Persistence in Therapy With Risperidone and Aripiprazole in Pediatric Outpatients: A 2-Year Naturalistic Comparison

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ABSTRACT

Objective: The practical effectiveness of second-generation antipsychotics in children and adolescents is an understudied issue. It is a crucial area of study, though, because such patients are often treated for long-lasting disorders.

Methods: We carried out a 24-month (March 2012–March 2014) observational study on an unselected population of pediatric outpatients treated with risperidone, aripiprazole, olanzapine, or quetiapine aiming to (1) describe drug use, (2) compare post hoc the discontinuation rates due to specific causes and dose adjustments by Kaplan-Meier analyses between drugs, and (3) analyze predictors influencing these outcomes by Cox multivariate models.

Results: Among 184 pediatric patients, 77% patients were prescribed risperidone, and 18% were prescribed aripiprazole. Olanzapine or quetiapine were scantly used; therefore, they were excluded from analyses. Risperidone was prevalent in younger, male patients with disruptive behavioral disorders; aripiprazole, in patients with tic disorders. Overall, discontinuations occurred mostly in the first 6 months, and, at 24 months, the discontinuation numbers were similar between users of risperidone and aripiprazole (41.5% vs 39.4%). In univariate analyses, dose reduction was higher for aripiprazole ($P = .033$). Multivariate analyses yielded the following predictors: for all-cause discontinuation, baseline severity (hazard ratio [HR] = 1.48, $P = .001$) and dose increase (HR = 3.55, $P = .001$); for patient-decided discontinuation, dose change (increase: HR = 6.43, $P = .004$; reduction: HR = 7.89, $P = .049$) and the presence of concomitant drugs (HR = 4.03, $P = .034$), while autistic patients discontinued less (HR = 0.23, $P = .050$); for clinician-decided discontinuation due to adverse drug reactions, baseline severity (HR = 1.96, $P = .005$) and dose increase (HR = 5.09, $P = .016$); for clinician-decided discontinuation due to inefficacy, baseline severity (HR = 2.88, $P = .014$) and the use of aripiprazole (HR = 5.55, $P = .013$); for dose increase, none; for dose reduction, the occurrence of adverse drug reactions (HR = 4.74, $P = .046$), while dose reduction was less probable in autistic patients (HR = 0.22, $P = .042$).

Conclusions: The findings of this study show a similarity between the overall effectiveness of risperidone and aripiprazole in a real-life pediatric outpatient setting.

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The use of second-generation antipsychotics (SGAs) in pediatric patients (children and adolescents) has increased substantially during the past decade, and SGAs are currently prescribed both in-label and off-label for a wide variety of disorders, such as schizophrenia spectrum disorders, irritability and aggression in autism spectrum disorders or intellectual disabilities, tic disorders and Tourette disorder, mood disorders (mainly bipolar), conduct disorders, attention-deficit/hyperactivity disorder (ADHD), eating disorders, anxiety disorders, and sleep disorders.[1–4] The use of SGAs has also been encouraged by the notion that they are safer than typical antipsychotics, mainly because of their better neurologic profile[5,6]; however, recent studies[7–12] have highlighted important safety concerns. The issue of safety remains insufficiently explored as risk is especially connected to long-term use, while labeling indications, and, therefore, most safety data, refer to short-term treatment. Moreover, children and adolescents seem to be more sensitive to several SGA-related adverse drug reactions (ADRs) than adults,[9,12,13] such as hyperprolactinemia, cardiovascular-related adverse events, weight gain and related metabolic features, and neurologic disturbances. Although many of these ADRs are characterized by progressive onset and remain as subclinical features for months or even years before clinical recognition, their impact on the maintenance of drug therapy is not negligible.[14] In this view, the overall persistence of patients in treatment may represent a more relevant outcome, as compared to safety measures. The main indicator of persistence in therapy is the time to all-cause drug discontinuation, which has also been recognized as an important outcome for clinical trials[15] because it reflects the overall judgment on the risk-benefit balance. The persistence in therapy with SGAs has been investigated in adults with schizophrenia, finding lower discontinuation rates with olanzapine, clozapine, and risperidone than with

Clinical Points

- The benefit-risk ratio of second-generation antipsychotics for the long-term treatment of pediatric outpatients is understudied. Measuring the persistence in therapy may provide more practical results as compared to clinical assessment scales, as it encompasses efficacy, safety, patients' compliance, and caregivers' attitude toward therapy at the same time.
- We found that risperidone and aripiprazole had similar effectiveness: by 24 months of follow-up, 41.5% patients on risperidone and 39.4% on aripiprazole discontinued therapy. The main reason for discontinuation was patient-decided (caregiver-decided), while clinical decisions connected to adverse drug reactions or inefficacy accounted for a minority of discontinuations. Interestingly, the use of aripiprazole was associated with dose reduction more than risperidone.
- Our data suggest that more collaboration is needed between clinicians and caregivers to limit the negative impact of subclinical adverse events on quality of life, such that discontinuation rates can be reduced. Therapeutic drug monitoring and pharmacogenetics may also make current antipsychotic therapies more "patient friendly" and improve compliance.

typical antipsychotics.[16,17] Another study[18] analyzed time and cause of discontinuation in patients with schizophrenia, finding clozapine to be at lower risk for all-cause discontinuation versus oral treatment with olanzapine. In pediatric patients, some studies[19,20] analyzed the rates of SGA discontinuation in patients with schizophrenia or psychosis, reporting different results depending on the study method. A drug claims–based study described that three–quarters of patients with schizophrenia discontinued their initial antipsychotic during the first 6 months of treatment,[19] while a naturalistic study in patients with first psychotic episodes demonstrated lower discontinuation rates during the first 6 months (44.5%), which increased to 70.9% after 2 years[20]; moreover, both studies[19,20] demonstrated no difference in discontinuation rates between SGAs. As opposed to studies on psychotic and schizophrenic pediatric patients, only 1 study[21] investigated the naturalistic use of SGAs in children and adolescents affected by any mental disorder, which is a situation typical of real-life tertiary care settings. Moreover, no systematic analysis of predictors associated with SGA discontinuation has yet been conducted on these mixed pediatric populations. This is surprising, as these populations constitute a significant number of SGA users in real-life, often under off-label prescriptions. Investigating unselected populations is crucial in light of the recent label extensions of risperidone and aripiprazole.[22–25] These extensions may lead to a further increase in the prevalence of use among pediatric and adolescent patients affected by diverse chronic psychiatric disturbances that require long-term (even life-long) drug therapy. In order to conduct a real-life investigation of the effectiveness of SGAs, we carried out a naturalistic, multicenter study of the use of SGAs in unselected pediatric patients of tertiary-care clinics aiming to (1) describe the use of SGAs in the study population; (2) compare the persistence in therapy in terms of dose adjustment and treatment discontinuation, based on the SGA chosen; and (3) analyze predictors influencing the persistence in therapy.

METHODS

Study Setting

The operational framework of the current study was an active pharmacovigilance project on the safety and efficacy of 4 SGAs (risperidone, aripiprazole, olanzapine, and quetiapine) in children and adolescents. It was approved by the Ethics Committees of the participating structures. The project was carried out in Italy between March 2012 and March 2014 by 2 pharmacology units (for monitoring and laboratory examinations) and 3 tertiary-care neuropsychiatry departments (for recruitment and clinical evaluation) that only follow outpatients undergoing routine neuropsychiatric rehabilitation (no inpatients or emergency admissions); therefore, the study sample was heterogeneous with respect to time since diagnosis and past treatments. While the principal clinical site recruited a balanced patient population, the other 2 clinical sites recruited patients according to their practice specialty, respectively, autism spectrum disorders and tic disorders (see Supplementary eTable 1 for more details). All clinicians who routinely managed therapies with SGAs were asked to participate. There was no selection of participating investigators, and all clinicians involved agreed to participate. They were informed about the methods and aims of the framework project, but not about the objective and outcomes of single post hoc studies. Inclusion criteria for the framework pharmacovigilance project were to be under 18 years of age, to take 1 of the 4 SGAs under study in scheduled daily oral administrations, and to have informed consent signed by the parents. No exclusion criterion was applied in terms of psychiatric condition, treatment indication, or use of additional drugs. New diagnoses were formulated according to *DSM-IV-TR*. Drug treatments were chosen only on the basis of clinical judgment, and treatment was open-label. As compared to the current Italian regulations, drug prescription in this study was mainly off-label (see Table 1). Following the clinical routine, neuropsychiatric control visits were scheduled approximately every 3 months. However, patients could be visited more often, based on medical needs and at clinicians' discretion. Caregivers were routinely instructed to refer any undesired event to the clinicians by phone contact. After this phone contact, 1 or more additional visits could be scheduled earlier than 3 months after drug initiation, as needed. Alternatively, clinicians could schedule control visits directly 2 to 4 weeks from drug prescription, in severe cases or when an adverse effect was suspected. Control visits comprised objective examination, neuropsychiatric examination, blood examination, electrocardiographs, assessment of ADRs, and therapy reassessment and adjustment.

Study Design

For this study, only a part of available data were selected, comprising patients' age; sex; neuropsychiatric diagnoses

Table 1. Summary of Official Therapeutic Indications in Italy and Main Off-Label Uses for Drugs Under Study

Official Indication	Age, y	Additional Off-Label Uses
Risperidone		
Schizophrenia	> 18	Behavioral disturbances, such as aggression, irritability, and agitation, in the context of autism spectrum disorders and/or intellectual disability. Treatment may last for months or years.
Manic episodes in bipolar disorders	> 18	
Aggressive behavior in Alzheimer's dementia	…	
Aggressive behavior in intellectual disability	> 5	Treatment may last up to 6 weeks.
Aripiprazole		
Schizophrenia	> 15	Behavioral disturbances, such as aggression, irritability, and agitation, in the context of autism spectrum disorders and/or intellectual disability. Treatment may last for months or years. Also used as a second-line medication for patients who are overweight or who experienced hyperprolactinemia with risperidone. Preferred over risperidone for patients who also display obsessions/compulsions or tics or who are diagnosed with Tourette disorder.
Manic episodes in bipolar disorders	> 13	
Prevention of relapse of manic episodes in bipolar disorders	> 18	
Olanzapine		
Schizophrenia	> 18	Used as a third-line medication for behavioral disturbances, such as aggression, irritability, and agitation, in the context of autism spectrum disorders and/or intellectual disability. Treatment may last for months or years.
Manic episodes in bipolar disorders	> 18	
Quetiapine		
Schizophrenia	> 18	Used as a third-line medication for behavioral disturbances, such as aggression, irritability, and agitation, in the context of autism spectrum disorders and/or intellectual disability. Treatment may last for months or years.
Treatment and prevention of relapse of manic and depressive episodes in bipolar disorders	> 18	

Symbol: … = no age limitation.

according to *DSM-IV-TR*; baseline severity as scored by the Clinical Global Impressions-Severity (CGI-S) scale[26]; drug-naive status; all drug therapies, with doses and dates of start and end; dose adjustments with date; and therapy discontinuations or switches with date and reason; regarding ADRs, only dates of occurrence were collected for the purpose of this work.

Patients were followed up to 24 months from enrollment, independent of time since diagnosis or past treatments. The persistence of patients with the initial drug was considered as a marker of effectiveness, and we analyzed factors that could have influenced such persistence. Primary outcomes were time to antipsychotic discontinuation (all-cause discontinuation); time to antipsychotic discontinuation due to families' decision to interrupt either the drug treatment or the whole neuropsychiatric care (patient-decided discontinuation); and time to antipsychotic discontinuation due to clinicians' decisions, with either ADRs or inefficacy as a reason (clinician-decided discontinuation due to ADR and clinician-decided discontinuation due to inefficacy). Secondary outcomes were time to antipsychotic dose increase or time to antipsychotic dose reduction. No patient was considered twice for either secondary or primary end points; the only possibility was that a patient could be considered first for 1 secondary end point (dose change) and subsequently for 1 primary end point (discontinuation); moreover, the occurrences of dose increase or reduction during any preceding visit were used as possible predictors of drug discontinuation. Accordingly, patients who switched drugs were excluded from later evaluations. All treatment-limiting adverse events were recorded.

Data Systematization and Analysis

Analyses of patients' demographic and clinical characteristics comprised drug type, drug dose, drug-naive status, presence of concomitant medications, age at enrollment, sex, baseline severity measured by the CGI-S scale, and *DSM-IV-TR* diagnosis group. Diagnoses were categorized as follows: disruptive behavioral disorders (mainly comprising agitation, irritability, and aggressive behavior) plus autism spectrum disorders, disruptive behavioral disorders plus intellectual disabilities, psychosis spectrum disorders, and tic disorders or Tourette disorder; other disorders (comprising bipolar disorders, obsessive-compulsive disorders, eating disorders, attention-deficit/hyperactivity disorders, conduct disorders, and oppositional-defiant disorders) were grouped together after data collection because of the limited number of patients with these diagnoses. Patient characteristics were described as either means with standard deviation or numbers and percentages. As shown in the results, due to the limited number of patients treated with olanzapine and quetiapine, our work focused on a risperidone versus aripiprazole comparison. Patient characteristics were compared between users of risperidone and aripiprazole by means of *t* tests for independent samples and χ^2 tests. The time course of risperidone and aripiprazole therapies was initially described in a simplified way, by detailing the numbers of patients who met each study outcome by definite time points: 3, 6, 9, 12, 18, and 24 months (study end). This use of time points was done to allow comparability with other studies, even if our assessments were not necessarily conducted at fixed times. Persistence in therapy was further analyzed by Kaplan-Meier curves with a nonparametric log-rank test comparing users of risperidone and aripiprazole, an approach that more accurately reflects the naturalistic design. Corrected analyses were carried out by Cox proportional hazards regressions, evaluating for each outcome the hazard ratios (HRs) associated with several factors, comprising drug type (risperidone vs aripiprazole), cumulative drug exposition until the outcome, drug-naive status defined as the absence of past scheduled treatments with psychoactive drugs,

presence of concomitant medications, age at enrollment, sex, *DSM-IV-TR* diagnosis group, baseline severity measured by the CGI-S scale, and occurrence of ADRs, dose increase, and dose reduction (only for models evaluating the discontinuation outcomes). For all statistical analyses, *P* values < .05 (2-tailed) were considered significant. Statistical analyses were conducted using SPSS version 22 (IBM, Chicago, Illinois).

RESULTS

Description of the Study Population

This effectiveness study comprised 184 pediatric patients, with mean ± SD age of 12.5 ± 3.1 years, who were predominantly boys (148, 80.4%). According to *DSM-IV-TR*, 59 patients (32.1%) were diagnosed with disruptive behavioral disorders plus autism spectrum disorders, 44 (23.9%) were diagnosed with disruptive behavioral disorders plus intellectual disabilities, 26 (14.1%) were diagnosed with tic disorders or Tourette disorder, 15 (8.2%) were diagnosed with psychosis spectrum disorders, and 40 (21.7%) were diagnosed with other disorders (comprising bipolar disorders, obsessive-compulsive disorders, eating disorders, attention-deficit/hyperactivity disorders, conduct disorders, and oppositional defiant disorders). Patients were mainly treated with risperidone (142, 77.2%) and, secondarily, with aripiprazole (33, 17.9%), followed by olanzapine (6, 3.3%) and quetiapine (3, 1.6%). Risperidone dose ranged from 0.25 to 4.5 mg/day (mean ± SD 1.41 ± 0.91), aripiprazole from 2.5 to 25 mg/day (mean ± SD 8.54 ± 5.34), olanzapine from 5 to 20 mg/day (mean ± SD 11.67 ± 6.83), and quetiapine from 100 to 300 mg/day (mean ± SD 216.7 ± 104.1). Overall, 61 patients (33.2%) were drug-naive. Forty patients took concomitant medications, on average 1.7 ± 1.1 different drugs per day. Valproate was the most frequent (administered to 17 patients), followed by methylphenidate and sertraline (5 patients each); melatonin, lithium carbonate, clothiapine as needed, and fluoxetine (3 each); delorazepam as needed, diazepam as needed, oxcarbazepine, hydroxyzine as needed, promazine as needed, biperiden, topiramate, carbamazepine, and haloperidol as needed (2 each); plus 14 other drugs used only by individual patients. When comparing patients treated with different SGAs, those treated with olanzapine and quetiapine could not be analyzed due to the limited prevalence of use; however, no clinically meaningful difference was noticed as compared with users of risperidone and aripiprazole. As shown in Table 2, patients treated with risperidone were younger and more predominantly male than those treated with aripiprazole. Aripiprazole was prescribed more often than risperidone to patients with

Table 2. Sample Characteristics[a]

Characteristic	Risperidone (n = 142)	Aripiprazole (n = 33)	*P* (*t* Test or χ^2)
Age at enrollment, y	11.9 ± 3.0	14.1 ± 3.0	< .001
Sex, male	121 (85.2)	20 (60.6)	.002
DSM-IV diagnostic group			
DBD + ASD	47 (33.1)	6 (18.2)	.093
DBD + ID	39 (27.5)	4 (12.1)	.065
PSD	10 (7.0)	4 (12.1)	.474
TD/TS	15 (10.6)	11 (33.3)	.002
Other	31 (21.8)	8 (24.2)	.764
CGI-S baseline severity	4.1 ± 1.4	4.4 ± 1.2	.414
Drug-naive	53 (37.3)	8 (24.2)	.155
Concomitant drugs	30 (21.1)	10 (30.3)	.258

[a]The distribution of clinical and demographic variables is shown with respect to the chosen drug. Continuous variables are shown as means ± SDs and were tested for differences by *t* tests. Categorical variables are shown as numbers and percentages and were tested for differences by χ^2 tests.

Abbreviations: CGI-S = Clinical Global Impressions-Severity scale, DBD + ASD = disruptive behavioral disorders plus autism spectrum disorders, DBD + ID = disruptive behavioral disorders plus intellectual disabilities, PSD = psychosis spectrum disorders, TD/TS = tic disorders or Tourette disorder.

Table 3. Schematized Time Course of Second-Generation Antipsychotic Therapies[a]

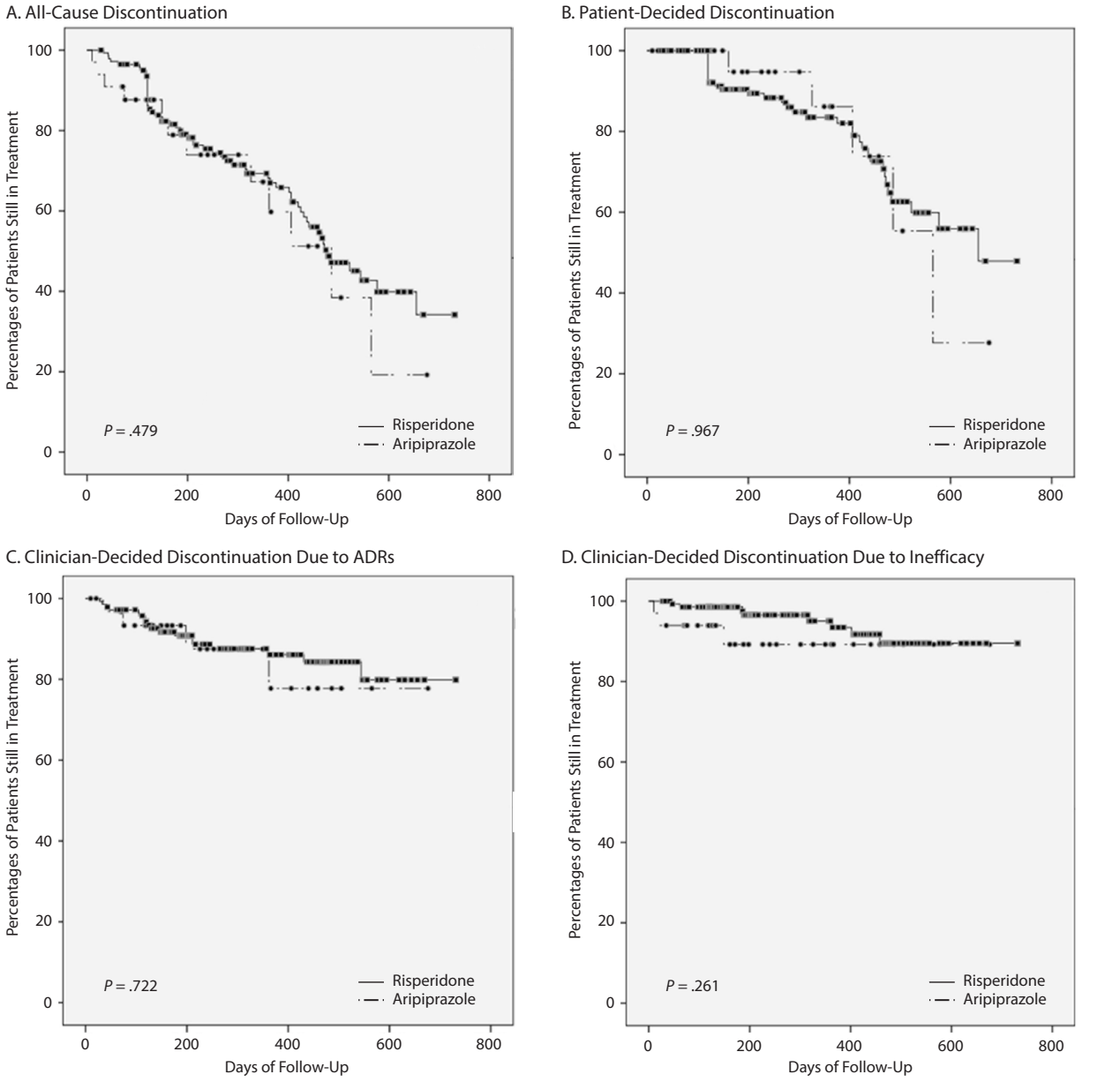
	Risperidone (n = 142)						Aripiprazole (n = 33)					
	Primary Outcomes				Secondary Outcomes		Primary Outcomes				Secondary Outcomes	
Time Point (Months)	ACD	PdD	CdD: ADR	CdD: Inef	DI	DR	ACD[b]	PdD	CdD: ADR	CdD: Inef	DI	DR
Events Occurred Between Each Time Point												
0–3	6 (4.2)	0	4 (2.8)	2 (1.4)	13 (9.2)	5 (3.5)	4 (12.1)	0	2 (6.1)	2 (6.1)	1 (3.0)	3 (9.1)
3–6	20 (14.1)	12 (8.5)	8 (5.6)	0	11 (7.7)	5 (3.5)	2 (6.1)	1 (3.0)	0	1 (3.0)	4 (12.1)	2 (6.1)
6–9	8 (5.6)	3 (2.1)	3 (2.1)	2 (1.4)	12 (8.5)	3 (2.1)	2 (6.1)*	0	1 (3.0)	0	2 (6.1)	2 (6.1)
9–12	4 (2.8)	3 (2.1)	0	1 (0.7)	6 (4.2)	2 (1.4)	1 (3.0)	1 (3.0)	0	0	1 (3.0)	1 (3.0)
12–18	18 (12.7)	13 (9.2)	2 (1.4)	3 (2.1)	2 (1.4)	1 (0.7)	3 (9.1)	2 (6.1)	1 (3.0)	0	0	0
18–24	3 (2.1)	2 (1.4)	1 (0.7)	0	2 (1.4)	0	1 (3.0)	1 (3.0)	0	0	0	0
Cumulative Events Occurred by Each Time Point												
0–3	6 (4.2)	0	4 (2.8)	2 (1.4)	13 (9.2)	5 (3.5)	4 (12.1)	0	2 (6.1)	2 (6.1)	1 (3.0)	3 (9.1)
0–6	26 (18.3)	12 (8.5)	12 (8.5)	2 (1.4)	24 (16.9)	10 (7.0)	6 (18.2)	1 (3.0)	2 (6.1)	3 (9.1)	5 (15.2)	5 (15.2)
0–9	34 (23.9)	15 (10.6)	15 (10.6)	4 (2.8)	36 (25.4)	13 (9.2)	8 (24.2)*	1 (3.0)	3 (9.1)	3 (9.1)	7 (21.2)	7 (21.2)
0–12	38 (26.8)	18 (12.7)	15 (10.6)	5 (3.5)	42 (29.6)	15 (10.6)	9 (27.3)*	2 (6.1)	3 (9.1)	3 (9.1)	8 (24.2)	8 (24.2)
0–18	56 (39.4)	31 (21.8)	17 (12.0)	8 (5.6)	44 (31.0)	16 (11.3)	12 (36.4)*	4 (12.1)	4 (12.1)	3 (9.1)	8 (24.2)	8 (24.2)
0–24	59 (41.5)	33 (23.2)	18 (12.7)	8 (5.6)	46 (32.4)	16 (11.3)	13 (39.4)*	5 (15.2)	4 (12.1)	3 (9.1)	8 (24.2)	8 (24.2)

[a]The numbers and percentages of patients who met each study outcome are reported. Numbers in the top half of the table refer to events that occurred between each time point; the lower half refers to the sum of events that occurred until each time point.

[b]ACD is the sum of all other primary outcomes except in the case of values indicated by an asterisk (*), which reflect the withdrawal of 1 patient from treatment because of resolution.

Abbreviations: ACD = all-cause discontinuation, CdD:ADR = clinician-decided discontinuation due to adverse drug reactions, CdD:Inef = clinician-decided discontinuation due to drug inefficacy, DI = dose increase, DR = dose reduction, PdD = patient-decided discontinuation.

Figure 1. Persistence in Therapy[a]



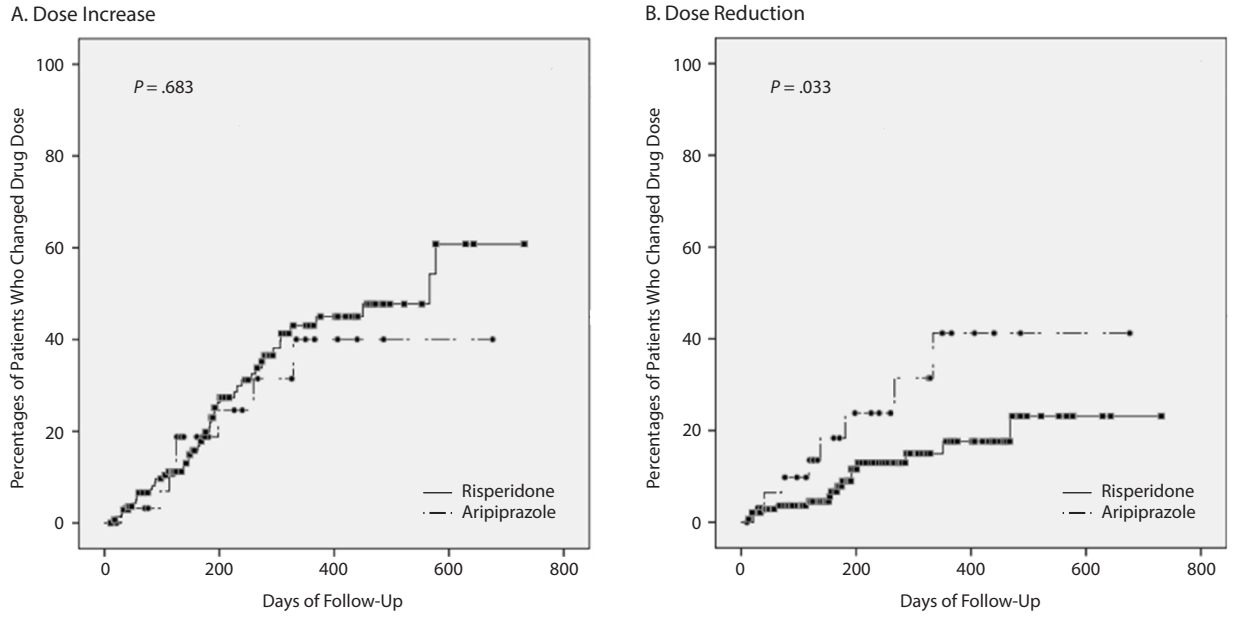
[a]Kaplan-Meier curves are reported. The 4 main outcomes are reported separately. Dots represent censored data.
Abbreviation: ADR = adverse drug reaction.

tic disorders or Tourette disorder ($P = .002$). No difference emerged in drug-naive status, presence of concomitant drugs, or presence of a specific class of concomitant drugs between users of risperidone or aripiprazole.

Persistence in Therapy

By the study end point of 24 months, 41.5% of patients (59/142) treated with risperidone discontinued therapy, as compared to 39.4% (13/33) with aripiprazole. By the study end, 32.4% of patients (46/142) treated with risperidone increased drug dose as compared to 24.2% (8/33) with aripiprazole; conversely, 11.3% (16/142) reduced the dose of risperidone, 24.2% (8/33) of aripiprazole. Schematized time courses are shown in Table 3 for comparative purposes, organized in 3-month intervals. However, study end points were not assessed at fixed time points, but following clinical practice, and they are more accurately described by Kaplan-Meier curves in Figures 1 and 2. The persistence of patients in therapy is reported with respect to all-cause discontinuation, patient-decided discontinuation, clinician-decided discontinuation due to ADR, and clinician-decided discontinuation due to inefficacy; no significant drug-related difference emerged (Figure 1), although aripiprazole tended to be discontinued by clinicians due to inefficacy earlier than risperidone (see Figure 1D). Dose adjustment was also analyzed by Kaplan-Meier curves (Figure 2), reporting that aripiprazole dose was reduced more often than was risperidone dose ($P = .033$; see Figure 2B).

Figure 2. Dose Adjustment[a]



[a]Kaplan-Meier curves are reported. The 2 secondary outcomes are reported separately. Dots represent censored data.

Factors Influencing the Persistence in Therapy

Multivariate Cox regression models were used to conduct corrected analyses. Tested factors were drug type (risperidone vs aripiprazole), cumulative drug dose taken until the outcome, drug-naive status, presence of concomitant medications, age at enrollment, sex, *DSM-IV-TR* diagnosis group (see descriptive data), baseline severity measured by the CGI-S scale, occurrence of ADRs, and occurrence of dose increase and reduction (only for models evaluating discontinuations). We report below only statistically significant predictors. For all-cause discontinuation, higher baseline severity (HR = 1.48; 95% CI, 1.17–1.88; $P = .001$) and dose increase (HR = 3.55; 95% CI, 1.68–7.48; $P = .001$) were predictors. For patient-decided discontinuation, the presence of a diagnosis of disruptive behavioral disorders plus autism spectrum disorders protected from discontinuation (HR = 0.23; 95% CI, 0.05–1.00; $P = .050$), while the presence of concomitant medications (HR = 4.03; 95% CI, 1.11–14.6; $P = .034$), dose increase (HR = 6.43; 95% CI, 1.79–23.12; $P = .004$), and dose reduction (HR = 7.89; 95% CI, 1.01–63.54; $P = .049$) favored discontinuation. Clinician-decided discontinuation due to ADRs was favored by higher baseline severity (HR = 1.96; 95% CI, 1.22–3.12; $P = .005$) and dose increase (HR = 5.09; 95% CI, 1.35–19.2; $P = .016$), while clinician-decided discontinuation due to inefficacy was favored by higher baseline severity (HR = 2.88; 95% CI, 1.24–6.66; $P = .014$) and by the use of aripiprazole as compared to risperidone (HR = 5.55; 95% CI, 2.34–129.22; $P = .013$). No significant result emerged regarding dose increase; dose reduction was less probable in the presence of disruptive behavioral disorders plus autism spectrum disorders (HR = 0.22; 95% CI, 0.05–0.95; $P = .042$), but was favored by the occurrence of ADRs (HR = 4.74; 95% CI, 1.03–21.74; $P = .046$); in this model, the use of aripiprazole was a nonsignificant predictor.

Treatment-Limiting Adverse Events

With respect to the 22 discontinuations due to ADRs, patients incurred 1 or more of the following events judged to be related to the drug under study: excessive appetite and clinically relevant weight increases (> 7%) in 12 cases (54.5%); hyperprolactinemia with complications in 6 cases (27.3%); gynecomastia in 2 male patients and amenorrhea in 4 female patients; and excessive elongation of the QT interval (> 460 ms) in 5 patients (22.7%), of which 2 also had syncope. In addition, 4 patients (18.2%) were excessively sedated, 3 (13.6%) had extrapyramidal symptoms, 2 (9.1%) showed hepatic toxicity as determined by serum aminotransferase levels, and 2 (9.1%) had paradoxical psychiatric reactions; single cases (4.5%) of seizures and severe myalgia were also registered.

Drug Switch

Following clinician-decided discontinuations, another drug was always prescribed, except for 1 case of resolution. Risperidone was substituted by aripiprazole in 51.9% cases (14/27), by olanzapine in 7.4% (2/27), and by quetiapine in 3.7% (1/27), while for the other cases (37%; 10/27), either haloperidol or chlorpromazine was chosen. Aripiprazole was substituted by risperidone in 57.1% of the cases (4/7) and by olanzapine in 14.3% (1/7), while in the other cases (28.6%; 2/7), a first-generation antipsychotic was chosen.

DISCUSSION

In this article, we addressed the issue of the long-term effectiveness of SGAs in a real-life tertiary-care pediatric

setting. We initially described the characteristics of the patients and of the drugs they used that were mostly off-label. Risperidone was widely used, probably because treatments may be started in-label in the short-term and only become off-label subsequently, when therapy lasts more than 6 weeks. Aripiprazole was also used in a sizable group of patients and was predominantly chosen for patients with tic disorders. This finding reflects the current off-label practice in Italy and is interesting in view of the most recent labeling indications in the United States that introduced aripiprazole for the treatment of Tourette disorder.[25] The scarce prevalence of use of olanzapine and quetiapine was probably due to the absence of an official indication for behavioral disturbances, but also due to the fact that they also represent third-line choices for off-label uses. Based on drug utilization, we only compared risperidone to aripiprazole with respect to the study aims. The 2 groups of patients were mostly homogeneous, and our patients' characteristics differentiate this sample from that of the only published study on SGAs in a similar setting.[21] The study from Baeza and colleagues[21] had a different distribution of diagnoses with more patients affected by psychosis spectrum disorders, possibly due to a vast recruitment of inpatients, while we enrolled only outpatients, a difference that has to be considered when comparing results. By describing the course of therapies in our sample, we found that discontinuation rates among users of risperidone and aripiprazole had the largest difference at 3 months (3.5% vs 12.1%), while the rates were almost identical at study end (24 months; 41.5% vs 39.4%). These discontinuation rates were markedly lower compared to the ones found by Baeza and colleagues,[21] who reported a 23% discontinuation rate at 3 months, which increased to 58.9% at 12 months. Similar to what they reported, most discontinuations in our study happened in the first 6 months of follow-up.

In addition to describing drug use, we were also able to compare the effectiveness of risperidone and aripiprazole by Kaplan-Meier analyses, finding that discontinuation was similar between the 2 SGAs for every discontinuation outcome. An interesting detail is that at the 1-year time point, aripiprazole was discontinued more often than risperidone by clinicians because of inefficacy. Another difference that emerged regarding secondary outcomes is that aripiprazole was more often subject to dose reduction. These 2 findings, taken together, may support the speculation that clinicians were less confident in using aripiprazole as compared to risperidone or, conversely, that aripiprazole was used more for off-label purposes.

Finally, we investigated predictors for each study outcome in multivariate analyses, finding interesting results—all-cause discontinuation was associated with higher baseline patient severity and dose increase, possibly indicating that dose adjustment and drug switch are frequent choices when treating severe outpatients, and still they may be associated with unfavorable treatment results. For patient-decided discontinuation, the presence of concomitant drugs and drug dosing adjustment (both increased and reduced) constituted predictors. This suggests that compliance to drug therapy may be reduced by a treatment regimen that is too complicated or is changed too often, because it may disrupt caregivers' trust.[27] Conversely, patients affected by autism spectrum disorders were less likely to discontinue drug treatment, a result that is consistent with the finding that parents of children with autism are significantly more adherent to drug therapies than to other treatments,[28] possibly due to the sizable and long-lasting effect of risperidone on irritability for patients with autism spectrum disorders.[29] On the side of clinical decisions, we observed that higher baseline patient severity again represented a predictor for discontinuation, as it did for all-cause discontinuation; furthermore, ADR-related discontinuation was increased by drug dose increase, suggesting that excessive up-titration of SGAs may not be an adequate strategy to achieve treatment effectiveness. Regarding inefficacy-related discontinuation, we confirmed that the use of aripiprazole increased risk; this result may warrant against performing excessive off-label use. Last, we observed that the occurrence of ADRs promoted SGA dose reduction, a result consistent with the aforementioned result regarding ADR-related discontinuation; the use of aripiprazole resulted to be a nonsignificant predictor, a puzzling finding as compared to the neat result of the univariate model.

The present study has the following limitations. Data were gathered within a large active pharmacovigilance project that may have encouraged families to continue the initial treatments, due to the perception of a better care level, and clinicians to monitor ADRs more strictly, preventing the usual heterogeneity that exists between the monitoring habits of different clinicians.[30] The naturalistic design led to a slight inhomogeneity of diagnoses, age, and sex among treatment groups, although it reflects the current prescription practice. Moreover, although this study was broadly inclusive, patients were actually recruited from 3 tertiary-care clinics with some diagnostic specificity (eg, some were renowned for treating autism, others for Tourette disorder); although this could account for the peculiarity of the diagnostic subgroups we reported, preliminary analyses (not shown) excluded that study site had any influence on the measured outcomes. Considering the statistical analyses that we carried out, controls could have been refined by considering the type of concomitant drugs used, the presence of nonpharmacologic treatments, the socioeconomic status of families, and other confounders, but such corrections could have fragmented the study sample excessively and, thus, were deemed to be beyond the purposes of this study. Further research is needed to confirm and expand the results relative to this study sample, as it may not be representative of all clinical settings. More SGAs should be investigated, in order to provide clinicians with a broader panel of real-life effectiveness data that could improve drug choice and suggest viable therapeutic alternatives.

The strength of our study is that we conducted a prospective long-term naturalistic study that is

immediately relevant to the clinical practice. It addresses several unmet needs of pediatric psychopharmacology, as our population mostly comprised patients with disruptive behavioral disorders and autism spectrum disorders or intellectual disabilities.[31] No significant difference in overall discontinuation emerged between risperidone and aripiprazole; only more discontinuation due to inefficacy was observed with aripiprazole, possibly due to a broader off-label use. As the impact of inefficacy-related discontinuation on the overall number of discontinuations is limited, this result indicates similar global effectiveness of risperidone and aripiprazole in a real-life pediatric tertiary-care setting. This is an intriguing result, in view of the better safety profile of aripiprazole, mainly in terms of weight gain and prolactin levels alteration[7–10]; our data suggest that this perceived favorable profile (not investigated in this study) did not actually affect the rate and time of treatment discontinuation. From a clinical point of view, it must be noted that the overall persistence in therapy was low, implying a need for improvement in both choice and management of antipsychotic therapies for pediatric patients. We observed how inefficacy and ADRs led to a relatively small number of discontinuations, as compared to a high caregiver-dependent discontinuation rate. This supports the notion that risperidone and aripiprazole may cause subclinical adverse events leading to "stigma" and decreases in the quality of life of families.[14] As reflected by our data, this may have favored dropouts before clinicians could recognize the true importance of subclinical events and adjust the therapies. These therapeutic failures may be prevented on one side by improving drug therapy with patient-tailored approaches, such as therapeutic drug monitoring[32] and pharmacogenetics.[33,34] On the other side, patient monitoring strategies should become more pervasive, in order to involve health care professionals and caregivers in a cooperative process that minimizes caregivers' discontent and improves the practical effectiveness of SGAs.

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Drug names: aripiprazole (Abilify), biperiden (Akineton), carbamazepine (Tegretol, Epitol, and others), clozapine (Clozaril, FazaClo, and others), diazepam (Valium and others), fluoxetine (Prozac and others), hydroxyzine (Atarax and others), lithium (Lithobid and others), methylphenidate (Ritalin and others), olanzapine (Zyprexa and others), oxcarbazepine (Trileptal and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), sertraline (Zoloft and others), promazine (Sparine and others), topiramate (Topamax and others), valproate (Depacon).

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Persistence in Therapy With Risperidone and Aripiprazole in Pediatric Outpatients: A 2-Year Naturalistic Comparison

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List of Supplementary Material for the article

1. **eTable 1** Patients Recruited by Each Study Site

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Supplementary eTable 1. Patients recruited by each study site.

	Naples	Catania	Bosisio Parini
N	96	46	44
DSM-IV Diagnostic group			
DBD+ASD	36	1	23
DBD+ID	32	4	8
PSD	15	0	0
TD/TS	1	22	3
Other	12	19	10

Legend.

The distribution of patients is shown with respect to the study site. DBD+ASD: disruptive behavioral disorders plus autism spectrum disorders; DBD+ID: disruptive behavioral disorders plus intellectual disabilities; PSD: psychosis spectrum disorders; TD/TS: tic disorders or Tourette's Syndrome.