Real-World Adverse Event Profile and Comorbidity Index in Children and Adolescents With Tourette Syndrome (TS) Treated With Dopamine D2 Receptor Antagonists

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*At time study was conducted.

BACKGROUND

- Psychiatric comorbidities are prevalent in Tourette syndrome (TS) populations[1]
- Dopamine D2 receptor antagonists/partial agonists (D2RAs) reduce tic severity but pose a substantial risk of adverse events (AEs; eg, metabolic/weight effects, sedation, extrapyramidal symptoms) that can negatively impact quality of life and treatment adherence[2-7]
  - Non-D2RA medications (eg, α-2 adrenergic agonists) are frequently administered to treat tics, but such use is off-label administration

OBJECTIVE

- To further explore the real-world incidence of AEs among children and adolescents with TS treated with D2RAs compared with a matched TS cohort without D2RA exposure

METHODS

- Data were analyzed retrospectively using an electronic health records database (TriNetX Dataworks-USA Network)
- The D2RA-exposed cohort was indexed at the first D2RA record (2011-2021; aripiprazole, haloperidol, olanzapine, pimozide, quetiapine, risperidone, or ziprasidone) with prior TS diagnosis during the baseline period (18 months before and including index): ICD-9-CM: 307.23/ ICD-10-CM: F952; the non-D2RA cohort was indexed on a randomly selected record with TS diagnosis (2011-2021)
- Patients in both cohorts were required to be 6 to 17 years of age on the index date and to have ≥1 health care encounter with any diagnosis code during both the baseline period and the 18-month follow-up period; individuals in each cohort were exact-matched based on age group, sex, index year, and region
- Baseline comorbidity index was calculated using a validated pediatric comorbidity index (higher scores represented increased hospitalization risk)
- During the follow-up period, incident AEs (ie, not present during baseline period) were identified based on a combination of diagnosis codes, anthropomorphic measurements (ie, body mass index z-score), and laboratory data and cohorts were compared using standardized mean difference (SMD; ≥|0.10| indicated meaningful imbalance)
  - AEs were prespecified based on consensus regarding clinical relevance and categorized according to body system (neuropsychiatric, cardiac, metabolic, or hematologic) and intensity (mild, moderate, or severe; **Table 1**)

Table 1. Categorization for Incident AEs

System	Intensity	Incident AE	ICD-9-CM Diagnosis Code(s)	ICD-10-CM Code(s)
Neuropsychiatric	Mild	Sleep disorders	780.5x	F519, G47x
		OCD	300.3	F42x, R4681
	Moderate	Dystonia	333.7, 333.6, 333.8	G241, G24
		Akathisia	333.99	G2571
		Other extrapyramidal symptoms*	333.9, 333	G26, G25
	Severe	Tardive dyskinesia	333.85	G2401
		Neuroleptic malignant syndrome	333.92	G210
		Suicidality†	E950-E959, V62.84	Y870, X60-X84, R45851
		Depression	311	F32x
Cardiac	Moderate	Orthostatic hypotension	458	I951
		QT prolongation	426.82	I4581
		Bradycardia/tachycardia	427, 785	R001, R000, I471, I472, I479
	Severe	Malignant arrhythmias‡	427.xx, 798.x	I49, I4721
		Myocarditis	422, 429	I40, I41, I514
Metabolic	Mild	Mild metabolic syndrome§	NA	NA
	Moderate	Moderate metabolic syndrome§	NA	NA
Hematologic	Moderate	Leukopenia/neutropenia	288	D70

*Restlessness, urge to move, fidgety, rocking, rigidity, stiffness, bradykinesia, tremor, or postural instability. †Suicidal ideation, suicidal behavior, or suicide attempts. ‡Including torsades de pointes. §Mild defined as 1-2 clinical features suggestive of metabolic syndrome conditions and moderate defined as 3-5 clinical features suggestive of metabolic syndrome conditions. Clinical features included body mass index z-score indicating obesity; hypertension; triglycerides ≥100 mg/dL; high-density lipoprotein cholesterol ≤50 mg/dL; prediabetes; diabetes; fasting glucose ≥110 mg/dL; and hemoglobin A_{1c} ≥5.7%.

AE = adverse event; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification; NA = not applicable; OCD = obsessive-compulsive disorder.

RESULTS

- 1684 individuals were included in each matched cohort (**Table 2**)
  - Mean (SD) baseline comorbidity index was higher for the D2RA-exposed versus nonexposed cohort (3.4 [3.5] vs 2.1 [2.5]; SMD = 0.44)

Table 2. Patient Demographic and Baseline Characteristics After Matching

Characteristic	D2RA-Exposed (n=1684)	D2RA-Nonexposed (n=1684)	SMD*
Age, y			
Mean (SD)	12.7 (2.9)	12.5 (2.9)	0.07
Median	13	13	—
Age group, n (%)			
6-11 y	576 (34.2)	576 (34.2)	0.00
12-17 y	1108 (65.8)	1108 (65.8)	0.00
Male, n (%)	1245 (73.9)	1245 (73.9)	0.00
Race, n (%)			
White	1290 (76.6)	1225 (72.7)	0.09
Black	87 (5.2)	105 (6.2)	−0.05
Asian	27 (1.6)	29 (1.7)	−0.01
American Indian or Alaska Native	11 (0.7)	7 (0.4)	0.03
Native Hawaiian or Other Pacific Islander	4 (0.2)	4 (0.2)	0.00
Missing	265 (15.7)	314 (18.6)	−0.08
Ethnicity, n (%)			
Not Hispanic or Latino	1428 (84.8)	1342 (79.7)	0.13
Hispanic or Latino	110 (6.5)	154 (9.1)	−0.10
Missing	146 (8.7)	188 (11.2)	−0.08
BMI category, n (%)†			
Underweight	54 (3.2)	55 (3.3)	−0.003
Normal weight	652 (38.7)	555 (33.0)	0.12
Overweight	171 (10.2)	118 (7.0)	0.11
Obesity	217 (12.9)	168 (10.0)	0.09
Missing	590 (35.0)	788 (46.8)	−0.24
Metabolic syndrome, n (%)			
Unknown	1347 (80.0)	1456 (86.5)	−0.17
Mild‡	318 (18.9)	216 (12.8)	0.17
Moderate‡	19 (1.1)	12 (0.7)	0.04
Neuropsychiatric comorbidities, n (%)			
Anxiety	998 (59.3)	680 (40.4)	0.38
ADHD	960 (57.0)	637 (37.8)	0.39
OCD	432 (25.7)	242 (14.4)	0.28
Depression/mood disorder	276 (16.4)	111 (6.6)	0.31
Autism spectrum disorder	256 (15.2)	135 (8.0)	0.23
Sleep disorder	200 (11.9)	137 (8.1)	0.12
Headache/migraine	147 (8.7)	150 (8.9)	−0.01
Suicidality/suicide attempt	134 (8.0)	24 (1.4)	0.31
Abnormal involuntary movements	81 (4.8)	82 (4.9)	0.00
Non-D2RA medications, n (%)			
Guanfacine	669 (39.7)	386 (22.9)	0.37
Clonidine	422 (25.1)	194 (11.5)	0.36
Topiramate	147 (8.7)	75 (4.5)	0.17
Botulinum toxin A	2 (0.1)	2 (0.1)	0.00
Other medications, n (%)			
Antidepressant	922 (54.8)	346 (20.5)	0.75
ADHD medication	621 (36.9)	331 (19.7)	0.39
Antianxiety§	340 (20.2)	122 (7.2)	0.38
Antiseizure¶	222 (13.2)	81 (4.8)	0.30

*SMD ≥|0.10| indicates meaningful imbalance between cohorts. †Underweight (BMI z-score <−1.6); normal weight (BMI z-score −1.6 to <1.0); overweight (BMI z-score 1.0 to <1.6); and obesity (BMI z-score ≥1.6). ‡Mild (1-2 metabolic syndrome conditions) and moderate (3-5 metabolic syndrome conditions). §Benzodiazepine (did not include clonazepam) or buspirone. ¶Did not include topiramate.

ADHD = attention-deficit/hyperactivity disorder; BMI = body mass index; D2RA = dopamine D2 receptor antagonist/partial agonist; OCD = obsessive-compulsive disorder; SMD = standardized mean difference.

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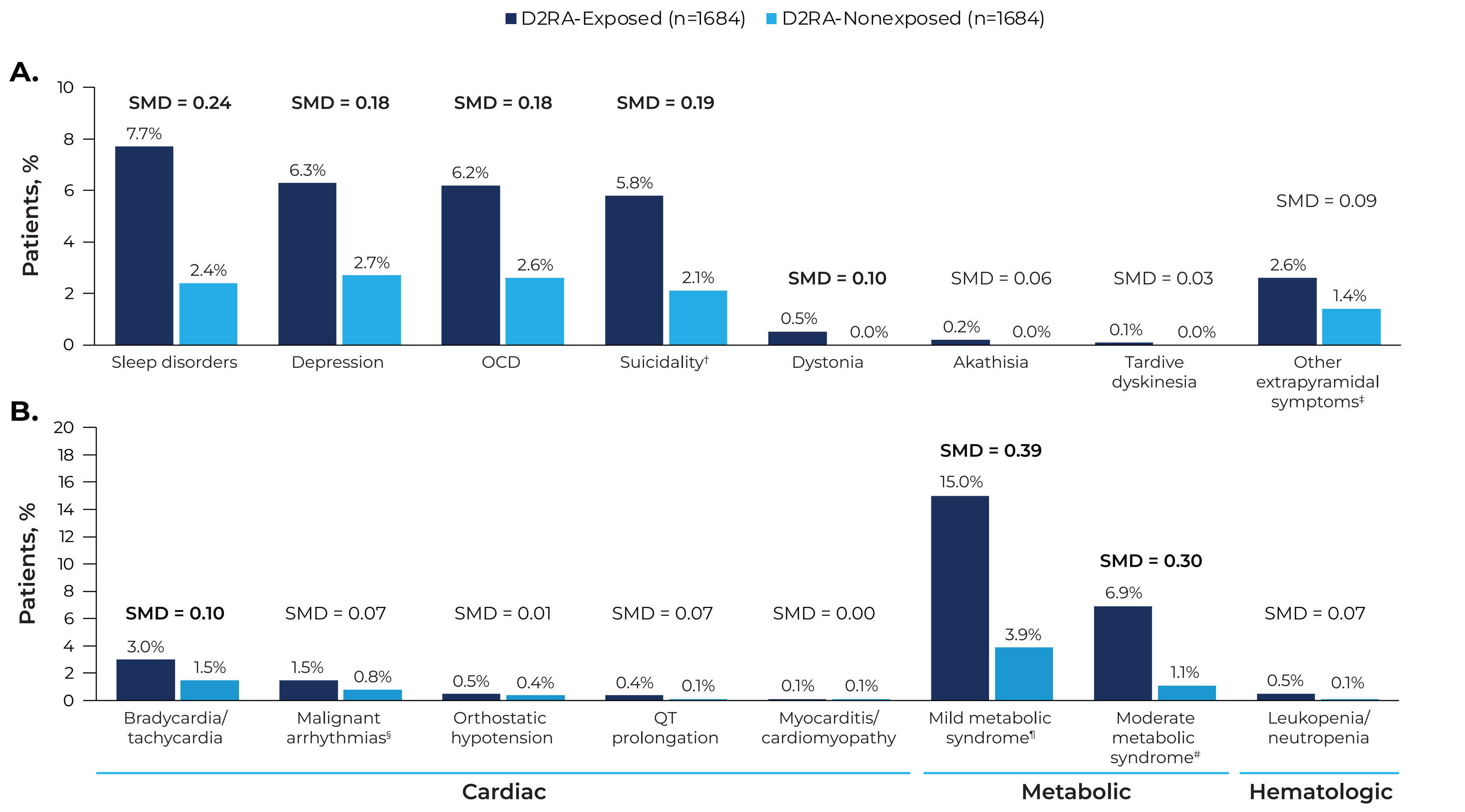
DISCLOSURES:

DAI reports being a clinical trial site investigator for Emalex Biosciences, Inc., and receiving funding from the National Institute of Neurological Disorders and Stroke and Teva Branded Pharmaceutical Products, R&D, Inc. JPS is a former employee of Thermo Fisher Scientific, a company that received funding from Emalex Biosciences, Inc., to conduct the analyses. FMD, FM, and CAP are employees of Thermo Fisher Scientific. DLG reports being a clinical trial site investigator for Emalex Biosciences, Inc., Neurocrine Biosciences, PTC Therapeutics, and Quince Therapeutics. He has received consulting fees from Acadia Pharmaceuticals, Emalex Biosciences, Inc., Health Advances, and Vima Therapeutics; travel support from Emalex Biosciences, Inc.; compensation for producing educational content for MEDLIVE and PTC Therapeutics; and book royalties from Elsevier and Wolters Kluwer. GBK, SDA, and FEM are employees of and have personal equity interest in Emalex Biosciences, Inc. SPW and TMC are employees of Paragon Biosciences, LLC, which has controlling equity interest in Emalex Biosciences, Inc.; additionally, they have personal equity interest in Emalex Biosciences, Inc. KKT reports being a clinical trial site investigator for Emalex Biosciences, Inc., receiving travel support from Emalex Biosciences, Inc., and receiving consulting fees from Frazier Life Sciences, Gerson Lehrman Group, Guidepoint Global, Health Advances, and Jazz Pharmaceuticals.

- Multiple types of incident AEs during follow-up were more common in the D2RA-exposed cohort than in the D2RA-nonexposed cohort (**Figure 1A** and **1B**)

Figure 1. Summary of Incident (A) Neuropsychiatric and (B) Cardiac, Metabolic, and Hematologic AEs*



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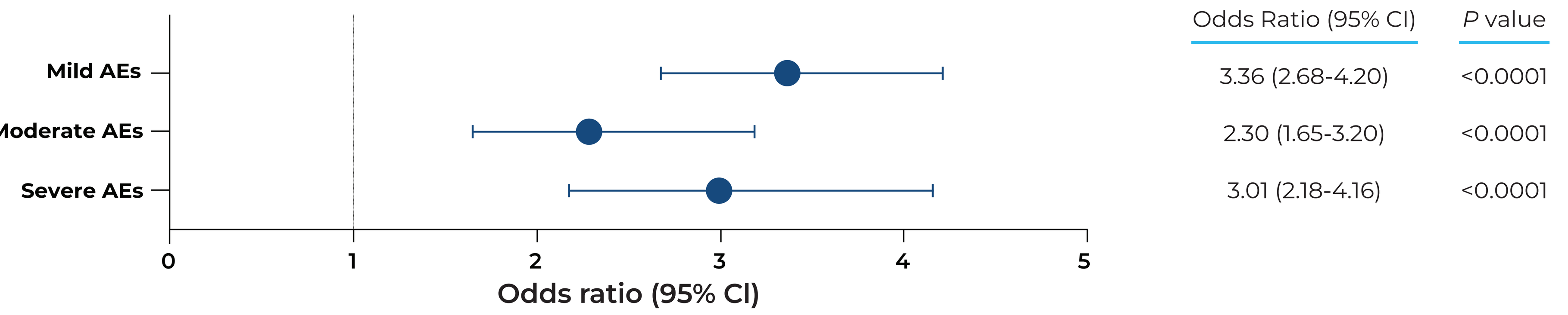
AE = adverse event; D2RA = dopamine D2 receptor antagonist/partial agonist; OCD = obsessive-compulsive disorder; SMD = standardized mean difference.

- After multivariable adjustment for demographic and baseline characteristics, children and adolescents in the D2RA-exposed cohort had higher odds of experiencing incident mild, moderate, or severe AEs than did those in the D2RA-nonexposed cohort (P<0.0001 for all; **Figure 2**)

Figure 2. Odds of Experiencing a Mild, Moderate, or Severe Incident AE in the D2RA-Exposed Cohort Compared With the D2RA-Nonexposed Cohort



AE = adverse event; D2RA = dopamine D2 receptor antagonist/partial agonist.

CONCLUSIONS

- In this real-world study of children and adolescents with TS, metabolic and neuropsychiatric AEs were more common among those treated with D2RAs
- Although causality cannot be inferred from the current study, treatment with D2RAs may contribute to increased odds of AEs analyzed and/or patients treated with D2RAs may have a greater burden of mental and physical health disorders, independent of exposure
- Alternative treatment strategies and pharmacologic interventions are needed that can provide sustained relief of symptoms with minimal risk of AEs