

Neuromotor Adverse Effects in 342 Youth During 12 Weeks of Naturalistic Treatment With 5 Second-Generation Antipsychotics

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Objective: Second-generation antipsychotic (SGA) effects in youth were monitored to quantify extrapyramidal side effects (EPS) and to identify risk profiles for treatment-emergent EPS.

Method: Data were analyzed for the nonrandomized, prospective Second-generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) inception cohort study. EPS were assessed at baseline and 4, 8, and 12 weeks after naturalistic SGA initiation for schizophrenia, mood, disruptive behavior, and autism spectrum disorders using the Simpson–Angus Scale (SAS), Barnes Akathisia Scale, Abnormal Involuntary Movement Scale (AIMS), and Treatment Emergent Side Effect Scale. Drug-induced parkinsonism was defined by incident mean SAS score >0.33 , anticholinergic initiation, or increasing total SAS score ≥ 2 in patients with baseline EPS.

Results: In 342 youth aged 13.6 ± 3.5 years (male = 58.2%, antipsychotic-naïve = 65.8%), 15.2% developed drug-induced parkinsonism. Raw SGA-grouped drug-induced parkinsonism rates were as follows: quetiapine = 1.5%, olanzapine = 13.8%, risperidone = 16.1%, ziprasidone = 20.0%, and aripiprazole = 27.3%. SGA type, dose, higher age, and lower baseline functioning were jointly

associated with drug-induced parkinsonism ($R^2 = 0.18$; $p < .0001$). Controlling for these factors, drug-induced parkinsonism rates were significantly lower only for quetiapine and olanzapine. Subjectively reported EPS (5%), EPS-related treatment discontinuation (3.3%), and anticholinergic initiation (3%) were infrequent. Anticholinergic initiation was most frequent with risperidone (10.2%; $p = .0004$). Treatment-emergent dyskinesia ranged from 4.5% (aripiprazole) to 15.5% (olanzapine). SGA type, younger age, white race/ethnicity, and baseline AIMS were jointly associated with treatment-emergent dyskinesia ($R^2 = 0.31$; $p < .0001$). Controlling for these factors, treatment-emergent dyskinesia rates differed among SGA subgroups, with higher rates with olanzapine and ziprasidone. At baseline, psychostimulant use was associated with dyskinesia, and number of psychotropic comedications was associated with subjective EPS.

Conclusion: In youth, SGA-related EPS rates did not generally exceed those reported in adults, with particularly low rates with quetiapine and olanzapine.

Key Words: extrapyramidal, parkinsonism, dyskinesia, second-generation antipsychotic, youth

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Second-generation antipsychotics (SGAs) have initially been greeted with enthusiasm due to their reduced risk of causing extrapyramidal side effects (EPS). Subsequently, the recognition of cardiometabolic risks has rightfully shifted safety concerns.¹ Nonetheless, EPS contribute to tolerability profile, treatment nonadherence,² and poor outcome.³

Incidence rates of EPS in youth are expected to exceed those in adults.⁴ Meta-analyses reported a 22% EPS rate

for adolescents receiving SGAs for psychosis,⁵ or 23%/25% for risperidone/aripiprazole,⁶ but reported rates vary largely depending on the SGA, study design, population, and methodology used to assess EPS.⁷ For aripiprazole, subject-/investigator-reported rates in randomized controlled trials (RCTs) ranged from 15%⁸ to 39%.^{9,10} For olanzapine, Simpson–Angus Scale (SAS)–based EPS rates varied from 0%¹¹ to 58%.¹² Similar divergence exists for patient-/investigator-reported rates with quetiapine (0%¹³–46%¹⁴). Dose-dependent EPS rates have been demonstrated for risperidone (patient/investigator report: 0% at ≤ 0.6 mg¹⁵ to 25% at ≥ 6 mg,^{15,16} or SAS-based 0%¹⁷–51%¹²). Few data have been published on EPS rates for ziprasidone (11%¹⁸–18%¹⁹). Rates of anticholinergic prescriptions vary between 12% for olanzapine²⁰ or across SGAs²¹ to 32% for risperidone.²⁰ These neuromotor side effect rates were gathered as part of RCTs or in cross-sectional studies, but prospective rates in psychiatric routine care with different SGAs in a contemporary cohort are lacking.



This article is discussed in an editorial by Dr. Jon McClellan on page 704.



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In this study, we assessed SGA use in routine child and adolescent psychiatry treatment to prospectively quantify prevalence and incidence rates of drug-induced parkinsonism, dyskinesia, and akathisia during the first 3 months of naturalistic use of SGAs; and to identify risk profiles for neuromotor side effects in this population.

METHOD

Data were collected from December 2001 to September 2007 during the nonrandomized Second-generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) study, an observational inception cohort study of antipsychotic medication use in routine clinical care. Inclusion/exclusion criteria and data collection strategies have been published previously,¹ but the current study was not restricted to antipsychotic-naïve patients. In short, children and adolescents aged 4 to 19 years who were initiating antipsychotic treatment based on clinician/family choice were included provided that baseline assessments occurred within 7 days of the current antipsychotic treatment. The following additional exclusion criteria were used: baseline use of anticholinergic medication, Tourette syndrome/tic disorder, catatonia, and antipsychotic switch explicitly because of EPS. Data from patients with sequential antipsychotic treatment trials were restricted to the first one. Participant data were recorded at baseline and at 4-, 8-, and 12-week follow-up.

Participants were recruited through the Zucker–Hillside Hospital, Queens, NY, and informed consent was obtained from all participants or guardians under protocols approved by the North Shore–Long Island Jewish Health System Institutional Review Board. All procedures were conducted in accordance with the ethical standards on human experimentation (institutional and national) and with the Declaration of Helsinki of 1975/2000.

Assessments

In addition to data collection as detailed earlier,¹ investigators used the following assessments for neuromotor adverse effects: Simpson–Angus Scale (SAS) for parkinsonism (threshold at mean SAS ≥ 0.33 for “parkinsonism”²²); the Abnormal Involuntary Movement Scale (AIMS; threshold for “dyskinesia” per Schooler and Kane criteria²³); and the Barnes Akathisia Rating scale (BARS; threshold at BARS total ≥ 1 for “akathisia”²⁴). For comparison with the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial, we also calculated rates using ≥ 1 for mean SAS scores, as in the CATIE trial primary analysis.²⁵

Participant reports of adverse events were recorded by the investigators with a modified version of the Treatment Emergent Symptoms Scale (TESS).²⁶

Data Analysis

Primary outcomes were the occurrence of drug-induced parkinsonism and treatment-emergent dyskinesia. Secondary outcomes were all other EPS-related outcomes.

To fulfill the definition of “drug-induced parkinsonism,” patients had to fulfill 1 or more of the following criteria: mean SAS > 0.33 in patients with baseline mean SAS ≤ 0.33 ; start of anticholinergic medication; or marked increase of total SAS ratings of ≥ 2 in patients with baseline positive rating for EPS.

Dyskinesia was considered as treatment-emergent dyskinesia in patients without dyskinesia in a prior rating, or as an increase of ≥ 2 on AIMS total rating in patients with dyskinesia at baseline. Akathisia was defined by a rating of > 1 on the BARS. A TESS sum score of neuromotor complaints was created, summing ratings for muscle pain/stiffness, joint pain/stiffness, dystonia,

dyskinesia, rigidity, tremor, cramps, and myoclonus (range, 8–32). Primary psychiatric diagnoses were grouped into hierarchical categories to reduce the number of factors for statistical analyses.¹

Group comparisons were performed using χ^2 tests, nominal logistic fits and analysis of variance (ANOVA), *t* tests, Fisher’s exact test, or Wilcoxon rank-sum tests as per data type and distribution. Two-sided tests with $\alpha = 0.05$ were used without correction for multiple comparisons because of the descriptive nature. To construct models of demographic and clinical variables associated with neuromotor variables, we conducted stepwise multivariate regression analyses. We used univariate analyses to screen for associations of neuromotor variables with age, sex, race/ethnicity, main psychiatric diagnosis, comorbidities, Children’s Global Assessment Scale (CGAS) scores, various aspects of medication information, and subsequent neuromotor ratings. Variables with marginal effects in these analyses ($p \leq .10$) were entered into the stepwise forward regression analysis process.

Mixed-models analysis was used to explore effects of time, medication class, and their interactions, followed by post hoc *t* tests. Statistical calculations used JMP 5.0.1 (SAS Institute Inc., Cary, NC).

RESULTS

Data from 1,105 clinical SGA treatment initiations were collected. Of these, 4-week visits were performed in 660 trials (59.7%) from 498 patients. A total of 162 repeat trials were excluded. SAS baseline ratings were available in 373 patients (74.9%). Of the patients, 32 (8.6%) were excluded because of Tourette/tic disorder ($n = 12$), catatonia ($n = 1$), and explicit switch due to EPS or baseline anticholinergic treatment ($n = 17$). One patient on clozapine was excluded, resulting in a total study cohort of 342 individuals.

All 342 patients participated in the baseline and 4-week visits, and 258 and 242 patients participated in the 8- and 12-week visits, respectively (see Table S1, available online, for breakdown per SGA group).

Based on clinical decisions by their treating psychiatrists unrelated to the study team, 342 patients (mean age = 13.6 ± 3.5 years; 58.2% male) were started on SGAs (aripiprazole: $n = 66$, olanzapine: $n = 58$, quetiapine: $n = 66$, risperidone: $n = 137$, ziprasidone: $n = 15$; Table 1). Because of the naturalistic nature of the study, demographic, clinical, and treatment characteristics of SGA groups differed. In particular, high proportions of antipsychotic-naïve patients were found in the olanzapine and risperidone groups, which also included more acutely and severely ill inpatients. Conversely, the ziprasidone and aripiprazole groups contained more chronically ill, antipsychotic-switching patients. In addition, high rates of non-antipsychotic comedications characterized the quetiapine and ziprasidone groups.

Baseline Neuromotor Characteristics

Detailed neuromotor characteristics for each single time point per SGA are listed in Table S1, available online. Baseline parkinsonism was present in 4.97% of patients and differed between SGA subgroups (from 0% in olanzapine to 20% in ziprasidone, $p = .01$; Table 2). SAS total baseline score was associated with higher age, antipsychotic switch, allocation to ziprasidone, and higher baseline CGAS score

TABLE 1 Demographic, Illness, and Treatment Characteristics

	Total n = 342	Aripiprazole n = 66 (19.30%)	Olanzapine n = 58 (16.96%)	Quetiapine n = 66 (19.30%)	Risperidone n = 137 (40.06%)	Ziprasidone n = 15 (4.39%)	p Value
Age, y, mean ± SD	13.6 ± 3.5	12.97 ± 3.41	14.21 ± 3.26	13.30 ± 3.15	13.71 ± 3.74	14.45 ± 3.11	.24
Sex, male, n (%)	199 (58.19)	44 (66.67)	39 (67.24)	28 (42.42)	82 (59.85)	6 (40.00)	.01*
Race, nonwhite, n (%)	186 (54.39)	33 (50.00)	34 (58.62)	39 (59.09)	74 (54.01)	6 (40.00)	.60
Primary Diagnosis, n (%)							.14
Mood spectrum disorders	158 (46.20)	27 (40.91)	29 (50.00)	40 (60.61)	58 (42.34)	4 (26.67)	
MDD	40 (11.67)	9 (13.64)	8 (13.79)	7 (10.60)	16 (11.67)	0 (0.00)	
BD	75 (21.92)	11 (16.67)	15 (25.86)	21 (31.82)	24 (17.59)	4 (26.67)	
Mood disorder NOS	43 (12.57)	7 (10.60)	6 (10.34)	12 (18.18)	18 (13.14)	0 (0.00)	
Schizophrenia spectrum disorders	91 (26.60)	17 (25.76)	16 (27.59)	10 (15.15)	42 (30.66)	6 (40.00)	
Schizophrenia, schizophreniform, schizoaffective disorder	36 (10.53)	7 (10.61)	11 (18.97)	2 (3.03)	12 (8.76)	4 (26.67)	
Psychotic disorder NOS	55 (16.08)	10 (15.15)	5 (8.62)	8 (12.12)	30 (21.90)	2 (13.13)	
Aggression spectrum disorder	93 (27.20)	22 (33.33)	13 (22.41)	16 (24.24)	37 (27.01)	5 (33.33)	
ASD	34 (9.94)	12 (18.18)	3 (5.17)	5 (7.85)	11 (8.03)	3 (20.00)	
ODD, CD	59 (17.25)	10 (15.15)	10 (17.24)	11 (16.67)	26 (18.98)	2 (13.33)	
Comorbid ADHD, n (%)	138 (43.28)	27 (40.91)	19 (43.94)	29 (43.94)	57 (41.61)	6 (40.00)	.77
Comorbid OCD, n (%)	19 (5.56)	3 (4.55)	3 (5.17)	4 (6.06)	7 (5.11)	2 (13.33)	.75
Comorbid SUD, n (%)	52 (15.21)	6 (9.09)	13 (22.41)	8 (12.12)	25 (18.25)	0 (0.0)	.08
Antipsychotic Exposure Before Trial							<.0001*
Antipsychotic history (≥1 mo off SGA)	57 (16.67)	13 (19.70)	12 (20.69)	12 (18.18)	17 (12.41)	3 (20.00)	
Antipsychotic switch	60 (17.54)	17 (25.76)	5 (8.62)	19 (28.79)	8 (5.84)	11 (73.33)	
Antipsychotic naive (≤1 wk lifetime)	225 (65.79)	36 (55.55)	41 (70.69)	35 (53.03)	112 (81.75)	1 (6.67)	
Prior SGA treatment, mo, median (25th, 75th percentiles)	0 (0, 2.5)	0 (0, 6.24)	0 (0, 1.25)	0 (0, 6.75)	0 (0, 0)	7.75 (2, 35.6)	<.0001*
CGAS/baseline, mean ± SD	36.7 ± 8.95	38.68 ± 7.88	32.07 ± 9.25	38.75 ± 8.31	36.52 ± 8.93	39.67 ± 9.05	<.0001*
Inpatients, n (%)	230 (67.25)	34 (51.52)	50 (86.21)	45 (68.18)	93 (67.88)	8 (53.33)	.001*
Non-SGA psychotropic comedication, n (%)	237 (62.30)	37 (56.06)	38 (65.52)	54 (81.82)	97 (70.80)	11 (73.33)	.03*
Total comedications, median (25th, 75th percentiles)	1 (0, 1.25)	1 (0, 1.25)	1 (0, 1)	1 (1, 2)	1 (0, 1)	1 (0, 2)	.06
Comedications, n (%)							
Psychostimulants	75 (21.99)	14 (21.21)	9 (15.52)	19 (28.79)	29 (21.32)	4 (26.67)	.50
Antidepressants	92 (26.90)	17 (25.76)	10 (17.24)	22 (33.33)	42 (30.66)	1 (1.09)	.08
Mood stabilizer (antiepileptic or lithium)	112 (32.72)	14 (21.21)	25 (43.10)	31 (46.97)	35 (25.55)	7 (46.67)	.002*
Lithium	50 (14.62)	5 (7.58)	11 (18.97)	17 (25.76)	12 (8.76)	5 (33.33)	.001*
Valproate	62 (18.13)	10 (15.15)	15 (25.86)	13 (19.70)	22 (16.06)	2 (13.33)	.50

TABLE 1 Continued

	Total n = 342	Aripiprazole n = 66 (19.30%)	Olanzapine n = 58 (16.96%)	Quetiapine n = 66 (19.30%)	Risperidone n = 137 (40.06%)	Ziprasidone n = 15 (4.39%)	p Value
SGA start before baseline assessment, n (%)	189 (55.26)	25 (37.88)	37 (63.79)	39 (59.09)	81 (59.12)	7 (46.67)	.02*
No. of days on new SGA before baseline assessment, mean ± SD	1.95 ± 2.88	1.25 ± 2.38	2.64 ± 3.67	1.86 ± 2.35	1.96 ± 2.76	2.73 ± 4.06	.07
Maximum CPZ equivalent dose, mean ± SD	194.5 ± 187.7	179.05 ± 112.14	215.52 ± 133.43	404.03 ± 277.97	95.84 ± 75.77	160.32 ± 78.02	<.0001*
No. of wk completed, mean ± SD	10.28 ± 3.46	10.40 ± 3.57	10.80 ± 2.63	10.26 ± 3.80	10.29 ± 3.41	7.69 ± 3.99	.04*
% CGAS Change, mean ± SE	45.82 ± 2.84	28.60 ± 6.07	78.32 ± 6.34	29.80 ± 6.18	51.53 ± 4.14	6.79 ± 6.80	.0001*
Continuation of SGA at 3 mo, n (%)	232 (68.44)	48 (73.8)	46 (79.31)	44 (67.69)	89 (64.96)	5 (35.71)	.01*

Note: ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; BD = bipolar disorder; CD = conduct disorder; CGAS = Children's Global Assessment Scale; CPZ = chlorpromazine; MDD = major depressive disorder; NOS = not otherwise specified; OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; SGA = second-generation antipsychotic; SUD = substance use disorder.

*Significant between-group differences ($p < .05$).

(full model $R^2 = 0.11$, $p < .0001$; see Table S2, available online).

Baseline dyskinesia was present in 7.1% (Table 2) without differences by SGA subgroup, but more frequent in switchers (13.33%) and in patients with prior antipsychotic exposure (12.28%; antipsychotic-naïve: 3.62%; $p = .006$, see Table S3, available online). Higher baseline AIMS scores were associated with younger age, comedication with psychostimulants, and higher number of prior antipsychotic trials (full model $R^2 = 0.16$, $p < .0001$; see Table S2, available online). Notably, psychostimulant use was not a proxy for attention-deficit/hyperactivity comorbidity, which did not enter the multivariate model.

Tremor was the most frequently reported neuromotor complaint at baseline (11.38%, see Table S3, available online); any moderate neuromotor complaint (>2 on TESS) was recorded for 35 participants (10.9%; without significant SGA subgroup difference, data not shown). Presence of a moderate neuromotor complaint at baseline was associated with the number of non-antipsychotic comedications, medication history (increased in antipsychotic-naïve participants) and diagnosis of mood spectrum or schizophrenia spectrum disorders (full model $R^2 = 0.13$, $p < .0001$; see Table S2, available online).

Baseline rates for parkinsonism did not differ ($p = .96$) by primary psychiatric diagnosis in a subgroup analysis of antipsychotic-naïve, medication-free participants ($n = 102$; see Table S3, available online). Dyskinesia was even significantly less frequent in schizophrenia spectrum disorders in this subgroup analysis (0% versus 11.36% and 12% in schizophrenia spectrum, aggression, and mood disorders, respectively; $p = .04$; see Table S3, available online).

Follow-Up Neuromotor Characteristics

Drug-Induced Parkinsonism. The overall 3-month incidence of drug-induced parkinsonism was low (15.2%; Table 2) and its severity was mild (SAS total score = 6.30 ± 4.13 in affected individuals [$n = 27$; at week 4]). Similarly, anticholinergic use (5.03%; table 2) and discontinuation due to EPS (3.27%, $n = 11$) were low.

The raw 3-month incidence of drug-induced parkinsonism differed between SGA subgroups ($p = .002$; Table 2), with highest rates in aripiprazole (27.27%) and lowest in quetiapine (1.52%). Similarly, prevalence rates at each time point and anticholinergic use differed ($p < .05$ for all comparisons; see Table S1, available online). Controlling for the factors age, SGA peak dose, and baseline CGAS score, significant SGA subgroup differences were identified, with the lowest rates of drug-induced parkinsonism in quetiapine and in olanzapine (full model $R^2 = 0.18$; $p < .0001$; see Table S2, available online). At week 12, significant within-group increases in SAS total ratings relative to baseline ($p < .001$) were present with aripiprazole, olanzapine, and risperidone, but not with quetiapine ($p = .30$). Because of the high dropout in the ziprasidone subgroup, an LOCF analysis was calculated for this group, which did not show a significant change in this group ($p = .79$).

TABLE 2 Neuromotor Characteristics of Study Sample

Baseline	Total N = 342	Aripiprazole n = 66	Olanzapine n = 58	Quetiapine n = 66	Risperidone n = 137	Ziprasidone n = 15	p Value
Parkinsonism (mean SAS >0.33), n (%)	17 (4.97)	6 (9.09)	0 (0.00)	3 (4.55)	5 (3.65)	3 (20.00)	.01*
SAS total, mean ± SD	0.70 ± 1.66	0.85 ± 1.63	0.31 ± 0.68	0.69 ± 1.71	0.60 ± 1.35	2.40 ± 4.29	.0004*
Dyskinesia, n (%)	24 (7.10)	7 (10.77)	4 (6.90)	6 (9.38)	6 (9.38)	1 (6.67)	.50
AIMS ^a total, mean ± SD	1.23 ± 2.12	1.45 ± 1.92	1.13 ± 2.81	1.23 ± 2.21	1.19 ± 1.84	1.13 ± 1.92	.92
Akathisia, n (%)	2 (0.58)	0	0	0	2 (1.46)	0	.36
Wk 12^b	n = 259	n = 49	n = 51	n = 50	n = 101	n = 8	
Antipsychotic dose, mean ± SD	N/A	11.76 ± 7.39	9.68 ± 6.85	231.9 ± 184.3	1.38 ± 1.17	63.3 ± 52.8	N/A
Drug-induced parkinsonism, n (%)	27 (10.42)	13 (26.53)	4 (7.85)	1 (2.00)	7 (6.93)	2 (25.00)	.0003*
SAS total, mean ± SD	1.29 ± 2.25	2.22 ± 2.74	1.02 ± 1.54	0.62 ± 1.14	1.11 ± 2.42	2.13 ± 3.87	.003*
Treatment-emergent dyskinesia, n (%) ^b	12 (4.63)	0 (0.00)	3 (5.88)	2 (4.00)	1 (0.98)	2 (25.00)	.05*
AIMS total, mean ± SD	1.62 ± 2.21	1.49 ± 1.41	1.67 ± 2.85	2.04 ± 2.79	1.43 ± 1.67	2.13 ± 3.44	.65
Akathisia, n (%)	7 (2.78)	3 (6.25)	2 (4.00)	0 (0.00)	2 (2.06)	0 (0.00)	.38
3-mo Frequencies (LOCF)	N = 342	n = 66	n = 58	n = 66	n = 137	n = 15	
Drug-induced parkinsonism, n (%)	52 (15.20)	18 (27.27)	8 (13.79)	1 (1.52)	22 (16.06)	3 (20.00)	.002*
Anticholinergic medication, n (%)	17 (5.03)	3 (4.76)	0 (0.0)	0 (0.0)	14 (10.22)	0 (0.0)	.0004*
Highest single SAS item score, mean ± SD	0.88 ± 1.00	1.14 ± 0.99	0.91 ± 0.85	0.55 ± 0.66	0.86 ± 1.08	1.13 ± 1.50	.01*
Significant, treatment-emergent dyskinesia, n (%)	28 (8.28)	3 (4.55)	9 (15.52)	6 (9.5)	6 (4.41)	4 (26.67)	.005*
Highest AIMS item during 3 mo, mean ± SD	0.91 ± 0.91	1.19 ± 0.84	0.80 ± 1.04	0.96 ± 0.98	0.84 ± 0.83	1.0 ± 1.0	.11
Akathisia, n (%)	16 (4.83)	5 (8.06)	3 (5.36)	1 (1.59)	7 (5.15)	0 (0.0)	.45
Neuroleptic malignant syndrome, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Discontinuation due to extrapyramidal side effect, n (%)	11 (3.27)	4 (6.15)	1 (1.72)	0 (0.0)	6 (4.48)	0 (0)	.008*

Note: AIMS = Abnormal Involuntary Movement Scale; LOCF = last observation carried forward; N/A = not applicable; SAS = Simpson—Angus Scale.
Significant between-group differences shown as *p < .05.
^aGroup comparisons remain insignificant after exclusion of previously antipsychotic-exposed participants with baseline dyskinesia.
^bSee Table S1, available online, for wk 4 and wk 8 data.

Anticholinergic comedication was most frequent with risperidone (10.22%; Table 2), in inpatients (7.02% versus 0.09% for outpatients; $p = .006$), in patients with schizophrenia spectrum disorder (12.5% versus 3.16% in mood disorders and 1.08% in aggression; $p = .001$) and with lower baseline CGAS scores (mean $\pm$ SE, 28.24 ± 1.74 versus 37.22 ± 0.49 ; $p < .0001$).

To facilitate comparison with the CATIE trial, we calculated rates of parkinsonism according to their primary threshold.²⁵ Using this definition, SGA subgroup comparisons were significant only for baseline (aripiprazole = 0%, olanzapine = 0%, quetiapine = 1.52%, risperidone = 0%, ziprasidone = 13.33%; $p = .001$; see Table S1, available online) and for week 8 (aripiprazole = 7.55%, olanzapine = 0%, quetiapine = 0%, risperidone = 2.02%, ziprasidone = 14.29%; $p = .03$; see Table S1, available online).

Significant dose effects of the antipsychotic medication were present in all agents but aripiprazole (correlation of SAS total score: risperidone [week 4: $R = 0.36$; $p < .0001$; week 12: $R = 0.28$; $p = .004$], olanzapine [week 12: $R = 0.34$; $p = .01$], quetiapine [week 4: $R = 0.30$; $p = .01$], ziprasidone [week 12: $R = 0.87$; $p = .004$]).

Treatment-Emergent Dyskinesia. The raw overall 3-month incidence of treatment-emergent dyskinesia was 8.28% and differed between SGA subgroups, ranging from 4.41% in the risperidone group to 26.67% in the ziprasidone group ($p = .005$; Table 2). Controlling for the factors baseline AIMS score, age, and race/ethnicity, SGA subgroups significantly differed, with higher rates of treatment-emergent dyskinesia in olanzapine and ziprasidone (full model $R^2 = 0.31$; $p < .0001$; see Table S2, available online). Dose effects on dyskinesia ratings were significant within SGA group only for risperidone at week 4 (highest single AIMS item [$R = -0.31$; $p = .0004$], AIMS total score [$R = -0.27$; $p = .0015$]).

AIMS sum scores did not differ between switchers and the remaining cohort at week 4 ($p = .97$), week 8 ($p = .09$), and week 12 ($p = .49$). Similarly, these groups showed comparable rates of treatment-emergent dyskinesia (at week 4, 8, or 12; $p > .5$ respectively), showing no confounding effect of withdrawal dyskinesia.

Akathisia. Observer-rated akathisia was rare throughout the study, with a cumulative rate of 4.83% for the entire cohort (Table 2), without dose effect or SGA group differences and with constant monthly rates of 2.3% to 2.7% (see Table S1, available online).

Participant-Reported Neuromotor Side Effects. Participant-reported akathisia rates were slightly higher than those assessed by observers (see Table S3, available online), with increased early rates for aripiprazole (week 4: 11.67%) and ziprasidone (week 4: 7.14%; versus rates of <2% in the other SGAs; $p = .006$; see Table S1, available online).

Frequencies for all other single neuromotor TESS items are listed in Table S3, available online (for the entire cohort, as no SGA group differences were found; all $p > .05$). Tremor was the most frequently reported complaint across SGAs, with 18% of participants reporting this at week 4. Higher tremor ratings at week 4 were associated with mood spectrum disorders, higher age, number of psychotropic

medications, and, controlling for these factors, were lower with aripiprazole (full model $R^2 = 0.14$; $p < .0001$, see Table S2, available online).

DISCUSSION

This is the largest cohort of youth formally assessed for EPS, and it is the first prospective direct comparison of neuromotor side effects of the 5 most used SGAs in a naturalistic setting. As SGAs are widely used off label, populations that are not included in RCTs are well represented in our study. A comparison of comedication use is highly illustrative of how little RCT cohorts compare to our routine care cohort: 69% of participants received additional psychotropic medication, most frequently stimulants, antidepressants, or mood stabilizers. By contrast, these rates range below 10% in the majority of RCTs.^{8,9,16,18,27}

Our study showed an overall rate of drug-induced parkinsonism of 15.2%, ranging from 1% for quetiapine to 27.7% with aripiprazole for the raw, observed rates. However, the clinical severity of parkinsonism was generally low, indicated by overall low rates of the following: subjective perception of any sort of muscle rigidity (mild in 5%); anticholinergic comedication use (3%); or treatment termination due to extrapyramidal symptoms (3%). Notably, in addition to SGA type and dose, higher age and lower baseline CGAS score were significant predictors of drug-induced parkinsonism.

The relative ranking of drug-induced parkinsonism rates across the examined 5 SGAs in our study is generally in accordance with earlier studies of SGAs in youth that examined only 1 SGA or, at most, 1 other SGA in the same study. However, the absolute rates and risk estimates differ to some degree. Controlling for the confounding factors (inherently associated with the naturalistic design), significant, independent SGA effects existed only for quetiapine (low EPS liability), olanzapine (low EPS liability), and ziprasidone (high EPS liability). Data from registration trials suggest that olanzapine (with rates <5%^{28,29}) followed by quetiapine (with rates of <5%³⁰ and 13%³¹) would be the least EPS-prone antipsychotics, roughly similar to our data. However, our data suggest an even lower EPS risk with quetiapine. Higher EPS rates than in our data were reported for aripiprazole (14%–39%^{8,10,32,33}). Roughly comparable rates were reported for risperidone (9–16%^{15,16,34}) and for ziprasidone (11%–24%^{18,35}).

In contrast to the relative ranking of EPS liability of individual SGAs, our EPS rates also differ from those obtained in SGA registration trials: participant-based EPS reports were higher throughout all registration trials, whereas rating scale-based frequencies were seemingly lower. However, anticholinergic use, likely in response to higher participant complaints of parkinsonism, was far higher in all registration trials compared to those in our study. This is particularly true for fixed-dose studies with rapid titration schemes.^{16,36} Thus, it is possible that liberal or preventive anticholinergic comedication may have led to low/absent parkinsonism rates in some cases and, in particular, may have masked rating scale-based changes in EPS

measures in these studies. Accordingly, SAS ratings were unchanged from baseline to endpoint in most registration trials.^{9,18,27-29,33} Similarly, reported parkinsonism rates in the risperidone registration trials were partly lower (4%–16%) than the raw cumulative rates in our study (16%), but anticholinergic use was very common and up to 10-fold higher, with 56%/38% in the high-/low-dose subgroups.³⁴ Likewise, anticholinergic use was also higher in the Treatment of Early-Onset Schizophrenia Spectrum disorders (TEOSS) trial,²⁰ with rates of 12% for olanzapine (0% in our study) and 33% for risperidone (10% in our study). Despite this difference, SAS-based rates of parkinsonism were also higher in the TEOSS trial, ranging above 20% for both olanzapine and risperidone. With mean doses of 9 mg of olanzapine and 1.5 mg of risperidone at week 4, the titration schedule in the majority of our study participants was somewhat slower than in the TEOSS study, which aimed at similar dose ranges by day. This difference in titration speed could explain the lower parkinsonism rate in our naturalistic study.

Participant-based reports of side effects were higher throughout all registration trials, except for tremor reporting, which was higher for all treatment subgroups in our study. Interestingly, tremor was also linked to psychotropic polypharmacy in our study, which was far less prevalent in the registration trials.

Apart from registration trials, there is also substantial variability of reported rates of EPS in other clinical trials. The low EPS rates with quetiapine observed in our study have not consistently been reported previously (0%¹³–46%¹⁴) but match smaller case series in youth.^{13,37} A similar variability in reported drug-induced parkinsonism rates exists for risperidone, with an absence of any drug-induced parkinsonism despite SAS-based ratings in a sizable cohort¹⁷ and contrasting high rates (~50%) in smaller cohorts using both rating scale-based assessments³⁸ and participant reports.³⁷ Finally, our SAS-based data, but not the anticholinergic use data, match the reported rates of drug-induced parkinsonism determined by use of anticholinergic comedication.¹⁹

Compared to studies in adults, our data do not support the idea that the risk of SGA-induced parkinsonism is generally elevated in youth,^{39,40} an idea generalized from observations of first-generation antipsychotics.⁴ This observation is in line with a previous indirect comparison of EPS and akathisia rates reported in RCTs of pediatric and adult patients with bipolar disorder.⁴¹ Similarly, compared to data from placebo-controlled RCTs in adults, lower rates of parkinsonism were found in our study (16%) for risperidone (adults: any significant EPS = 23%, anticholinergic use = 27%⁴²) and particularly for quetiapine (1.5% in our study; adults: significant EPS = 11%, anticholinergic use = 7%⁴³). Comparable rates were found for olanzapine (anticholinergic use = 13%⁴⁴). Similarly, rates of drug-induced parkinsonism for aripiprazole in our study (27%) roughly match those reported in adults (adults: significant EPS = 31%, anticholinergic use = 17%⁴⁵). Nevertheless, these data from usual care of youth are not suitable to refute a higher general sensitivity in antipsychotic-treated youth for EPS, as clinicians seem to have used a more cautious

titration schedule and lower maximum dose in the pediatric population. Anticholinergics were barely used in our naturalistic cohort (3%, very likely reflective of the mild severity of the EPS), possibly to avoid adverse cognitive effects.

The comparison of EPS frequencies among studies is largely hampered by an inconsistent use of measures for parkinsonism. Although the use of anticholinergics as a proxy for EPS seems rational,⁴⁶ these rates are typically far lower (disregarding the rate of underdiagnosed EPS) than those derived from either participant report or scale-based ratings. Moreover, even when scale-based ratings are used, there is a wide variability of SAS thresholds used, despite a clear original definition.²² Several current pediatric RCTs reported relative risks for SAS-measured EPS, without specifying thresholds.^{11,13,17,19,20,28,47} Most surprisingly, however, EPS rates reported in the CATIE study,²⁵ ranging from 4%–8% only, were obtained with a 6-item SAS,⁴⁸ whereas the original SAS contains 10 items, and parkinsonism was defined at a threshold of a mean SAS of ≥ 1 (original threshold = >0.3).²² Defining parkinsonism at this threshold would have resulted in parkinsonism rates $<3\%$ in our data and no discrimination of SGA classes with regard to neuromotor side effects. Although it may have been more appropriate to use a validated threshold in a landmark trial,²² there have also been rightful concerns regarding the originally defined SAS threshold. Testing the SAS against the Unified Parkinson's Disease Rating Scale^{49,50} showed high sensitivity but low specificity.^{51,52} An actimetric study,⁵² in line with an imaging study,⁵³ suggested that raising SAS thresholds to 0.65 doubled the specificity without reducing sensitivity. While inappropriately high thresholds may result in missed diagnoses of drug-induced parkinsonism,⁵⁴ inappropriately low thresholds may result in a problematic overlap of negative symptoms with EPS. Conversely, an all-too-quick attribution of any movement symptom during antipsychotic treatment as a drug-induced movement disorder carries the risk of missing underlying organic conditions such as Wilson's, systemic lupus, neuroakanthocytosis, spinocerebellar ataxia or adrenoleukodystrophy, all of which may begin in youth.

Our study found relatively high rates of baseline dyskinesia, mostly but not exclusively in participants with prior antipsychotic use. In contrast to the suggestion of a genuinely schizophrenia-inherent motor syndrome,⁵⁵ dyskinesia rates were relatively lower in antipsychotic-naïve participants with schizophrenia spectrum disorders compared to mood and aggression spectrum disorder, and parkinsonism rates did not differ across diagnostic groups. Importantly, stimulant use was associated with baseline dyskinesia, a phenomenon that is recognized as a rare side effect,⁵⁶ but may be more prevalent when the stimulant is used as part of polypharmacy. We refrain from discussing our 3-month data in the context of literature on tardive dyskinesia, as its formal definition requires persistence past this time frame.⁵⁷

Being naturalistic, this study is limited in multiple ways. Baseline differences of SGA subgroups reflect clinician treatment choices, with olanzapine and risperidone as first-line treatments in antipsychotic-naïve and more severely ill participants during the initial SATIETY study period. Thus,

raw EPS rates in our study should not be interpreted without considering the context of confounding factors that have been controlled for in the multivariate analyses. The observation period of 12 weeks was sufficient to address the occurrence of parkinsonism, but dyskinesia needs to be analyzed in a cohort followed for a longer time. The sample size of 342 starters and 250 full completers is insufficient to discover rare side effects; pharmacovigilance systems are more suitable for this purpose, but often lack detailed information and rating scale-based assessments. As this is not an RCT, no causations can be inferred. The observations are merely associational, yet clinically relevant. Not all baseline assessments were performed before SGA initiation; the mean duration before assessments was only 2 days. Raters were not blinded. The neuromotor rating scales have not been validated in children. We could include only a small number of participants with ziprasidone. Although this subgroup differed in multiple ways from the majority, we kept this group to add to the scarce database for ziprasidone in youth.

In summary, we observed the lowest rates of parkinsonism with quetiapine and olanzapine, and the highest anticholinergic use with risperidone, yet low treatment discontinuations for EPS. A surprisingly large number of youth had dyskinesia at baseline, which was associated with psy-

chostimulant use. Incident dyskinesia was highest with olanzapine. Our data support that SGAs used in children and adolescents have, in general, relatively few neuromotor side effects, yet these differ among individual agents and are likely affected by initial dosing and titration strategies. These individual patterns need to be considered in the context of medication- and patient-related tolerability and efficacy profiles of SGAs,⁵⁸ as well as patient and family preferences and choices, when making treatment decisions. &

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Clinical Guidance

- Overall rates of drug-induced parkinsonism during clinically adapted second-generation antipsychotic (SGA) treatment were low, indicating that the short-term neuromotor adverse effects of SGAs during routine care are not a major clinical problem.
- During naturalistic treatment, particularly low rates of drug-induced parkinsonism were found with quetiapine, indicating that youth prone to extrapyramidal adverse effects might benefit from this drug choice.
- Beyond SGA choice, drug-induced parkinsonism was associated with higher dose, higher age, and lower baseline functioning:
 - Cautious dosing seems advisable not only in young children but also in adolescents.
 - Cautious dosing seems advisable also in low-functioning youth.
- Psychotropic polypharmacy was associated with increased rates of tremor and dyskinesia, highlighting the need for carefully weighing the indications of each and every psychotropic medication in the therapeutic management plan.

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TABLE S1 Detailed Neuromotor Outcomes in Study Sample

Baseline	Total N = 342	Aripiprazole n = 66	Olanzapine n = 58	Quetiapine n = 66	Risperidone n = 137	Ziprasidone n = 15	p value
Parkinsonism (mean SAS>0.33), n (%)	17 (4.97)	6 (9.09)	0 (0.00)	3 (4.55)	5 (3.65)	3 (20.00)	.01*
SAS total, mean ± SD	0.70 ± 1.66	0.85 ± 1.63	0.31 ± 0.68	0.69 ± 1.71	0.60 ± 1.35	2.40 ± 4.29	.0004*
Dyskinesia, n (%)	24 (7.10)	7 (10.77)	4 (6.90)	6 (9.38)	6 (9.38)	1 (6.67)	.50*
AIMS total, mean ± SD	1.23 ± 2.12	1.45 ± 1.92	1.13 ± 2.81	1.23 ± 2.21	1.19 ± 1.84	1.13 ± 1.92	.92
Akathisia, n (%)	2 (0.58)	0	0	0	2 (1.46)	0	.36
Wk 4	n = 331	n = 65	n = 55	n = 62	n = 134	n = 15	
Antipsychotic dose, mean ± SD	N/A	10.36 ± 6.97	8.99 ± 5.22	245.5 ± 187.38	1.58 ± 1.29	80.0 ± 44.08	N/A
Parkinsonism (mean SAS>0.33), n (%)	32 (9.67)	11 (16.92)	2 (3.64)	2 (3.23)	12 (8.96)	5 (3.33)	.002*
Drug-induced parkinsonism, ^a n (%)	27 (8.16)	9 (13.85)	2 (3.64)	0 (0.00)	13 (9.70)	3 (20.00)	.01*
SAS total, mean ± SD ^a	1.21 ± 2.33	1.67 ± 2.54	0.87 ± 1.32	0.53 ± 0.95	1.27 ± 2.63	2.87 ± 3.87	.002*
Dyskinesia, n (%)	21 (6.38)	4 (6.15)	7 (12.73)	5 (8.20)	4 (2.99)	1 (7.14)	.16
Treatment-emergent dyskinesia, n (%)	11 (3.40)	1 (1.56)	4 (7.27)	2 (3.33)	4 (2.99)	1 (7.14)	.52
AIMS total, mean ± SD	1.45 ± 2.17	1.37 ± 1.71	1.54 ± 2.98	1.81 ± 2.34	1.31 ± 1.92	1.35 ± 1.56	.36
Akathisia, n (%)	8 (2.33)	3 (4.62)	1 (1.82)	1 (1.64)	2 (1.48)	1 (6.67)	.52
+Anticholinergic, n (%)	10 (2.92)	2 (3.03)	0 (0.0)	0 (0.0)	8 (5.87)	0 (0.0)	.02*
>2 in a neuromotor TESS item; n (%)	17 (5.45)	5 (8.47)	3 (5.77)	3 (5.08)	6 (4.69)	0 (0.00)	.73
TESSsum ^b , median (25th, 75th percentiles)	8 (8, 9)	8 (8, 9)	8 (8, 9)	8 (8, 8)	8 (8, 9)	8 (8, 8)	.40
Akathisia/TESS ≥ 2, n (%)	12 (3.75)	7 (11.67)	1 (1.89)	0 (0.00)	3 (2.26)	1 (7.14)	.006*
Wk 8	n = 249	n = 53	n = 46	n = 48	n = 98	n = 6	
Antipsychotic dose, mean ± SD	N/A	11.80 ± 7.82	9.39 ± 6.17	246.3 ± 184.9	1.69 ± 1.42	73.3 ± 43.2	N/A
Parkinsonism (mean SAS >0.33), n (%)	22 (8.66)	12 (22.64)	3 (6.38)	1 (2.08)	5 (5.05)	1 (14.29)	.004*
Drug-induced parkinsonism, ^a n (%)	21 (8.27)	11 (20.75)	3 (6.38)	0 (0.00)	6 (6.06)	1 (14.29)	.001*
SAS total, mean ± SD ^a	1.12 ± 2.28	2.22 ± 3.01	0.87 ± 1.51	0.40 ± 0.74	0.91 ± 1.99	2.43 ± 5.99	.0002*
Dyskinesia, n (%)	17 (6.80)	2 (3.92)	6 (13.33)	5 (10.20)	3 (3.06)	1 (14.29)	.11
Treatment-emergent dyskinesia, n (%)	8 (3.2)	1 (1.96)	3 (6.67)	2 (4.08)	2 (2.02)	0 (0.00)	.59
AIMS total, mean ± SD	1.55 ± 2.13	1.40 ± 1.41	1.51 ± 2.91	2.04 ± 2.62	1.36 ± 1.67	2.28 ± 2.49	.31
Akathisia, n (%)	6 (2.33)	3 (5.66)	1 (2.13)	0 (0.00)	2 (1.98)	0 (0.00)	.40
+Anticholinergic, n (%)	13 (3.80)	3 (4.55)	0 (0.0)	0 (0.0)	10 (7.30)	0 (0.0)	.006*
>2 in a neuromotor TESS item; n (%)	8 (3.27)	2 (4.08)	1 (2.22)	4 (8.33)	1 (1.03)	0 (0.00)	.20
TESSsum ^b , median (25th, 75th percentiles)	8 (8, 9)	8 (8, 8)	8 (8, 9)	8 (8, 8)	8 (8, 9)	8 (8, 9)	.45
Akathisia/TESS ≥ 2, n (%)	5 (2.02)	3 (6.12)	0 (0.00)	0 (0.00)	1 (1.00)	1 (16.67) ^c	.01*
Wk 12	n = 259	n = 49	n = 51	n = 50	n = 101	n = 8	
Antipsychotic dose, mean ± SD	N/A	11.76 ± 7.39	9.68 ± 6.85	231.9 ± 184.3	1.38 ± 1.17	63.3 ± 52.8	N/A
Parkinsonism (mean SAS>0.33), n (%)	29 (11.20)	13 (26.53)	4 (7.85)	3 (6.00)	7 (6.93)	2 (25.00)	.003*
Drug-induced parkinsonism, ^a n (%)	27 (10.42)	13 (26.53)	4 (7.85)	1 (2.00)	7 (6.93)	2 (25.00)	.0003*
SAS total, mean ± SD ^a	1.29 ± 2.25	2.22 ± 2.74	1.02 ± 1.54	0.62 ± 1.14	1.11 ± 2.42	2.13 ± 3.87	.003*

TABLE S1 Continued

Wk 12 Antipsychotic dose, mean $\pm$ SD	n = 259 N/A	n = 49 11.76 $\pm$ 7.39	n = 51 9.68 $\pm$ 6.85	n = 50 231.9 $\pm$ 184.3	n = 101 1.38 $\pm$ 1.17	n = 8 63.3 $\pm$ 52.8	N/A
Dyskinesia, n (%)	20 (7.72)	2 (4.17)	6 (11.76)	6 (12.00)	4 (3.92)	2 (25.00)	.07
Treatment-emergent dyskinesia, ^b n (%)	12 (4.63)	0 (0.00)	3 (5.88)	2 (4.00)	1 (0.98)	2 (25.00)	.05*
AIMS total, mean $\pm$ SD	1.62 $\pm$ 2.21	1.49 $\pm$ 1.41	1.67 $\pm$ 2.85	2.04 $\pm$ 2.79	1.43 $\pm$ 1.67	2.13 $\pm$ 3.44	.65
Akathisia, n (%)	7 (2.78)	3 (6.25)	2 (4.00)	0 (0.00)	2 (2.06)	0 (0.00)	.38
+Anticholinergic, n (%)	10 (2.92)	3 (4.55)	0 (0.0)	0 (0.0)	12 (8.76)	0 (0.0)	.002*
>2 in any neuromotor TESS item; n (%)	5 (2.0)	0 (0.00)	1 (2.17)	0 (0.00)	3 (3.09)	1 (12.50)	.14
TESSsum ^b , median (25th, 75th percentiles)	8 (8, 9)	8 (8, 8.5)	8 (8, 9)	8 (8, 8)	8 (8, 9)	8.5 (8, 9)	.32
Akathisia/TESS $\geq$ 2, n (%)	4 (1.62)	2 (4.44)	0 (0.00)	0 (0.00)	1 (2.00)	1 (12.50)	.03*
Parkinsonism per CATIE threshold							
Baseline, n (%)	3 (0.88)	0 (0.00)	0 (0.00)	1 (1.52)	0 (0.00)	2 (13.33)	.0001*
Wk 4, n (%)	9 (2.72)	3 (4.62)	0 (0.00)	0 (0.00)	5 (3.73)	1 (6.76)	.23
Wk 8, n (%)	7 (2.76)	4 (7.55)	0 (0.00)	0 (0.00)	2 (2.02)	1 (14.29)	.03*
Wk 12, n (%)	6 (2.32)	1 (2.04)	0 (0.00)	0 (0.00)	4 (3.96)	1 (12.50)	.12

Note: AIMS = Abnormal Involuntary Movement Scale; CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness; N/A = not applicable; SAS = Simpson—Angus Scale; TESS = Treatment-Emergent Symptoms Scale.

^aGroup comparisons remain significant if restricted to antipsychotic-naïve patients.

^bTESSsum reflects sum of 8 neuromotor complaints.

^cFor this TESS assessment, n = 6.

*Significant between-group differences (p < .05).

TABLE S2 Baseline and 4-Week Rating Scale–Based Neuromotor Characteristics by Baseline Medication Status and Diagnostic Subgroup

Time	Outcome	Antipsychotic-Naive (n = 221)	Antipsychotic History ^a (n = 57)	Antipsychotic Switch (n = 60)	p
Baseline	Parkinsonism, n (%)	8 (3.56)	2 (3.51)	9 (11.67)	.03
	SAS total, mean ± SD	0.55 ± 1.35	0.49 ± 1.05	1.41 ± 2.70	.001
	Significant dyskinesia, n (%)	8 (3.62)	7 (12.28) ^b	8 (13.33) ^b	.006
	AIMS total, mean ± SD	1.00 ± 1.54	1.79 ± 2.97	1.60 ± 2.79	.013
	Akathisia, n (%)	1 (0.44)	1 (1.75)	0 (0.00)	.41
4-wk	Parkinsonism, n (%)	18 (8.14)	4 (7.69)	18 (8.14)	.09
	SAS total, mean ± SD	1.16 ± 2.32	0.94 ± 1.41	1.66 ± 2.91	.23
	Significant dyskinesia, n (%)	13 (5.91)	4 (7.84)	5 (8.47)	.72
	AIMS total, mean ± SD	1.30 ± 0.14	1.86 ± 0.30	1.68 ± 0.28	.51
	Akathisia, n (%)	6 (2.71)	0 (0.00)	2 (3.45)	.44
Subgroup Results for Antipsychotic-Naive, Baseline Medication-Free Participants (n = 102)					
	Outcome	Aggression Spectrum Disorder (n = 44)	Mood Spectrum Disorder (n = 25)	Schizophrenia Spectrum Disorder (n = 33)	p
Baseline	Parkinsonism, n (%)	3 (6.82)	2 (8.00)	2 (6.06)	.96
	SAS total, mean ± SD	0.48 ± 0.27	0.88 ± 0.36	0.85 ± 0.31	.56
	Significant dyskinesia, n (%)	5 (11.36)	3 (12.00)	0 (0.0)	.04
	AIMS total, mean ± SD	1.77 ± 0.29	1.84 ± 0.38	0.42 ± 0.33	.004
	Parkinsonism, n (%)	4 (9.76)	0 (0.0)	4 (12.0)	.08
4-wk	SAS total, mean ± SD	0.78 ± 0.34	0.52 ± 0.44	1.72 ± 0.39	.09
	Significant dyskinesia, n (%)	3 (7.14)	1 (4.0)	0 (0.0)	.17
	AIMS total, mean ± SD	1.98 ± 0.28	1.88 ± 0.37	0.53 ± 0.32	.002

Note: AIMS = Abnormal Involuntary Movement Scale; SAS = Simpson–Angus Scale.

^aAntipsychotic history: at least 1 mo off antipsychotics.

^bIn these patients, the mean number of prior antipsychotic trials was 2 (±1), and the mean duration antipsychotic treatment was 14.38 (±16.96) mo.

TABLE S3 Specific Reported Neuromotor Side Effects: Treatment-Emergent Symptoms Scale (TESS), Total Cohort

TESS Item Rating ≥2	Baseline; n (%)	Wk 4, n (%)	Wk 8, n (%)	Wk 12, n (%)
Tremor	37 (11.38)	44 (18.63)	37 (15.85)	43 (17.34)
Muscle pain/stiffness	9 (2.8)	26 (8.02)	16 (6.45)	11 (4.45)
Joint pain/stiffness	21 (6.50)	19 (5.9)	9 (3.61)	8 (3.23)
Rigidity	3 (0.6)	6 (1.87)	5 (2.4)	1 (0.40)
Myoclonus	19 (5.77)	18 (5.32)	13 (5.26)	8 (3.23)
Cramps	9 (2.8)	8 (2.5)	1 (0.4)	5 (2.1)
Dystonia	3 (0.6)	2 (0.06)	0 (0.00)	0 (0.00)
Dyskinesia	3 (0.6)	2 (0.06)	2 (0.8)	5 (1.63)