Clinical Phenotype of Tardive Dyskinesia in Bipolar Disorder

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Abstract:

Purpose: Recognizing the negative impact that antipsychotic-induced movement disorders have on the quality of life and treatment outcomes in bipolar disorder (BD), this study aimed to assess clinical correlates and antipsychotic use patterns of tardive dyskinesia (TD+) in BD.

Materials and Methods: Participants with and without TD were included. Clinical variables were compared using *t*-test and χ^2 test. Antipsychotic use patterns in TD+, including number of trials, mean doses, and estimated cumulative exposure, were assessed in a case-only analysis.

Results: The prevalence rate of TD was 5.1%. In comparison to the TD− group (n = 1074), TD+ participants (n = 58) were older, more likely to be female and have type I bipolar illness. There were 60.3% of the TD+ group that continued using antipsychotics at study entry and had a mean cumulative exposure to antipsychotics of 18.2 ± 15.6 years. Average dose, in haloperidol equivalents, was 5.9 ± 3.5 mg and 77.7% of the trials were second-generation antipsychotics.

Conclusions: This study confirms previously identified TD risk factors, such as age, sex, and bipolar subtype in a large BD cohort. Limitations included a cross-sectional design and the lack of tardive illness severity assessment. As atypical antipsychotics continue to be primary mood stabilization treatment, attempting to harmonize large data sets to identify additional biomarkers of tardive risk will optimize individualized care for patients with BD.

Key Words: antipsychotics, bipolar disorder, tardive dyskinesia

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Over a period of approximately 15 years (2000–2015), utilization of secondary-generation antipsychotics (SGAs) in the United States for bipolar disorder (BD) has increased more than 4-fold; this is a reflection of substantial development programs that have led to 10 SGAs indicated for acute mania, bipolar depression, and/or maintenance treatment.[1,2] Although not Food and Drug Administration-approved, arguably, clozapine is one of the most effective mood stabilizers for BD.[3] On balance, antipsychotic treatment selection in BD is a clinical recommendation that beyond pharmacologic profile, may be influenced by formulary, insurance coverage, marketing campaigns, access to health care, and cost.[1] Because of a variety of clinical and health care factors, haloperidol continues to be regularly used for agitation and acute mania with many other first-generation antipsychotics (FGAs) still used off-label in the treatment of BD.[2] This persistent clinical use is despite the FGA association with a higher incidence of mood destabilization and risk of movement disorders, such as tardive dyskinesia (TD).[4–6]

Tardive dyskinesia is a disabling and potentially irreversible movement disorder that may appear after long-term treatment with antipsychotic agents, especially FGAs.[7] While the annual incidence and overall prevalence rate of TD is lower in SGA versus FGA compounds, especially in those without previous exposure to FGAs, the breadth of utilization SGAs, with Food and Drug Administration indications for schizophrenia, acute mania, bipolar depression, bipolar maintenance, and treatment resistant depression, is far greater than current or historic FGA utilization; thus, treatment-emergent TD remains as a clinically relevant concern.[8,9] There is some data to suggest that BD patients, versus patients with schizophrenia, have higher rates of TD. It is unclear if this is disease specific, confounded by age and sex or more related to an on/off dosing pattern (ie, adjunct to mood stabilizer in acute mania).[10,11] In a study assessing the risk of TD in Afro-Caribbean patients with severe mental illness, the number of prior neuroleptic interruptions longer than 3 months increased the occurrence of TD; when the number of prior discontinuations were dichotomized (≤2 vs >2) that odds ratio increased to 3.29 (CI 1.27–8.49).[12] Further, changes in antipsychotic treatment due to adverse effects, such as TD, have been linked to an increase in mood-related hospital admissions and exacerbation of BD.[13,14]

Recognizing the negative impact of antipsychotic-induced movement disorders, this study aimed to assess clinical risk factors for TD in a large cohort of patients with BD. In addition, we examined antipsychotic use patterns among patients with TD.

MATERIALS AND METHODS

Participants included in this analysis represent individuals enrolled in the Mayo Clinic Bipolar Biobank. The comparison groups were participants with a clinical diagnosis of TD+ and a control group currently on antipsychotics at time of study enrollment without TD diagnosis (TD−). The study recruited patients with a BD diagnosis aged between 18 and 80 years from 2009 through 2016. Key collaborating sites included the Lindner Center of Hope/University of Cincinnati College of Medicine (Cincinnati, Ohio), University of Minnesota (Minneapolis, Minnesota), Universidad Autónoma de Nuevo León (Monterrey, Mexico), and Universidad de los Andes (Santiago, Chile); further details on sites, population and inclusion criteria for the Bipolar Biobank

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have been previously published.[15] Every participant provided written informed consent to participate in the biobank.

Information on participants' demographics was obtained through the Bipolar Biobank Patient Questionnaire, a self-applied questionnaire. The Bipolar Biobank Clinical Questionnaire, a clinician-applied tool developed to identify clinical phenotypes of the illness including additional psychiatric comorbidities (current and lifetime), such as TD and current antipsychotic medications. Clinical diagnosis of TD was identified and confirmed by a psychiatrist on the research team through review of the Bipolar Biobank Clinical Questionnaire; no corresponding measurement or assessment scales for TD were used. For those available, diagnostic confirmation was made by data from electronic health records (EHR). Lack of standardized tools for diagnosis of TD (ie, Abnormal Involuntary Movement Scale) may have led to an increased risk for underreporting and underestimation of mild cases and quantification of illness severity. We compared demographic and clinical risk factors between TD+ (n = 58) and TD− (n = 1074) groups. The different sites were represented among the TD+ group: Mayo Clinic (n = 32), Lindner Center of HOPE (n = 18), University of Minnesota (n = 7), and Universidad Autonoma de Nuevo Leon (n = 1).

Antipsychotic drug exposure was harvested from the EHR for patients from the Mayo Clinic site and specific variables included the following: (a) total number of antipsychotics at study enrollment, (b) number of antipsychotic trials referenced in the EHR, (c) mean antipsychotic dose per trial, and (d) mean lifetime exposure. Antipsychotic doses were standardized through conversion to haloperidol equivalents (HALeqs) based on published equivalent doses for FGA and SGA.[16] An exploratory analysis was conducted to compare antipsychotic use patterns in TD+ between participant self-report European ancestry (EA) (n = 50) and non-European ancestry (nEA) (n = 8), which included African American(n = 4), Native American (n = 2) and Hispanic (n = 2) patients.

Statistical analysis was done using RStudio. Demographic and clinical features of TD+ and TD− were analyzed using descriptive statistics and compared using *t*-test and χ^2 test. Mean and standard deviations were summarized for continuous variables related to antipsychotic use and comparison between nEA and EA using *t*-test.

RESULTS

The overall prevalence rate of TD in our sample was 5.1%. As presented in Table 1, TD+ participants, in comparison to TD−, were significantly older (47.9 ± 11.5 vs 40.8 ± 14.6; $P = 0.0001$), more likely to be female (75.9% vs 63.4%; $P = 0.05$), and have a bipolar I subtype diagnosis (89.7% vs 76.2%; $P = 0.02$). Alcohol, but not other substances, use was significantly more common in the TD− group (22.8% vs 39.7%; $P = 0.01$).

Differences in mean number of antidepressants and benzodiazepines among patients with and without TD did not vary significantly (antidepressants, 0.7 ± 0.7 vs 0.5 ± 0.6; $P = 0.06$; benzodiazepines, 0.5 ± 0.6 vs 0.5 ± 0.5; $P = 0.87$).

There were 60.3% of TD+ participants that continued on an antipsychotic at time of biobank enrollment, and mean lifetime exposure to antipsychotics was 18.2 ± 15.6 years (n = 21). Among patients with TD+, purely SGA exposure was identified in 55.2% (n = 32). On average, TD+ participants had a history of 4.3 ± 2.4 antipsychotic trials, of which 77.7% were with SGAs. Overall mean dose of antipsychotic medications (n = 46), converted to HALeq, was 5.96 ± 3.5 mg. There were no significant differences between FGA (n = 7) and SGA (n = 45) mean doses (6.8 ± 4.3 vs 5.5 ± 3.1 mg; $P = 0.36$).

In an exploratory subanalysis, the percentage of nEA participants, compared with EA participants, with a prior FGA trial was higher (36.8% vs 19.5%; $P = 0.03$), as well as the number of FGA antipsychotic trials (1.8 ± 2.3 vs 0.8 ± 1.1; $P = 0.05$), but not SGA trials (3.0 ± 1.7 vs 3.2 ± 1.7; $P = 0.76$). Likewise, mean antipsychotic doses were higher in the nEA group (10.4 ± 6.0 vs 5.3 ± 2.5; $P = 0.001$) compared with EA participants.

DISCUSSION

This study reported a prevalence rate of TD of 5.1%. This is likely an underestimate, given risk data from meta-analyses may reflect a treatment-seeking patient group versus, for example, mean TD prevalence was 25.3% in a meta-analysis (20.7% current SGA treatment vs 30.0% FGA treatment). It is recognized that TD prevalence rates vary greatly, depending on the clinical setting.[9] For example, patients with a serious mental illness in long term care facilities have reported TD prevalence rates as high as 54%.[4]

These data confirm nonmodifiable clinical risk factors of TD in BD, namely older age, gender and bipolar I subtype. Older age has been linked to an increased risk for TD influenced by factors such as brain vulnerability, polypharmacy, early extrapyramidal symptoms and antipsychotic dose exposure.[17] Similarly, patients with BD-I subtype are more likely to use antipsychotics as antimanic mood stabilizers, especially in the presence of psychotic features.[1,11,18] In this line, although not significant, history of psychosis was more common in TD+ participants, which might suggest an increased exposure to antipsychotics. Although less consistently reported, female sex has been associated with more frequent and more severe TD.[19] Although African ancestry has been reported as a risk factor for TD, we did not find a significant difference in TD by ancestry. This might be an underestimation because of the low number of participants of African ancestry in our sample. Likewise, although the overall TD+ versus TD− analysis did not find difference by ancestry (yes/no), a smaller (n = 58), exploratory analysis did identify differences on patterns of antipsychotic use. Current or lifetime alcohol use disorder was more common among TD− patients in this study; this finding is in contrast with literature that have suggested an increased vulnerability for TD in patients with chronic use of alcohol and antipsychotic use.[20] Our sample did (or did not have) active alcohol use and did not quantify duration of sobriety which contribute to this unexpected finding. Further studies on the impact of alcohol and other substances on the risk for developing TD are required. Other known risk factors, including comorbidities, such as diabetes mellitus and history of electroconvulsive therapy and lithium therapies, were not assessed. Given the small sample size, deeper assessments of genetic risk for TD+, such as DRD2 polymorphisms, were not conducted nor were analysis of nonmodifiable environmental risk factors.[20]

Antipsychotic dosage, in addition to class, has been associated with a significant increase in risk of TD.[18,19] A retrospective data analysis in a large cohort of US psychiatric patients (n = 189,415) reported an overall average daily dose of antipsychotic, converted to HALeq, of 4.2 ± 3.8 mg in BD (n = 66,723) and 5.6 ± 4.6 mg in TD+ BD (n = 381; 24.2%).[18] The mean antipsychotic dose reported in our TD+ cohort (5.96 ± 3.5 mg) is similar to the larger cohort TD+ group. For instance, a previous study assessing antipsychotic use patterns in an inpatient BD cohort (n = 139) from South Korea, reported an overall HALeq dose of more than 13 mg[2]. Although there is less TD risk with SGAs, maintenance treatment with these drugs continue to pose a risk for TD, especially in patients with prior exposure to FGAs.[8] This prescribing trend suggests monitoring for TD is an important element to the clinical treatment plan, especially when planning for intermittent antipsychotic treatment, a recognized risk factor for TD.[12]

TABLE 1. Comparison of Demographic and Clinical Variables Between TD+ and TD− BD Patients

	Total (N = 1132)		TD+ (n = 58)		TD− (n = 1074)		
Variables	**n**	**%**	**n**	**%**	**n**	**%**	***P***
Age (mean ± SD)	41.2 ± 14.6		47.9 ± 11.5		40.8 ± 14.6		**0.0001**
Race and ethnicity							0.59
European ancestry	939	83.7	50	86.2	889	83.6	
Non-European ancestry	183	16.3	8	13.8	175	16.4	
Sex							**0.05**
Male	407	36.0	14	24.1	393	36.6	
Female	725	64.0	44	75.9	681	63.4	
SCID diagnosis							**0.02**
Bipolar I	871	76.9	52	89.7	819	76.2	
Bipolar II	261	23.1	6	10.3	255	23.7	
History of psychosis							0.28
Yes	548	50.1	32	57.1	516	49.7	
No	546	49.1	24	42.9	522	50.3	
Current substance use							
Alcohol	430	38.8	13	22.8	417	39.7	**0.01**
Cocaine	144	13.2	6	10.7	138	13.3	0.58
Methamphetamine	73	6.6	4	7.1	69	6.6	0.87
Heroin	48	4.4	1	1.8	47	4.5	0.33
Narcotics	104	9.5	4	7.0	100	9.6	0.52

Statistically significant values are marked in bold.

Analysis within the TD+ group suggests different patterns of antipsychotic use in bipolar patients of non-European ancestry that are in line with previous reports of increased rates of prescription for antipsychotics overall and FGAs among BD patients.[21–23] However, given the underpowered nature of this analysis because of the small sample size of nEA, it is not possible to draw conclusions. Further assessment of patterns of antipsychotic use in the context of race/ethnicity in bipolar research and bipolar biobanks is needed and may have diagnostic and treatment implications. Lastly, we did not assess occupational status and other social determinants of health variables and other nonbiological factors that may contribute to antipsychotic drug selection, and subsequent TD risk. In addition, it is necessary to determine the need for long-term antipsychotic treatment for BD, considering the existence of mood stabilizers that entail less risk for adverse effects.

Overall, this study has several strengths. First, the clinical correlates identified within our TD+ group were compared with a large BD TD− control group and was consistent with previous reports in the literature.[24] Second, examination of antipsychotic use in TD+ utilizing EHR provided a comprehensive understanding of treatment history and minimizes risk of recall bias.

Our study has limitations that need to be considered. First, the cross-sectional retrospective design may limit the possibility of establishing a relationship between time of exposure and TD and accurately estimate antipsychotic exposure. Second, the small sample size did not allow for multivariate analyses. Third, no measures of illness severity were used to rate TD; however, the diagnosis was documented by psychiatrists. Fourth, antipsychotic use patterns in the TD− controls were not collected, which curtailed the possibility to compare between groups. Fifth, use of anticholinergic drugs was not quantified in this study. Finally, although most of our population was of European ancestry and may not be representative of the general population, it is representative of the racial-ethnic demographics of the main study sites (Minnesota and Ohio).

Our findings are consistent with previous evidence suggesting an association of TD with older age, female sex, and bipolar I subtype. As atypical antipsychotics continue to be primary mood stabilization treatment, it will be important for future clinical studies to identify and harmonize large data assessing additional biomarkers of tardive risk so as to optimize individualized care for patients with BD.

AUTHOR DISCLOSURE INFORMATION

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