment discontinuation and attitude toward antipsychotic medication in an adolescent population, we collected data on treatment discontinuation and attitude toward antipsychotic medication from a comparative, randomized, flexible-dose, controlled trial of olanzapine versus quetiapine in first-episode early-onset psychosis. The marked increase in prescriptions of antipsychotic medications in adolescents in recent decades[28,29] highlights the importance of assessing antipsychotic medication discontinuation in that population.

Methods

Subjects

The final sample of this study was composed of 42 patients (34 males [82.9%] and 8 females [17.1%]: mean age [SD], 16.1 [1.3]; range, 12-18 years). Adolescents, ages 12-18, consecutively admitted to the Adolescent Unit of Hospital General Gregorio Marañón (Madrid, Spain) between November 2002 and December 2005 with a first lifetime admission for a first episode of psychosis (< 6 month history of psychotic symptoms) were asked to participate in a comparative, randomized, flexible-dose, controlled trial of olanzapine versus quetiapine. They and their parents/guardians were given written and verbal explanations of the study. Of the 53 patients who met these criteria, 3 patients refused to participate. Thus, 50 patients were enrolled in the trial. All enrolled patients received risperidone (doses, 2-6 mg) during the first 3-5 days of hospitalization. After stabilization on risperidone, participants were randomized to receive either olanzapine or quetiapine. Stratified random sampling into quetiapine or olanzapine groups was based on the age and gender of the participants. The administered dose was determined by the psychiatrists, according to their clinical judgment. Adjunctive medications were allowed, except for antipsychotic medications other than olanzapine or quetiapine. Exclusion criteria were: substance misuse or a medical disorder clinically considered to be the major cause of positive psychotic symptoms; mental retardation; pervasive developmental disorder; any organic disorder of the nervous central system; history of traumatic brain injury with loss of consciousness; pregnancy; and breast-feeding. Substance abuse over the 6 months of treatment was evaluated according to DSM-IV criteria.

In order to compare attitude toward antipsychotic medication with all-cause treatment discontinuation among adolescents with a first episode of psychosis, we collected data on attitude toward antipsychotic medication and treatment discontinuation from this trial. Of these 50 patients enrolled in the clinical trial, 8 patients refused to answer the Drug Attitude Inventory (DAI). Of the 42 patients who comprised the final study sample, 21 (50%) were naïve to antipsychotic treatment, ie, they had no exposure to antipsychotics prior to enrollment.

The study was approved by the Ethics and Clinical Research Committees of Hospital General Gregorio Marañón (Madrid, Spain). All legal representatives signed the written informed consent before enrollment and patients assented to participate in the study.

Assessment of Treatment Discontinuation

Patients were assessed for all-cause treatment discontinuation at baseline (all patients on risperidone), 15 days (patients on either olanzapine or quetiapine), 30 days (patients on either olanzapine or quetiapine), 90 days (patients on either olanzapine or quetiapine), and 180 days (patients on either olanzapine or quetiapine). All patients were initially prescribed risperidone at baseline; continued with risperidone for 3-5 days, and then were randomized either to olanzapine or quetiapine.

Patients who informed the interviewer that they had stopped taking their medication for more than 24 hours were placed in the treatment discontinuation group. For patients who appeared to be unreliable historians, the interviewer reviewed the questions with an additional informant (eg, parent) to corroborate the information provided.

Measure of Attitude Toward Antipsychotic Medication

Attitude toward antipsychotic medication was assessed using the Spanish version of the 10-item DAI.[30] The DAI is a self-reported instrument based on true-false statements about the patient's experience with psychotropic medications. The DAI is scored from −1 to + 1. Some statements are worded in a positive direction (eg, "I feel more normal when on my medications"), and some are worded negatively (eg, "It is unnatural for my mind and body to be controlled by medications"). Score ranges from −10 to + 10, with higher scores indicating a more positive attitude toward medication. The DAI was administered at baseline (all patients on risperidone), 15 days (patients on either olanzapine or quetiapine), 30 days (patients on either olanzapine or quetiapine), 90 days (patients on either olanzapine or quetiapine), and 180 days (patients on either olanzapine or quetiapine) after commencing the study medication.

Other Clinical and Sociodemographic Measurements

All clinical variables were assessed by 4 experienced psychiatrists from the Adolescent Unit (MP, DM, AR-S, and CA).

Psychopathology was measured using the Spanish version of the Positive and Negative Syndrome Scale (PANSS),[31-34] which has been previously validated.[32,34] Intraclass correlation coefficients (ICC) for the 4 psychiatrists ranged from 0.72 to 0.96.

Diagnostic information was collected at baseline using the Kiddie-Sads-Present and Lifetime Version (K-SADS-PL),[35] Spanish translation,[36] and was confirmed at 6 months, using DSM-IV criteria.[37] Diagnoses were made by a certified psychiatrist experienced in child and adolescent psychiatry and with formal training in the use of the semi-structured interview (OM). All diagnoses were reassessed after 6 months. Given the study sample, diagnoses were categorized as schizophrenia (19 subjects), bipolar disorder (14 subjects), and other psychoses (9 subjects), the latter including schizoaffective disorder (2 subjects), depression with psychotic features (1 subject), schizophreniform disorder (1 subject), and psychosis not otherwise specified (NOS) (5 subjects).

Statistical Analysis

Mean, standard deviation (SD), and sample size were used to describe continuous variables, and frequencies and percentages to describe discrete variables. The χ^2 test was used to assess the relationship between categorical variables. Continuous variables were compared across treatment groups by analysis of variance (ANOVA). ANOVA for repeated measures was used to compare DAI score at baseline with DAI scores during the 6-month follow-up (15 days, 30 days, 90 days, and 180 days). To evaluate the relationship between attitude toward antipsychotic medication (assessed with DAI) and all-cause treatment discontinuation (as the outcome variable), 2 Cox regression analysis models were used. The first model assessed the relationship between DAI at baseline (all patients on risperidone) and all-cause treatment discontinuation. The second model assessed the relationship between DAI at 15 days (patients on either olanzapine or quetiapine) and all-cause treatment discontinuation. Hazard ratios (HR) from the Cox regression analyses were adjusted for gender, age, race, antipsychotic drug (olanzapine or quetiapine), antipsychotic naïve condition before enrolling in the trial (as a dichotomous yes/no variable), and psychopathology (as PANSS total score). All statistical tests were 2-tailed. The level of significance was set at $P < .05$. Data exploration was performed using SPSS for Windows version 12.0.

Results

Subjects

A total of 42 patients completed the DAI (DAI responders), while 8 patients refused to complete the DAI items (DAI non-responders). The 42 DAI responders formed the study sample. Age ($P = .504$), gender ($P = .124$), race ($P = .311$), antipsychotic drug (quetiapine or olanzapine) ($P = 1.000$), antipsychotic-naïve condition ($P = 1.000$), diagnosis ($P = .920$), and treatment discontinuation ($P = 1.000$) were not significantly different between DAI responders and DAI non-responders. However, DAI responders had lower PANSS total scores than DAI non-responders (93.6 [18.3] vs 128.0 [12.3], $P < .001$).

Of the 42 patients who formed the study sample, only 29 (69%) continued the medication through the entire 6-month follow-up, while 13 (31%) discontinued the medication. No significant differences in age ($P = .684$), gender ($P = .398$), race ($P = .350$), diagnosis ($P = .717$), antipsychotic naïve condition ($P = .836$), or type of antipsychotic treatment ($P = .899$) were observed between patients who discontinued the medication and those who completed the 6-month follow-up. The sociodemographic characteristics of the 42 participants are summarized in Table 1.

Treatment Discontinuation

Figure 1 illustrates the survival rates of all-cause discontinuation over the follow-up period. Of the 13 patients (31%) who discontinued their antipsychotic medication; 4 discontinued due to lack of antipsychotic efficacy, 5 were lost to follow-up; and 4 were withdrawn due to poor adherence to treatment.

Attitude Toward Antipsychotic Medication

DAI scores over the 6-month follow-up were: baseline (0.7 [4.0]), 15 days (2.6 [4.3]), 30 days (2.4 [4.8]), 90 days (3.0 [3.8]), and 180 days (2.6 [3.9]). As shown in Figure 2, DAI scores were greater than 0 at all assessments, which means that general patient attitude toward medication was positive. The DAI score at 15 days was significantly higher than at baseline ($P = .021$), while differences between DAI score at baseline and at 30 days ($P = .194$), 90 days ($P = .091$), or 180 days ($P = .462$) were not significant. DAI scores were not related to specific causes of treatment discontinuation (lack of efficacy, loss to follow-up, and poor treatment adherence; all $P > .05$).

DAI score at baseline was significantly higher in patients who completed the follow-up than in those who discontinued the antipsychotic medication ($P = .021$). No significant differences in DAI scores at 15 days ($P = .484$), 30 days ($P = .456$), or 90 days ($P = .534$) were observed between patients who discontinued the medication and those who completed the 6-month follow-up.

No significant differences in any DAI scores (baseline, 15 days, 30 days, 90 days, or 180 days) were found between treatment groups (quetiapine vs olanzapine) at any assessment (all $P > .05$).

Relationship Between Treatment Discontinuation and Attitude Toward Medication

The relationship between treatment discontinuation (as the outcome variable) and attitude toward medication at baseline (all patients on risperidone) and at 15 days (patients on either olanzapine or quetiapine) was assessed by means

Table 1. Sociodemographic and Clinical Characteristics of Sample (n = 42)

Age, mean (SD), y	16.1 (1.3)
Sex, mean (SD), n (%)	
Male	34 (81.0)
Female	8 (19.0)
Race or ethnic group, n (%)	
Caucasian	34 (81.0)
Caribbean black	1 (2.4)
Hispanic	6 (14.3)
Gipsy	1 (2.4)
DSM-IV diagnosis at 6 months, n (%)	
Schizophrenia	19 (45.2)
Psychotic bipolar disorder	14 (33.3)
Other psychosis	9 (21.4)
Never treated with antipsychotic medication, n (%)	21 (50.0)
Antipsychotic treatment, n (%)	
Olanzapine	22 (52.4)
Quetiapine	20 (47.6)
Substance abuse (DSM-IV criteria), n (%)	1 (2.4)

No significant differences in age (P = .684), gender (P = .398), race (P = .350), diagnosis (P = .498), previous antipsychotic treatment (P = 0.836), or antipsychotic treatment of study (olanzapine or quetiapine) (P = .899) were observed between patients who discontinued the medication and those who completed the 6-month follow-up.

of 2 Cox regression analyses. As shown in Table 2, higher DAI scores at baseline were related to lower treatment discontinuation (adjusted hazard ratio [HR] = 0.81; 95% CI, 0.68-0.96); P = .016). In contrast, DAI scores at 15 days were unrelated to treatment discontinuation (adjusted HR = 1.0; 95%CI, 0.82-1.23); P = .998).

Discussion

The results of this study show that a better attitude toward antipsychotic medication at first lifetime psychiatric admission for a first early-onset psychotic episode (ie, at the study baseline assessment) was significantly related to lower all-cause treatment discontinuation. It has been previously reported that antipsychotic drug discontinuation in adolescent population increases the risk of clinical relapse and poor outcome.[24] Hence, our results suggest that antipsychotic discontinuation in first-episode adolescent psychosis patients may be related to initial attitude toward antipsychotic medication.

Adolescence is a period of life transition from parental and social dependence to individual independence. This stage involves extensive physical and emotional changes. Suffering from a severe psychiatric disease, such as psychosis, may interfere with the normal growth and developmental processes during this period. Adolescents with visible changes in physical appearance (such as weigh gain or EPS due to antipsychotic drugs) are at risk for social adjustment difficulties, and they are specifically predisposed to noncompliance with medical treatments that have a detrimental affect on physical appearance.[38-40] Indeed, becoming part of

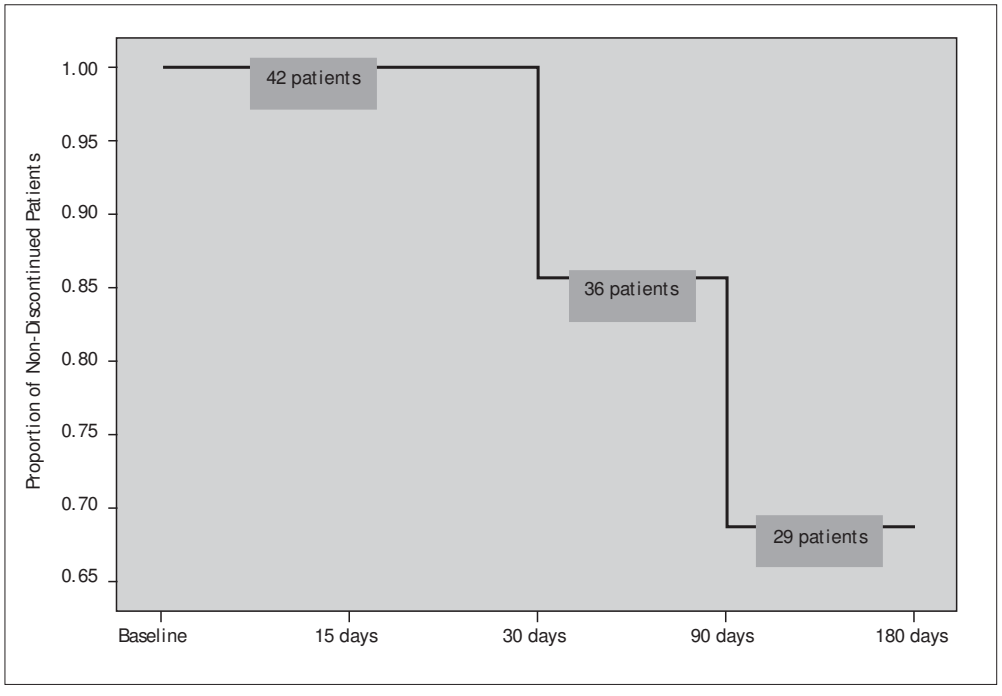

Figure 1. Discontinuation for any cause during the 6-month follow-up.

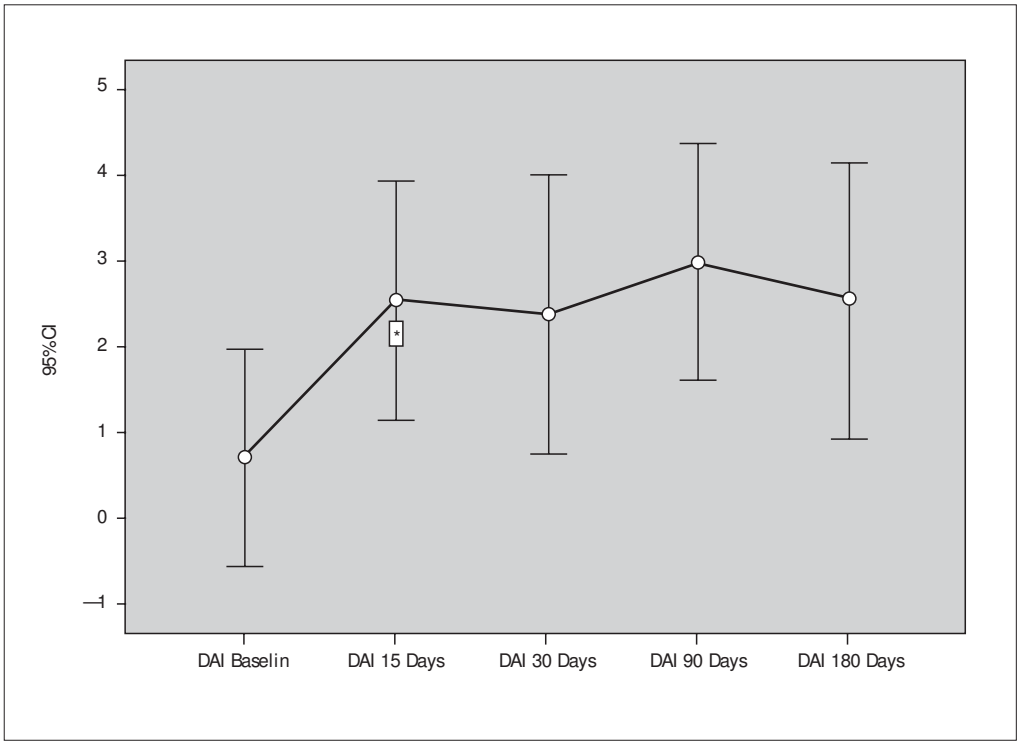

Figure 2. DAI scores (mean and 95%confidence interval) during the 6-month follow-up. DAI indicates drug attitude inventory; CI, confidence interval. Although DAI scores range from −10 to + 10, the Figure shows only the interval from −1 to + 5. Comparison with DAI at Baseline $P < .05$.

Table 2. Relationship Between Treatment Discontinuation and Attitude Toward Medication

	All-Cause Treatment Discontinuation —DAI at Baseline	All-Cause Treatment Discontinuation —DAI at 15 Days
DAI at baseline	Adjusted HR = 0.811 (95%CI, 0.684-0.961), $P = .016$	
DAI at 15 days		Adjusted HR = 1.015 (95%CI, 0.828-1.243), $P = .888$
Gender	Adjusted HR = 0.351 (95%CI, 0.043-2.883), $P = .330$	Adjusted HR = 0.520 (95%CI, 0.057-4.732), $P = .562$
Age	Adjusted HR = 0.927 (95%CI, 0.554-1.550), $P = .772$	Adjusted HR = 0.790 (95%CI, 0.427-1.463), $P = .454$
Race	Adjusted HR = 1.385 (95%CI, 0.706-2.717), $P = .343$	Adjusted HR = 1.030 (95%CI, 0.580-1.828), $P = .920$
Antipsychotic drug[a]	Adjusted HR = 1.227 (95%CI, 0.331-4.544), $P = .759$	Adjusted HR = 1.423 (95%CI, 0.281-7.211), $P = .670$
Absence of previous treatment with antipsychotic[b]	Adjusted HR = 0.764 (95%CI, 0.233-2.505), $P = .657$	Adjusted HR = 1.036 (95%CI, 0.240-4.468), $P = .962$
Psychopathology (PANSS total score at baseline)	Adjusted HR = 0.980 (95%CI, 0.940-1.022), $P = .341$	
Psychopathology (PANSS total score at 15 days)		Adjusted HR = 1.015 (95%CI, 0.995-1.099), $P = .078$

DAI indicates drug attitude inventory; HR, hazard ratio; CI, confidence interval.
[a]Antipsychotic drug: olanzapine or quetiapine.
[b]Absence of previous treatment with antipsychotic treatment before enrolling in the trial, as a dichotomous (yes/no) variable.

a peer group is a very important aspect of adolescent life, and the stigma of a psychiatric diagnosis and interruptions of daily activities by treatment requirements may make it difficult to feel part of a peer group. Adolescent patients tend to feel that they need to hide their medical conditions from peers to avoid negative appraisals and stigmatization.[41] Thus, different feelings of embarrassment about taking medication may contribute to antipsychotic discontinuation during adolescence.[2,6,15,20,22] In this sense, assessing attitude toward antipsychotic medication provides a useful instrument to predict risk of medication discontinuation in this population.

Our results show that attitude toward medication over follow-up was positive (all DAI scores were greater than 0). However, as shown in Figure 2, DAI scores tended to increase throughout the study, especially during the first 2 weeks. This is in line with previous reports on DAI increases during the initial weeks of antipsychotic follow-up[26] and the importance of assessing attitude toward medication in the early stages of antipsychotic treatment.

It is worth noting that rates of antipsychotic discontinuation in adolescence[21] have been reported to be similar to those found in adult schizophrenia patients.[3] Our results showed a lower rate of drug discontinuation during the 6-month follow-up (31%) than other 12-month follow-up studies (about 70%).[21] However, our discontinuation rate (31%) was higher than that found in a 3-month follow-up in first-onset psychosis (19%).[6]

This study had limitations that could potentially impact the generalizability of the findings. Firstly, the small sample size may limit the study's ability to detect differences (type II error) and makes it difficult to do any sort of subgroup analyses, eg, between different diagnoses. Secondly, this study did not employ an objective measure of adherence, such as plasma levels of antipsychotics. Adherence was assessed by questioning patients and their parents. Thirdly, there was a wide range of concomitant medications, including benzodiazepines, antidepressants, anticonvulsants, lithium, and anticholinergics. Although the wide variety of prescriptions may have affected analyses of attitude toward antipsychotic medication, the results may be more generalizable to the adolescent population than studies comprising carefully selected, homogenous groups of patients. Fourthly, the DAI focuses on rather global aspects of medication benefits, and not medication-specific effects or side effects. Fifthly, patients were recruited on admission to a psychiatric hospital, which may bias the findings toward individuals with more severe illness. Nevertheless, hospitalization was the general rule for a psychotic episode in children and adolescents and there were no private facilities for hospitalizing children and adolescents in our region when this study was conducted. Thus, we believe that our study sample was representative of adolescent psychosis in our region. Finally, we used a heterogeneous sample of diagnoses, which in turn may be important in terms of generalization of the results.

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