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Diagnostic Trends and Prescription Patterns in Disruptive Mood Dysregulation Disorder and Bipolar Disorder

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Objective: Disruptive mood dysregulation disorder (DMDD) was introduced in *DSM-5* to distinguish a subset of chronically irritable youth who may be incorrectly diagnosed and/or treated for pediatric bipolar disorder (BPD). This study characterized the rate of new treatment episodes and treated prevalence of BPD and DMDD from a longitudinal electronic health record database and examined the impact of DMDD on prescription trends.

Method: A retrospective cohort study using 2008-2018 Optum electronic health record data was conducted. Youth aged 10 to < 18 years with ≥ 183 days of database enrollment before the study cohort entry were included. Annual new treatment episode rates per 1,000 patient-years and treated prevalence (%) were estimated. Prescriptions for medications, concomitant diagnoses, and acute mental health service use for 2016-2018 were evaluated.

Results: There were 7,677 youths with DMDD and 6,480 youths with BPD identified. Mean age (13-15 years) and ethnicity were similar for both groups. A rise in new treatment episode rates (0.87-1.75 per 1,000 patient-years, $p < .0001$) and treated prevalence (0.08%-0.35%, $p < .0001$) of DMDD diagnoses (2016-2018) following diagnosis inception was paralleled by decreasing new treatment episode rates (1.22-1.14 per 1,000 patient-years, $p < .01$) and treated prevalence (0.42%-0.36%, $p < .0001$) of BPD diagnoses (2015-2018). More youth in the DMDD group were prescribed medications compared with the BPD group (81.9% vs 69.4%), including antipsychotics (58.9% vs 51.0%). Higher proportions of youth with DMDD vs youth with BPD had disruptive behavior disorders (eg, 35.9% vs 20.5% had oppositional defiant disorder), and required inpatient hospitalization related to their mental health disorder (45.0% vs 33.0%).

Conclusion: Diagnosis of DMDD has had rapid uptake in clinical practice but is associated with increased antipsychotic and polypharmacy prescriptions and higher rates of comorbidity and inpatient hospitalization in youth with a DMDD diagnosis compared with a BPD diagnosis.

Key words: antipsychotics, bipolar disorder, disruptive mood dysregulation disorder, pediatric

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With the publication of *DSM-5* in 2013, a new diagnostic entity entered the psychiatric nosology—disruptive mood dysregulation disorder (DMDD). DMDD is a childhood-onset depressive disorder that is characterized by a persistently irritable or angry mood that is punctuated by frequent and disproportionally severe temper outbursts.[1,2] According to *DSM-5*, DMDD can be diagnosed only in children older than 6 years of age, and onset must be observed by the age of 10 years, with a minimum symptom duration of 1 year. Per its definition, patients cannot have both DMDD and bipolar disorder (BPD).[1,2] At the time of its inclusion into current nosology, it was assumed that the prevalence of DMDD during a 6-month to 1-year epoch would be approximately 2%-5%, based on extrapolation from rates of chronic and severe persistent irritability.[1]

On a related note, in the years before the release of *DSM-5*, the rates at which youths were given the diagnosis of BPD substantially increased.[3-5] With this increase, concerns were raised that chronically irritable youth without spontaneous mood episodes who also had explosive outbursts were erroneously being given a diagnosis of BPD.[1]

During the time before the release of *DSM-5*, 2 other salient events also occurred. First, new data supporting the efficacy of several antipsychotics in the treatment of BPD were reported.[6] Second, the rates at which antipsychotic medications, particularly atypical antipsychotics, were prescribed to children and adolescents substantially increased during the period 1993-2010.[7,8] These trends raised concern regarding the potential adverse effects of antipsychotics and a relative paucity of data concerning long-term

safety of these medications in children and adolescents.[8-10] When taken together, the association between the putative overdiagnosis of BPD[3-5] coupled with the substantial rise in the use of antipsychotic medications in youth[7,8] led to concerns that many children and adolescents were being erroneously prescribed antipsychotics owing to BPD being misdiagnosed. The DMDD diagnosis was developed, in part, in hopes of addressing this concern.[1]

The purpose of this study was to describe the rate of new treatment episodes and treated prevalence of the diagnosis of BPD and DMDD in clinical practice in youth, based on analysis of treatment episodes from a longitudinal dataset that both preceded and subsequently overlapped the introduction of the DMDD diagnosis in 2013, to determine the impact of DMDD on the diagnosis of BPD. An additional goal was to describe the demographic and clinical characteristics of groups of youth with either BPD or DMDD. Because concern regarding the improper prescription of antipsychotics to children and adolescents was a factor leading to the creation of DMDD, psychiatric medications prescribed to each of these groups were also considered.

METHOD

Study Setting

This was a retrospective cohort study covering the period from January 1, 2008, to December 31, 2018. The study included youth aged 10 to <18 years with an electronic health record (EHR) in the Optum (Optum, Inc, Eden Prairie, Minnesota) EHR database during the study period.[11] The age range selected for study was based on recommendations regarding the age range in which BPD can be reliably diagnosed in children and adolescents in routine clinical practice.[12]

Two key outcomes of interest in this study were the diagnostic categories, BPD and DMDD. BPD was coded in the database using *International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification* (*ICD-9-CM, ICD-10-CM*) (see Supplement 1, available online). In the *ICD-9-CM* system, however, DMDD maps to the nonspecific diagnosis code 296.99 for "other specified episodic mood disorder," which includes additional diagnostic categories. Therefore, in this study, DMDD was defined by the *ICD-10-CM* code F34.81, which is specific to the DMDD diagnosis.

For the purposes of this study, a youth was included as a patient with BPD or DMDD if they were documented as having the same diagnosis at 2 separate visit dates. This criterion was used to eliminate patients who may have been given the diagnosis of BPD or DMDD temporarily on a provisional or rule out basis. To be consistent with the *DSM-5* diagnostic requirement that DMDD and BPD cannot coexist,[1] patients were excluded from the analysis if they had simultaneous diagnoses of BPD and DMDD recorded at the same visit.[1] The index date (cohort entry date) for the study analysis was defined as the date on which a subject had been continuously enrolled in the database for a minimum period of 6 months (183 days).[13,14]

Databases

The Optum EHR database was used for this study.[11] Optum partners directly with multispecialty medical groups, integrated delivery networks, and hospital chains to extract data from their EHRs and various information technology systems in the United States. The data are then normalized, validated, and aggregated to provide a longitudinal database of patient care, comprising secondary, de-identified, structured (coded) data and unstructured (natural language processing–derived) data.[11,15-17] Natural language processing technology is used to extract data directly from practitioner notes, including patient symptoms, rationale concerning prescription choices, family history, and medication changes. For this study, however, only structured data (ie, coded data) were included in the analysis. Additional information on the Optum EHR database is provided in Supplement 1, available online. The Optum EHR database has been used in a number of previous studies.[18-22]

All data used in this study were de-identified, following the Health Insurance Portability and Accountability Act of 1996 de-identification statistical rules by the data vendor.[11,15-17,22] This study did not involve active enrollment of patients, and no data were collected directly from individuals. All data are compliant with the Health Insurance Portability and Accountability Act of 1996. Therefore, the study did not require institutional review board approval.

Although DMDD was included in *DSM-5* as a diagnosis in October 2013, the Optum EHR database did not start implementing *ICD-10-CM* codes until October 2015. Consequently, at the time of this study, while BPD diagnostic data were available for the period 2008-2018, DMDD diagnostic data, based on *ICD-10-CM* coding, were available in the database only beginning in October 2015. As noted above, in the interval between the publication of *DSM-5* and the implementation of *ICD-10-CM* codes in the Optum EHR database, patients with a diagnosis of DMDD received the nonspecific *ICD-9-CM* code 296.99 for "other episodic mood disorder." Therefore, the 2016-2018 period was selected to calculate annual new treatment episode rates and the treated prevalence of clinical diagnoses of DMDD.

Demographic and Clinical Characteristics

Demographic characteristics were summarized for the cohort of youth with new treatment episode diagnoses of

BPD and DMDD. The demographic characteristics evaluated included age, gender, race, and ethnicity and regional distribution of cases of BPD and DMDD. Information on type of insurance coverage (based on encounter records) was available in the database and summarized for each diagnostic cohort.

The clinical characteristics summarized for each diagnostic cohort included comorbid psychiatric diagnoses, acute mental health service use, and prescription records. A comorbid condition was defined as any psychiatric diagnosis and concurrent treatment, such as any psychiatric prescription, that occurred within 6 months before or on or after the first diagnosis of the outcome of interest, respectively. Acute mental health service use was defined as any psychiatric hospitalization or emergency department visit linked to the primary diagnosis of BPD or DMDD that occurred during the period following from the new treatment episode diagnosis of BPD or DMDD until the end of the study observation period. The methodology used to identify and select the concurrent prescription records, the comorbid diagnoses, and episodes of acute mental health service utilization is described in detail in Supplement 1, available online.

Statistical Analyses

The study was designed and executed as an exploratory, descriptive study with 2 primary goals: to describe the occurrence of clinical diagnoses of BPD and DMDD over time and to document the rates and types of medication prescribing in these groups of patients. No specific hypothesis or inferential testing with statistical adjustment was proposed or undertaken in this descriptive study. However, we have reported 95% CIs for new treatment episode rates, the treated prevalence, and all proportions or rates in this study. Data sampling was not performed because all patients in the database were considered for inclusion in the study; the patients who met the study inclusion criteria were included in the analysis.

Descriptive analyses were performed to characterize the patient demographics, clinical characteristics (ie, comorbid diagnoses and mental health service use), socioeconomic characteristics, and concurrent treatments for the incident BPD cohort for the periods 2008-2013 and 2016-2018 and for the incident DMDD cohort for the period 2016-2018. The 2008-2013 period provides data on youth with a diagnosis of BPD before the introduction of the DMDD diagnosis in *DSM-5* in October 2013. The 2014-2015 period was excluded from the analysis because during these years the DMDD diagnosis had come into effect but was coded in the Optum EHR database using a nonspecific *ICD-9-CM* code (ie, 296.99 for "other episodic mood disorder"). Continuous data were expressed as mean and SD. Dichotomous and categorical data were expressed as counts and percentages of patients in the categories, followed by 95% CI.

The rates of occurrence of the clinical diagnoses of BPD and DMDD presented in this article were derived from an analysis of new treatment episodes (ie, clinical visits associated with the diagnosis) for the disorder of interest in the Optum database. Therefore, the terms new treatment episodes and treated prevalence are used to distinguish these rates from standard epidemiological definitions of incidence and prevalence.

New treatment episode refers to the first occurrence of the outcome of interest during the study period (ie, diagnosis of DMDD or BPD). For new treatment episode rate calculations, a 6-month (183-day) washout period for the outcomes of interest was applied to exclude all prevalent cases that occurred within 183 days before and on the index date. Patients were followed from the index date until the first occurrence of the outcome of interest, death, end of the enrollment in the database, or end of the study period, whichever occurred first. Annual new treatment episode rates per 1,000 patient-years (PY) and 95% CIs were calculated for the BPD diagnosis over the period 2008-2018 and for the DMDD diagnosis for the 2016-2018 period.[13,14] A sensitivity analysis using a 12-month washout period was performed to assess the impact of a longer washout period on the new treatment episode rate calculations. For the treated prevalence calculation, if a patient was a case (defined by any occurrences of the outcome of interest) in the previous annual period or was a case during the 6 months (183 days) on or before the cohort entering date, the patient was considered a prevalent case in the rest of the study period. Annual treated prevalence and 95% CIs were calculated for the BPD diagnosis over the period 2008-2018 and for the DMDD diagnosis over the 2016-2018 period. Trend analyses using Poisson regression also were performed to assess new treatment episode rate and treated prevalence trends over the period 2008-2018 for BPD and the period 2016-2018 for DMDD.

To more fully assess the impact of the introduction of the DMDD diagnosis in 2013 on the subsequent diagnosis and treatment of BPD in youth, the data for the 2016-2018 time period (the period when the *ICD-10* codes for both BPD and DMDD were available in the database) were analyzed to determine the proportions of patients with medication prescriptions in each diagnostic cohort both before and following the first occurrence of the diagnosis.

A subset of patients was identified in the 2016-2018 time period whose diagnosis was changed from a preceding diagnosis of BPD to DMDD or from a preceding diagnosis of DMDD to BPD. Post hoc analyses were also conducted

in this subset of patients to examine the impact of the diagnostic change on the medications that they were prescribed. All analyses were carried out using SAS 9.4 (SAS Institute, Cary, North Carolina). Unless otherwise noted, data are presented as means (SD) or proportions (95% CI).

RESULTS

In the 2008-2013 period, 11,475 youths with BPD were identified, and in the 2016-2018 period, 6,480 youths with BPD and 7,677 youths with DMDD were identified (Table 1). There were 1,931 youths who had simultaneous diagnoses of both BPD and DMDD during the study period and were excluded from the analysis. A cohort eligibility flowchart is presented in Figure S1, available online. All additional results are included in Tables S1-S11 and Figures S1-S3, available online.

Demographic Characteristics

In comparison with the DMDD cohort in the 2016-2018 period, the BPD cohort from the same period was slightly older (mean [SD] age 14.8 [2.0] years vs 13.2 [2.2] years), had fewer male patients (41.1% [95% CI 39.9%-42.3%] vs 64.3% [95% CI 63.3%-65.4%]), and comprised more White youth (76.6% [95% CI 75.6%-77.6%] vs 73.2% [95% CI 72.2%-74.1%]) and fewer Black youth (12.3% [95% CI 11.5%-13.1%] vs 16.6% [95% CI 15.7%-17.4%]). The overall ethnicity profile was similar across the 2 groups, however (Table 1).

More than half of both the BPD (52.7%) and DMDD (62.3%) cases in the 2016-2018 period were from the Midwest region of the United States, while only 5.7% and 3.4%, respectively, were from the West census region. Approximately one-third of patients in both of these diagnostic groups were covered by commercial (private) insurance (29.9% [95% CI 29.8%-30.1%] vs 27.9% [95% CI 27.8%-27.9%]), another one-third were covered by Medicaid (29.9% [95% CI 29.8%-30.1%] vs 30.8% [95% CI 30.7%-30.9%]), and a slightly smaller proportion were uninsured (23.5% [95% CI 23.4%-23.6%] vs 27.3% [95% CI 27.2%-27.4%]), respectively.

Clinical Characteristics

In the 2008-2013 period, 80.0% of children and adolescents with a diagnosis of BPD had a comorbid psychiatric diagnosis. Following the introduction of the DMDD diagnosis, the proportion of youth with BPD and comorbid conditions in the 2016-2018 period increased to 89.8%. In that same 3-year period, the proportion of youth with DMDD and comorbid conditions was 97.3%. Of note, substantially higher proportions of disruptive behavioral disorders (Table 2), including attention-deficit/hyperactivity disorder (ADHD) (71.7% [95% CI 70.7%-72.7%] vs 47.8% [95% CI 46.6%-49.0%]) and oppositional defiant disorder (35.9% [95% CI 34.8%-37.0%] vs 20.5% [95% CI 19.5%-21.5%]), were diagnosed in the DMDD cohort compared with the BPD cohort in the 2016-2018 time period.

In the 2016-2018 period, the proportion of youth with emergency department visits was comparable between the 2 diagnostic cohorts (15.7% [95% CI 14.8%-16.6%] of youth with BPD vs 17.9% [95% CI 17.1%-18.8%] of youth with DMDD). However, a greater proportion of youth with DMDD had an inpatient hospitalization related to their mental health disorder (45.0% [95% CI 43.8%-46.1%]) vs youth with BPD (33.0% [95% CI 31.8%-34.1%]).

New Treatment Episode Rates and Treated Prevalence of Clinical Diagnoses of BPD and DMDD

There was a statistically significant ($p < .0001$) increase in new treatment episode rate of BPD new clinical diagnoses from 0.91 [95% CI 0.86-0.97] per 1,000 PY in 2008 to 1.21 [95% CI 1.17-1.26] per 1,000 PY in 2013. Thereafter the new treatment episode rate was generally stable until 2015, after which it appears to have declined over the years 2015-2018 (from 1.22 [95% CI 1.1.7-1.26] to 1.14 [95% CI 1.08-1.20] per 1,000 PY, $p < .01$) (Figure 1A; Figure S2 and Tables S1a and S2, available online). During the period 2016-2018, the new treatment episode rate of DMDD clinical diagnoses showed a statistically significant ($p < .0001$) rapid increase from 0.87 [95% CI 0.84-0.91] per 1,000 PY in 2016 to 1.75 [95% CI 1.67-1.82] per 1,000 PY in 2018, when it was 53.5% higher than the BPD rate of 1.14 [95% CI 1.08-1.20] per 1,000 PY in the same year. Of note, the sensitivity analysis results based on a 12-month washout period showed almost identical new treatment episode rates over these periods for both BPD and DMDD (Table S3, available online).

A similar pattern was also found over this period for the treated prevalence of the 2 diagnostic cohorts. The annual treated prevalence for the BPD clinical diagnoses mirrored the rise in new treatment episodes, showing a steady increase ($p < .0001$) from 2008 to a peak in 2015 and 2016, after which the BPD treated prevalence began to decline (Figure 1B; Figure S3 and Tables S1b and S4, available online). The treated prevalence of DMDD clinical diagnoses showed a rapid increase ($p < .0001$) from 2016 to 2018, when it was nearly identical with the treated prevalence of BPD. The detailed trend analysis results for the new treatment episode rates and treated prevalence of BDP over 2008-2018 and DMDD over 2016-2018 are presented in Figures S2 and S3, and Tables S2 and S4, available online.

TABLE 1 Demographic Characteristics of Youth Diagnosed With Pediatric Bipolar Disorder (BPD) (2008-2013 and 2016-2018) or Disruptive Mood Dysregulation Disorder (DMDD) (2016-2018) in the United States

Characteristic	BPD (2008-2013)		BPD (2016-2018)		DMDD (2016-2018)	
N	11,475		6,480		7,677	
	Mean (SD) n (%)	(95% CI)	Mean (SD) n (%)	(95% CI)	Mean (SD) n (%)	(95% CI)
Age, y	14.11 (2.14)		14.79 (2.00)		13.24 (2.20)	
Gender						
Male	5,950 (51.9)	(50.9-52.8)	2,666 (41.1)	(39.9-42.3)	4,939 (64.3)	(63.3-65.4)
Female	5,510 (48.0)	(47.1-48.9)	3,807 (58.8)	(57.6-60.0)	2,731 (35.6)	(34.5-36.6)
Unknown	15 (0.1)	(0.1-0.2)	7 (0.1)	(0.0-0.2)	7 (0.1)	(0.0-0.2)
Race						
White	8,939 (77.9)	(77.1-78.7)	4,964 (76.6)	(75.6-77.6)	5,616 (73.2)	(72.2-74.1)
Black	1,434 (12.5)	(11.9-13.1)	796 (12.3)	(11.5-13.1)	1,272 (16.6)	(15.7-17.4)
Asian	39 (0.3)	(0.2-0.5)	31 (0.5)	(0.3-0.7)	46 (0.6)	(0.4-0.8)
Other/unknown	1,063 (9.3)	(8.7-9.8)	689 (10.6)	(9.9-11.4)	743 (9.7)	(9.0-10.3)
Ethnicity						
Hispanic	567 (4.9)	(4.5-5.3)	564 (8.7)	(8.0-9.4)	529 (6.9)	(6.3-7.5)
Non-Hispanic	10,277 (89.6)	(89.0-90.1)	5,507 (85.0)	(84.1-85.9)	6,713 (87.4)	(86.7-88.2)
Unknown	631 (5.5)	(5.1-5.9)	409 (6.3)	(5.7-7.0)	435 (5.7)	(5.2-6.2)
Regional distribution of BPD and DMDD cases						
Midwest	6,420 (56.0)	(55.0-56.9)	3,416 (52.7)	(51.5-54.0)	4,782 (62.3)	(61.2-63.4)
Northeast	1,275 (11.1)	(10.5-11.7)	870 (13.4)	(12.6-14.3)	922 (12.0)	(11.3-12.7)
South	2,016 (17.6)	(16.9-18.3)	1,443 (22.3)	(21.3-23.3)	1,281 (16.7)	(15.9-17.5)
West	908 (7.9)	(7.4-8.4)	370 (5.7)	(5.1-6.3)	264 (3.4)	(3.0-3.9)
Other/unknown	856 (7.5)	(7.0-7.9)	381 (5.9)	(5.3-6.5)	428 (5.6)	(5.1-6.1)
Type of insurance, number of medical records						
Commercial	350,392 (28.8)	(28.7-28.8)	167,721 (29.9)	(29.8-30.1)	249,009 (27.9)	(27.8-27.9)
Medicaid	395,707 (32.5)	(32.4-32.6)	167,637 (29.9)	(29.8-30.1)	275,169 (30.8)	(30.7-30.9)
Medicare	14,071 (1.2)	(1.1-1.2)	2,050 (0.4)	(0.4-0.4)	4,008 (0.5)	(0.4-0.5)
Other payor type	32,916 (2.7)	(2.7-2.7)	10,303 (1.80)	(1.8-1.9)	14,759 (1.7)	(1.6-1.7)
Uninsured	240,643 (19.8)	(19.7-19.8)	131,630 (23.5)	(23.4-23.6)	244,245 (27.3)	(27.2-27.4)
Unknown	184,775 (15.2)	(15.1-15.2)	80,817 (14.4)	(14.3-14.5)	106,858 (12.0)	(11.9-12.0)

Note: *The denominators for the percentages reported in the table are the total numbers of patients with BPD and DMDD identified from the database in each period (as given in the first row of the table) or the total number of medical records for each type of insurance. The insurance data are not mutually exclusive because patients could have more than one type of insurance coverage.*

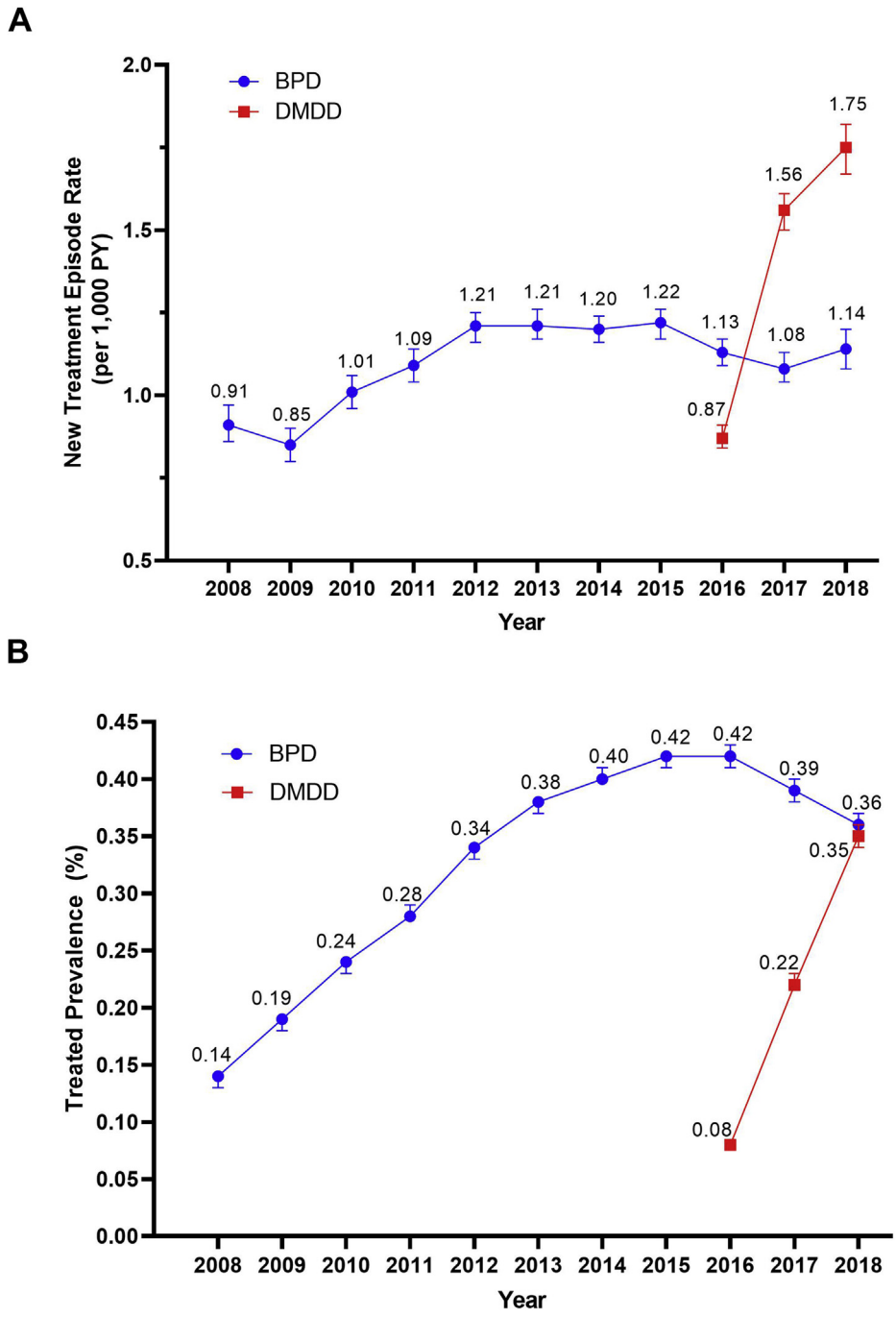
TABLE 2 Comorbid Conditions of Youth Diagnosed With Pediatric Bipolar Disorder (BPD) (2008-2013 and 2016-2018) or Disruptive Mood Dysregulation Disorder (DMDD) (2016-2018) in the United States

Comorbid condition	BPD (2008-2013)		BPD (2016-2018)		DMDD (2016-2018)	
N	11,475		6,480		7,677	
	n (%)	**(95% CI)**	**n (%)**	**(95% CI)**	**n (%)**	**(95% CI)**
ADHD	5,663 (49.4)	(48.4-50.3)	3,098 (47.81)	(46.6-49.0)	5,506 (71.7)	(70.7-72.7)
ODD	2,361 (20.6)	(19.8-21.3)	1,330 (20.5)	(19.5-21.5)	2,754 (35.9)	(34.8-37.0)
CD	1,564 (13.6)	(13.0-14.3)	1,018 (15.7)	(14.8-16.6)	2,077 (27.1)	(26.1-28.1)
IED	337 (2.9)	(2.6-3.3)	111 (1.7)	(1.4-2.0)	334 (4.4)	(3.9-4.8)
SUD	1,165 (10.2)	(9.6-10.7)	1,045 (16.1)	(15.2-17.0)	759 (9.9)	(9.2-10.6)
ASD	928 (8.1)	(7.6-8.6)	571 (8.8)	(8.1-9.5)	1,260 (16.4)	(15.6-17.2)
Anxiety disorders	2,454 (21.4)	(20.6-22.1)	3,089 (47.7)	(46.5-48.9)	3,855 (50.2)	(49.1-51.3)
PTSD	1,100 (9.6)	(9.1-10.1)	1,092 (16.9)	(15.9-17.8)	1,036 (13.5)	(12.7-14.3)
OCD	390 (3.4)	(3.1-3.7)	221 (3.4)	(3.0-3.9)	329 (4.3)	(3.8-4.7)
Depressive disorder[a]	3,821 (33.3)	(32.4-34.2)	3,245 (50.1)	(48.9-51.3)	5,381 (70.1)	(69.1-71.1)
Mental health service use						
Inpatient	3,494 (30.5)	(29.6-31.3)	2,136 (33.0)	(31.8-34.1)	3,451 (45.0)	(43.8-46.1)
ED	1,620 (14.1)	(13.5-14.8)	1,016 (15.7)	(14.8-16.6)	1,376 (17.9)	(17.1-18.8)

Note: ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CD = conduct disorder; ED = emergency department; IED = intermittent explosive disorder; OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; PTSD = posttraumatic stress disorder; SUD = substance use disorder.

[a]*Includes major depressive disorder and dysthymic disorder.*

FIGURE 1 New Treatment Episode Rates and Treated Prevalence of Pediatric Bipolar Disorder (BPD) and Disruptive Mood Dysregulation Disorder (DMDD) Among Youth 10 to <18 Years of Age in the United States



Note: (A) New treatment episode rates per 1,000 PY of BPD (2008-2018) and DMDD (2016-2018). (B) Annual treated prevalence (%) of BPD (2008-2018) and DMDD (2016-2018). Error bars reflect 95% CIs. Some 95% CIs in panel (B) are obscured by the main data points. PY = patient-years.

Concurrent Medication Prescriptions

Examination of concurrent medication prescription data from the 2 patient cohorts in the 2016-2018 period revealed that youth with a DMDD diagnosis were more likely to be prescribed any medication compared with youth with a BPD diagnosis (81.9% [95% CI 81.0%-82.8%] in DMDD group vs 69.4% [95% CI 68.3%-70.6%] in BPD group). In addition, youth in the DMDD group were more likely than youth in the BPD group to be prescribed 2 different medications (23.9% [95% CI 23.0%-24.9%] DMDD vs

19.7% [95% CI 18.7%-20.7%] BPD) or 3 or more different medications at the same time (45.0% [95% CI 43.9%-46.1%] in DMDD group vs 37.4% [95% CI 36.2%-38.6%] in BPD group) (Table S5, available online).

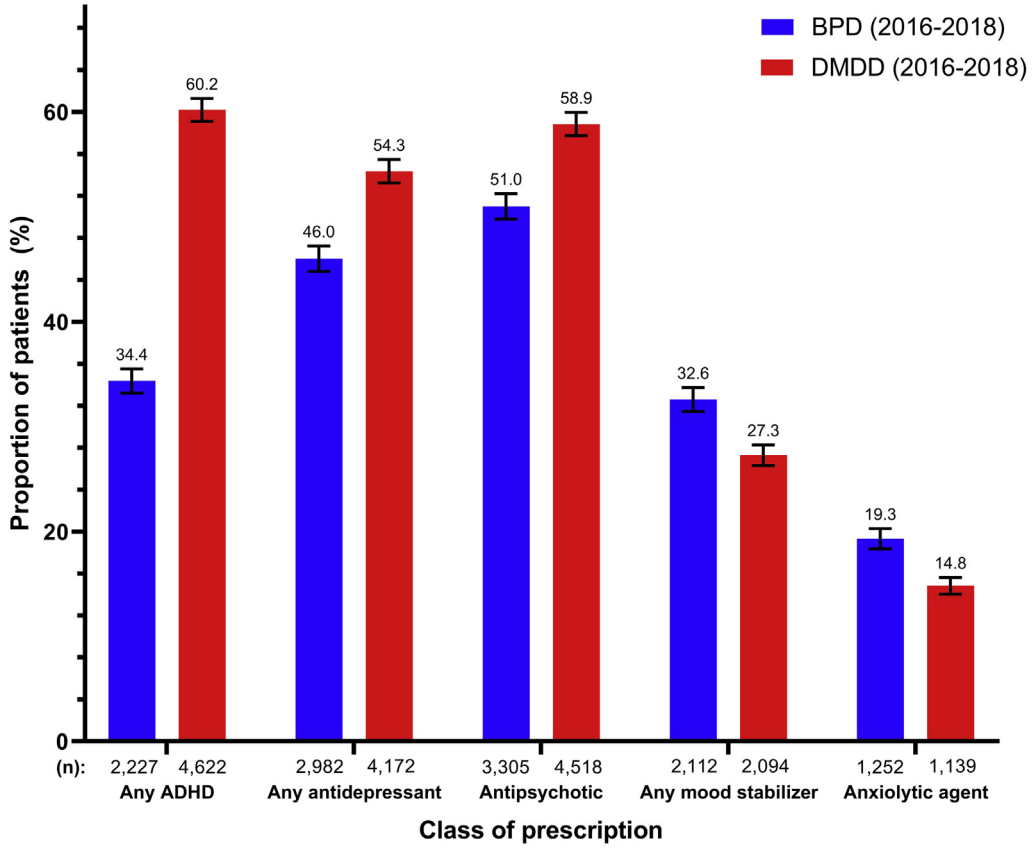
Specifically, prescriptions of ADHD medications, antidepressants, and antipsychotic medications were higher in the DMDD cohort compared with the BPD cohort. The proportion of youth with DMDD who were prescribed any ADHD medication was nearly twice that of the BPD group (60.2% [95% CI 59.1%-61.3%] in DMDD group vs 34.4% [95% CI 33.2%-35.5%] in BPD group) (Figure 2; Table S6, available online). Nearly 60% of youth with DMDD (58.9% [95% CI 57.8%-60.0%]) received an antipsychotic prescription compared with 51% [95% CI 49.8%-52.2%] of youth with BPD. In contrast, a greater proportion of youth with BPD were prescribed mood stabilizers or anxiolytics. Data on prescriptions of specific medications are presented in Table S7, available online.

Changes in Medication Prescriptions Before and Following New Treatment Episodes of DMDD or BPD

Within the 2016-2018 period, in the 6 months following the new treatment episode of BPD or DMDD, there was a rise in prescription of all drug categories, accompanied by a decrease in the proportion of patients in either diagnostic group who received no prescriptions (to 34.7% [95% CI 33.5%-35.8%] of youth with BPD and 21% [95% CI 20.1%-21.9%] of youth with DMDD) and an increase in the proportion of youth who were prescribed 3 or more medications at the same time (to 31.4% [95% CI 30.3%-32.5%] of youth with BPD and 39% [95% CI 37.5%-39.7%] of youth with DMDD) (Tables S8 and S9, available online).

The proportion of patients with DMDD who were given prescriptions increased across all drug categories following the first treatment episode of DMDD, with the largest increase observed in the prescription of antipsychotics (from 31.8% [95% CI 30.8%-32.9%] to 54.7% [95% CI 53.6%-55.8%]). However, mood stabilizer prescriptions increased

FIGURE 2 Comparison of Concurrent Prescriptions to Patients With Disruptive Mood Dysregulation Disorder (DMDD) or Pediatric Bipolar Disorder (BPD) Diagnoses by Drug Class for 2016-2018 (Within 6 Months Before and Following the New Treatment Episode)



Note: *Antipsychotic/antidepressant combination drugs not included because there were only 4 documented prescriptions in this class of medications. Error bars reflect 95% CIs. ADHD = attention-deficit/hyperactivity disorder.*

in the BPD cohort and somewhat exceeded that of the DMDD cohort following the first treatment episode of BPD (ie, 30.3% [95% CI 29.2%-31.5%] vs 24.9% [95% CI 23.9%-25.9%], respectively). Before the first treatment episode, prescriptions of mood stabilizers in the DMDD cohort had exceeded the BPD cohort (14.0% [95% CI 13.2%-14.8%] vs 10.9% [95% CI 10.2%-11.7%], respectively) (Tables S10 and S11, available online).

Youth Whose Diagnosis Changed From DMDD to BPD or From BPD to DMDD in 2016-2018

A subset of youth was identified in the 2016-2018 dataset who at different times were given either a diagnosis of BPD or a diagnosis of DMDD (but not both simultaneously). Of the BPD cohort, 96 (1.5%) youths were identified to have had a DMDD diagnosis before the date of their new treatment episode for the BPD diagnosis (hereafter referred to as the DMDD-to-BPD subgroup). Out of the DMDD cohort, 430 (5.6%) youths were identified to have had a BPD diagnosis before the date of their new treatment episode for the DMDD diagnosis (hereafter referred to as the BPD-to-DMDD subgroup).

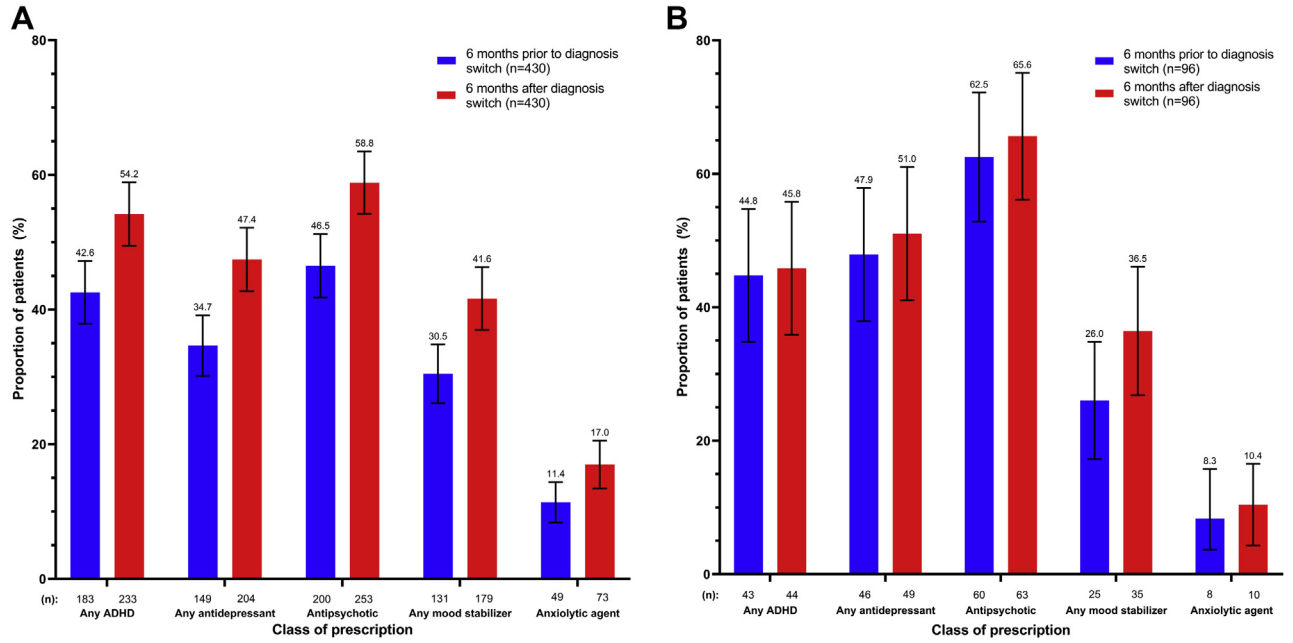
Medication Prescriptions in Youth Whose Diagnosis Changed

Over the 6-month period before the new treatment episode (during which youth in the DMDD-to-BPD group were presumed to have a diagnosis of DMDD and youth in the BPD-to-DMDD group were presumed to have a diagnosis of BPD), the number of prescriptions for antidepressants and antipsychotics was higher in the DMDD-to-BPD group than in the BPD-to-DMDD group, while mood stabilizers and anxiolytic medications were more commonly prescribed in the BPD-to-DMDD group (Figure 3).

In the 6-month period following the new treatment episode (when the presumptive diagnosis switched to DMDD in the BPD-to-DMDD group and to BPD in the DMDD-to-BPD youth), prescriptions of all classes of medications, including mood stabilizers, increased substantially in the BPD-to-DMDD group. For example, the proportion of youth in the BPD-to-DMDD group who were prescribed antipsychotics increased from 46.5% [95% CI 41.8%-51.23%] before the new treatment episode to 58.8% [95% CI 54.2%-63.5%] following the change in diagnosis and the proportion prescribed mood stabilizers increased from 30.5% [95% CI 26.1%-34.8%] to 41.6% [95% CI 37.0%-46.3%].

During this same period, however, the proportion of youth in the DMDD-to-BPD group (now presumed to have a diagnosis of BPD) who were prescribed ADHD medications, antidepressants, or antipsychotic medications remained relatively stable. Before the new treatment episode, the proportion of prescriptions of antipsychotics was 62.5% [95% CI 52.8%-72.2%], and following the switch in diagnosis it was 65.6% [95% CI 56.1%-75.1%]. The only drug class

FIGURE 3 Comparison of Concurrent Prescriptions Among Youth With a Diagnosis of Disruptive Mood Dysregulation Disorder (DMDD) or Pediatric Bipolar Disorder (BPD) in Whom Diagnosis Was Switched



Note: (A) Cohort that switched diagnosis from BPD to DMDD. (B) Cohort that switched diagnosis from DMDD to BPD. Error bars reflect 95% CIs. ADHD = attention-deficit/hyperactivity disorder.

with a notable change in prescribing following the change in diagnosis to BPD was mood stabilizers, which increased from 26.0% [95% CI 17.3%-34.8%] of patients before the change in diagnosis to 36.5% [95% CI 26.8%-46.1%] following the change in diagnosis. All additional results are included in Tables S1-S11, available online.

DISCUSSION

This retrospective cohort study with longitudinal health information of more than 25,000 patients within the Optum EHR database demonstrates that the DMDD diagnosis, introduced with publication of *DSM-5* in 2013, was rapidly incorporated into clinical practice. Based on the present analyses, clinicians in practice now appear to be diagnosing DMDD in youth more frequently than BPD. The statistically significant rise in the new treatment episode rates of youth 10-17 years of age in whom DMDD is being diagnosed in clinical practice has been paralleled by a statistically significant decrease in new treatment episodes rates and treated prevalence of the BPD clinical diagnosis. In 2018, the new treatment episode rate per 1,000 PY was 1.75 [95% CI 1.67-1.82] for clinical diagnoses of DMDD compared with 1.14 [95% CI 1.08-1.20] for BPD, and the overall trend suggests that this difference will only increase in the future. It appears that DMDD is now being diagnosed in a substantial number of youth who before 2013 may have received a diagnosis of BPD.

DMDD was added to *DSM-5* to address concerns "about the appropriate classification and treatment of children who present with chronic, persistent irritability relative to children who present with classic (ie, episodic) bipolar disorder" and to correct what was viewed as an inappropriate overdiagnosis of BPD in some youth.[1] The results of the current study suggest that introduction of the DMDD diagnosis might be achieving the stated goal of reducing the overdiagnosis of youth with BPD.

Few studies have assessed the incidence and prevalence rate of DMDD or BPD over time, either in epidemiological studies based on research assessments or in clinical practice samples of convenience. The data presented in this study provide a comprehensive overview of new treatment episode rates and treated prevalence trends in clinical diagnosis of BPD and DMDD, which, to our knowledge, is the only published data of this kind for children and adolescents. Estimates of BPD incidence range from 0.07 to 0.28 per 1,000 PY with a global prevalence of 48.8 million.[23-26] Of note, one study estimated an incidence rate of 0.11 per 1,000 PY in Danish youth aged 13-18 from inpatient data records (1995-2010), which was lower than our U.S. data (1.01 per 1,000 PY).[26] A number of studies have also estimated the prevalence rates of DMDD, with substantial variability between estimates (0.79%-9.2%), likely owing to differences in assessment methods.[27-30] One study that analyzed the prevalence of DMDD symptoms of 6 to 12-year-olds in the general population using maternal ratings found a prevalence of 9.2%.[27] Similarly, a parent-structured clinical interview of 6-year-olds from the Stony Brook Temperament Study reported a DMDD prevalence of 8.2%.[31] Conversely, a substantially lower prevalence (0.79%) was found in a study that used self-reported retrospective data in primary school–aged children.[28] A recent retrospective chart review study from a single center documented a significant decrease in diagnosis of BPD in children and adolescents admitted to a psychiatric hospital following the introduction of DMDD in *DSM-5*, from 35% (125/355) of admissions in 2013 to 19% (25/135) of admissions in 2015, while about one-third of patients received the diagnosis of DMDD in 2015.[32]

In contrast, the present study was based on a large population-based cohort of youth with DMDD or BPD extracted from a longitudinal U.S. EHR database, which captured clinical diagnostic information using *ICD-9* and *ICD-10* codes, and also included demographic and prescription information. The availability of longitudinal data allowed for assessment of the impact of the introduction of the DMDD diagnosis in 2013 on the rate of new treatment episodes of BPD in youth as well as related shifts in patterns of medication prescribing following the new treatment episode.

An important question is whether availability of the DMDD diagnosis has had a significant impact on the treatment of children and adolescents with BPD or DMDD and, specifically, whether the availability of the diagnosis has led to a reduction in the use of antipsychotic medications, which was a driving concern underlying the development of the DMDD diagnosis.[32] The results of the current study, however, suggest that prescription trends may have moved in the opposite direction. Youth who received the DMDD diagnosis were more likely to be prescribed any ADHD and antidepressant medication, more likely to be prescribed multiple drugs at the same time, and more likely to be prescribed antipsychotic medications. These trends were also apparent in the subset of adolescents whose diagnosis was changed from BPD to DMDD, while in the case of adolescents whose diagnosis changed in the opposite direction, from DMDD to BPD, the proportion treated with antipsychotics stayed the same or increased only slightly.

There are a number of limitations to bear in mind when considering the study results. As is the case in any administrative claims—or EHR-based study without outcome validation/adjudication—outcome misclassification is a possibility. Accuracy of diagnoses may be limited, as clinical diagnoses were not verified and confirmed by a structured

interview; also, no information was available on diagnostic subtypes of BPD. In addition, in the absence of lifetime diagnostic histories, it is not possible to determine whether the new treatment episode as defined in this study reflects the actual age at which patients may have first met diagnostic criteria for DMDD or BPD. Diagnosis codes may be incorrect or may be included as part of the diagnostic rule-out process rather than as an indication of actual disease itself. Requiring that patients included in the analysis had to have received the diagnosis at 2 different visits may have at least partly addressed this issue. In addition, prescription data are only a proxy for actual use of the medication; it is possible that even if prescribed a certain medication, the patient may not actually have taken it. In addition, these data do not allow us to separate diagnostic changes that occurred in BPD as a result of the introduction of the DMDD diagnosis in 2013 from the effect of the concurrent changes in BPD diagnostic codes that occurred with the shift from *ICD-9* to *ICD-10*. Finally, the study may not be representative of all patients in all settings; it did not include children < 10 years of age (in whom BPD or DMDD is also diagnosed) or patients outside the United States. In addition, a larger proportion of patients with BPD and DMDD in the study were from the US Midwest census region, and a smaller proportion were from the Western census region.

Study Implications

DMDD was developed, in part, in hopes of addressing concerns that many youth were being erroneously prescribed antipsychotics owing to a misdiagnosis of BPD. The results of the present study suggest that the introduction of the DMDD diagnosis has been associated with the expected reductions in new treatment episode rates and treated prevalence of BPD. However, it does not appear that there has been a concomitant reduction in the use of antipsychotics and polypharmacy in these youth.

For both BPD and DMDD, a substantial number of patients received psychopharmacological treatment, and many were prescribed polypharmacy. Several medications have received U.S. Food and Drug Administration approval for the treatment of BPD.[33] However, there is much less empirical evidence about what roles pharmacotherapy may have in the treatment of DMDD.[34] Based on the prescribing practices observed in this study, methodologically rigorous research into the medication treatment of DMDD seems an unmet medical need.

Whereas this was an exploratory study, additional studies should specifically examine the potential contribution of demographic factors and geographic region to the observed decline in BPD diagnoses reported here. Furthermore, studies designed to identify the factors driving the differences in prescription rates between youth with BPD and youth with DMDD would add to the knowledge base in this area. Inclusion of a cohort of youth with a primary diagnosis of oppositional defiant disorder (with or without ADHD) would also be informative given the high overlap with the diagnosis of DMDD and frequent use of second-generation antipsychotic medications in these patients.[8,35,36]

In conclusion, to our knowledge this is the first report of the rates of new treatment episodes and treated prevalence of DMDD and BPD clinical diagnoses in youth using longitudinal, real-world data extracted from a large EHR database. As such, it has not been replicated or examined using other claims and EHR databases. We observed that diagnosis of DMDD has had rapid uptake in clinical practice but is associated with increased antipsychotic and polypharmacy prescriptions and higher rates of comorbidity and inpatient hospitalization in youth with a DMDD diagnosis compared with a BPD diagnosis. To confirm or refute the initial findings of this work, future research is needed, including medical chart review studies to confirm outcomes, confounder adjustment, and estimation with other databases.

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Writing — original draft: Findling, Zhou, George, Chappell
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