Personalized Medicine in Psychiatry 37-38 (2023) 100101

Contents lists available at ScienceDirect

Personalized Medicine in Psychiatry

journal homepage: www.sciencedirect.com/journal/personalized-medicine-in-psychiatry

Health disparities in the treatment of bipolar disorder

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ARTICLE INFO

Keywords:
Bipolar disorder
Lithium
Antipsychotics
Mood stabilizers
Racial disparities
Gender disparities

ABSTRACT

Background: Therapeutic options for bipolar disorder vary based on individual presentation and phase of illness. In addition to well documented disparities in diagnosis, racial and gender differences in treatment complicate efforts to provide effective individualized treatment to patients with bipolar disorder. The present work was undertaken to identify the persistence of racial and gender disparities across diverse community and national populations and to compare treatment disparities in bipolar disorder with those observed for schizophrenia.
Methods: Commonly prescribed treatments for bipolar disorder and schizophrenia were quantified using information gathered from the All of Us Research Program and de-identified electronic health records at the University of Mississippi Medical Center.
Results: Black patients with bipolar disorder, in comparison to white patients, had significantly less utilization of lithium, lamotrigine, and antidepressants, but greater utilization of haloperidol and other first-generation antipsychotics. Disparities in antipsychotic use were reduced in patients with schizophrenia compared to those with a bipolar diagnosis.
Conclusions: The disparities enumerated here have real world clinical implications. Black patients with bipolar disorder have less utilization of lithium, the gold standard mood stabilization treatment. Further community-guided research to better understand the origins of these disparities and clinical trials to evaluate non-antipsychotic mood stabilization treatment for bipolar disorder across populations is warranted.

Introduction

Preferred pharmaceutical treatments for bipolar disorder depend on many factors notably including phase of illness, side effect profiles, and drug-drug interactions [1]. The consideration of genetic factors influencing drug response have also begun to emerge as important considerations. In addition to pharmacokinetic genetic variation for antipsychotics [2,3] and antidepressants [4], a growing body of literature has begun to identify genetic factors associated with likelihood of response to lithium [5–7]. Given the side effect profile of lithium and its accompanying monitoring requirements [8], this is likely an area for which personalized medicine in psychiatry will have an important role.

Despite its role as a gold standard first-line intervention [9], Black patients with bipolar disorder have consistently been shown to be less likely to receive lithium as part of their treatment [10]. Conversely, multiple studies have shown that Black patients with bipolar disorder are prescribed antipsychotics at a higher rate than white patients [11–13], in particular high-potency off-label first-generation antipsychotics [11]. Stage of illness, presentation at diagnosis, access to care, patterns of help-seeking behavior, and racial bias in symptom misattribution have all been hypothesized to account for these diagnostic and treatment differences [10,14,15]. As personalized medicine practices develop for the treatment of bipolar disorder it will be important to ensure that these health disparities are not perpetuated.

Diagnosis represents the first point at which disparities arise and opportunities for evidence-based personalized medicine are lost. A large

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https://doi.org/10.1016/j.pmip.2023.100101

Available online 9 March 2023

proportion of individuals with bipolar disorder are initially misdiagnosed [16,17] and this delay in diagnosis negatively impacts opportunities for evidence-based treatment for mood stabilization. Misdiagnosis of bipolar disorder as major depressive disorder may contribute to antidepressant monotherapy treatment and undue risk of treatment failure or antidepressant-induced mania [18] and a misdiagnosis of schizophrenia limits the opportunity for treatment with lithium and/or mood-stabilizing anticonvulsants [19,20]. Extensive evidence from multiple studies in various settings examined over the last several decades points to a higher risk of a schizophrenia-spectrum clinical misdiagnosis in Black vs white patients with bipolar disorder [15,21–24]. Extensive evidence exists demonstrating similar rates of bipolar disorder across racial groups when properly controlled [24–27] and there have been some suggestions of a reversal of misdiagnosis trends [15], but nevertheless they have been largely stable for more than thirty years [28] and persist across nations [29]. These findings underscore the importance of appropriate diagnosis in the treatment of bipolar disorder and emphasize the need for better and more rigorous clinical screening.

A proper diagnosis is only the start of the process for appropriate treatment. Here we sought to demonstrate that disparities in treatment continue to persist after diagnosis and that they are not confined to any specific locale or treatment setting. In the process, we also compared the data from bipolar disorder to disparities in the context of schizophrenia to determine whether they may be unique or represent a larger biases within psychiatry more generally. Using patient records available through the *All of Us* Researcher Workbench and University of Mississippi Medical Center Patient Cohort Explorer, this cross-sectional study aims to recapitulate findings of disparities in diagnosis and treatment of bipolar disorder that would indicate their persistence in multiple diverse settings by practicing clinicians exposed to a broad variety of patient presentations. These contemporary, diverse, settings offer a broad picture of disparities in the treatment of bipolar disorder that persist to the present. A full account of these differences may drive efforts to change diagnostic and prescription practices, as well as contribute to a growing literature documenting disparity in psychiatric diagnosis and treatment.

Methods

The NIH-funded *All of Us* Research Program is an effort to accelerate health research by enabling individualized care through engagements that nurture relationships with participant and community partners; delivering the largest, most robust biomedical data set; and catalyzing an ecosystem of researchers and supporters. The *All of Us* Research Program includes a national database of health data from a diverse group of participants enrolled by over 100 partner organizations in all 50 states. The demographically, geographically, and medically diverse group of participants consent prior to participation and are informed as to the goals of the program and the details of participation. Study participants share multiple types of data, including electronic health records, surveys, baseline physical measurements, biological specimens, and genomics under necessary safety and security safeguards to ensure participant privacy. A national, open resource of de-identified data is broadly accessible by utilizing open-source software and tools through the *All of Us* Researcher Workbench. The *All of Us* dataset v4 included a total population of 315,298 individuals.

The University of Mississippi Medical Center (UMMC) serves a large and uniquely diverse patient population. The UMMC Department of Psychiatry and Human Behavior operates 21 inpatient beds and multiple outpatient clinics and encounters more than 10,000 unique patients annually including more than 665 patients with bipolar disorder. The UMMC Patient Cohort Explorer is an internal database containing de-identified information on patient encounters from UMMC hospitals and clinics including both inpatient and outpatient. The database allows the user to search and apply filters, including demographic factors, diagnoses, and medications, to the UMMC patient population. Using this database, all unique patients encountered by the UMMC Department of Psychiatry and Human Behavior between January 1, 2013, and December 31, 2020, were identified (n = 44,580).

In both data sets, individuals were identified as carrying a bipolar diagnosis following any encounter in the UMMC Department of Psychiatry and Human Behavior with an ICD-10-CM code of F31.x (n = 2,968), including bipolar 1 and bipolar 2 in various phases of illness and degrees of diagnostic specificity. Similarly, individuals were identified as carrying a schizophrenia diagnosis following any UMMC Psychiatry encounter with an ICD-10-CM code of F20.x (schizophrenia, n = 2,345) and F21 (schizotypal disorder, n = 33). For the purposes of this study, individuals carrying schizoaffective (F25.x, n = 309), delusional (F22, n = 402), other psychotic disorder (F23, F24, F28, or F29; n = 976), or manic episode (F30.x; n = 62) diagnoses but not schizophrenia or bipolar disorder were excluded. The *All of Us* dataset v4 included 8,330 individuals diagnosed with bipolar disorder and 2,580 individuals with schizophrenia.

Although a diversity of racial and ethnic backgrounds were present in both the *All of Us* and the UMMC data (including American Indian or Alaska Native, Asian, and multiracial), the research presented here focuses exclusively on non-Hispanic Black and white patient populations for which substantial numbers of patients were encountered, providing sufficient statistical power for further analysis. Gender in the *All of Us* and UMMC data reflects self-identification from patients. The demographic breakdown of the population as a whole, as well as patients with bipolar and schizophrenia diagnoses, is shown Table 1.

Using information gleaned from the *All of Us* Researcher Workbench and electronic health records in the UMMC Patient Cohort Explorer, medications for the treatment of a bipolar disorder and schizophrenia were interrogated. In addition to lithium, prescription histories were searched for anticonvulsants FDA approved for the treatment of bipolar disorder as well as antipsychotics and antidepressants (specific medications are enumerated in Supplemental Table S1). No differentiation in prescription use was made with regards to route of administration, duration of action (e.g., depot formulations), or generic versus branded.

Differences between groups were calculated as relative risk ratios following standard approaches. 95% confidence intervals and significance was calculated following the procedures described in Altman, 1991 [30]. The deidentified, aggregate data from UMMC that support the findings of this study are available from the corresponding author upon reasonable request. Data from *All of Us* is available through the *All of Us* Researcher Workbench.

Results

After implementation of the exclusion criteria, in the *All of Us* data set 2.6% of the 315,298 participating individuals carried a diagnosis of bipolar disorder. Between January 1st, 2013, and December 31st, 2020, 44,580 patients meeting criteria were seen by the Department of Psychiatry and Human Behavior at UMMC and 6.7% of these received a bipolar diagnosis. The estimated population prevalence for bipolar disorder is generally thought to be 1–2% [26,31] though in the US National Comorbidity Survey Replication the prevalence was 2.6% [32]. Regardless of the exact prevalence, the *All of Us* data set prevalence is reasonably similar as befits a community sample while the UMMC Department of Psychiatry and Human Behavior prevalence is greater as reflects a clinical psychiatric population. By comparison, 0.8% of participants from the *All of Us* cohort and 5.3% of patients seen by the UMMC Department of Psychiatry and Human Behavior had a schizophrenia diagnosis. The prevalence of disease in the *All of Us* dataset was comparable to estimated prevalence between 0.5 and 1% [33,34], while higher in the clinical psychiatric population at UMMC.

Disparities in treatment of patients with bipolar disorder by race and gender are shown in Table 2 and Table 3 respectively. Of patients diagnosed with bipolar disorder, 864 (13.5%) in the *All of Us* dataset

Table 1
Gender and race of patients with bipolar disorder and schizophrenia at the University of Mississippi Medical Center and *All of Us* Dataset v4.

UMMC Department of Psychiatry					*All of Us* Dataset v4				
n = 44580		Black	white	other	n = 315298		Black	white	other
		47.4%	42.7%	9.9%			21.6%	52.9%	25.5%
Male	43.1%	19.2%	19.3%	4.7%	Male	37.7%	9.0%	20.2%	8.6%
Female	56.9%	28.3%	23.4%	5.2%	Female	60.1%	12.2%	31.9%	16.0%
					other	2.2%	0.5%	0.9%	0.9%
Bipolar					Bipolar				
n = 2968		Black	white	other	n = 8330		Black	white	other
		35.1%	56.0%	8.9%			26.6%	52.8%	20.6%
Male	39.8%	15.2%	21.4%	3.2%	Male	36.3%	9.6%	19.4%	7.3%
Female	60.2%	19.8%	34.6%	5.8%	Female	59.9%	16.3%	31.6%	12.0%
					other	3.8%	0.7%	1.8%	1.4%
Schizophrenia					Schizophrenia				
n = 2353		Black	white	other	n = 2580		Black	white	other
		67.7%	28.2%	4.1%			47.6%	28.6%	23.8%
Male	62.5%	43.3%	16.6%	2.7%	Male	57.7%	26.9%	17.2%	13.6%
Female	37.5%	24.4%	11.6%	1.4%	Female	38.1%	19.1%	10.2%	8.8%
					other	4.2%	1.6%	1.2%	1.5%

were treated with lithium, while at UMMC 275 (9.3%) received similar treatment. Black patients with bipolar disorder, regardless of gender, were less likely to have lithium prescribed than white patients with bipolar disorder in both patient populations (RR = 0.66 and 0.56 for *All of Us* and UMMC, respectively). In both the *All of Us* and UMMC data sets, there was no difference in lithium utilization across genders (RR = 1.07 and 0.99, respectively), though this obscured the fact that in Black patients with bipolar disorder females tended to receive lithium prescriptions more often than men (RR = 0.72 and 0.80, respectively) with the opposite occurring in white patients (RR = 1.20 and 1.11, respectively). This finding was only significant in the *All of Us* dataset, though the estimated magnitude was similar in the underpowered UMMC sample.

The prevalence of mood-stabilizing anticonvulsant use for the three FDA-approved medications for the treatment of bipolar disorder was also evaluated. In the *All of Us* dataset, 1,423 participants with bipolar disorder (22.2%) had received lamotrigine, 1,112 participants (17.4%) had received valproate, and 434 participants (6.8%) had received carbamazepine. In comparison, at UMMC, 305 patients with bipolar disorder (11.3%) were prescribed lamotrigine, 626 patients (23.2%) were treated with valproate, and 66 patients (2.2%) were prescribed carbamazepine. In both the *All of Us* and UMMC patient populations, lamotrigine was significantly less likely to be prescribed to Black patients with bipolar disorder than white patients with the same diagnosis (RR = 0.43 and 0.28, respectively) and to males compared to females (RR = 0.64 and 0.40, respectively). The racial disparity was also observed for carbamazepine in the *All of Us* sample (RR = 0.51), though prescription numbers were too low at UMMC to be powered for subgroup analysis, and the gender disparity was absent in both datasets. Valproate saw no usage difference between white and Black patients in the *All of Us* data (RR = 0.95), but a statistically significant greater usage in Black patients with bipolar disorder at UMMC (RR = 1.68). Also, in both datasets males were more likely to have been prescribed valproate than females regardless of race (RR = 1.25 and 1.70, respectively).

Antidepressant use in patients with bipolar disorder was common both in the *All of Us* dataset, 4,282 participants (66.8%), and the UMMC dataset, 1,659 individuals (61.4%). In both datasets, Black patients with bipolar disorder were significantly less likely to receive antidepressants than white patients regardless of gender (RR *All of Us* = 0.91, RR UMMC = 0.78), though this disparity was among the smaller magnitudes observed. Similarly, in both populations males were less likely to have been prescribed antidepressants than females, regardless of race (RR *All of Us* = 0.88, RR UMMC = 0.86).

Antipsychotics were more commonly prescribed to patients with bipolar disorder than any mood stabilizer in both the *All of Us* and UMMC populations. In the national *All of Us* set, 4,026 participants (62.8%) with bipolar disorder had received antipsychotics with 2,158 individuals (33.7%) receiving treatment with FGAs and 3,542 individuals (55.3%) receiving treatment with SGAs. 1,167 participants (18.2%) had received haloperidol. At UMMC, 2,219 patients with bipolar disorder (82.1%) were treated with an antipsychotic, including 1,322 patients (48.9%) treated with a first-generation antipsychotic (FGA) and 1,953 patients (72.3%) treated with a second-generation antipsychotic (SGA). Haloperidol specifically was prescribed to 1,283 (47.5%) patients with bipolar. While in the *All of Us* dataset, racial differences in antipsychotic medications were limited to haloperidol and FGAs (RR = 1.34 and 1.18, respectively), at UMMC all classes of antipsychotics were more likely to be prescribed to Black patients with bipolar disorder compared to white patients (RR haloperidol = 1.61, RR FGA = 1.57, RR SGA = 1.17, RR any antipsychotic = 1.15). Across populations and races, males with bipolar disorder were more likely to have received haloperidol than females (RR *All of Us* = 1.28, RR UMMC = 1.43). This pattern carried over to all FGAs at UMMC (RR = 1.42) since FGA usage was dominated by haloperidol, but in the *All of Us* population increased usage of non-haloperidol FGAs actually led to an inversion of the disparity observed (RR = 0.87) with females prescribed more FGAs than males, a pattern driven solely by white populations. While SGAs showed similar racial disparities, if attenuated, in the UMMC population, no racial disparities in SGAs were observed in the population from *All of Us* or gender disparities in either group.

To determine if the racial disparities in treatment were specific to bipolar disorder, antipsychotic prescribing patterns for schizophrenia were also studied. Table 4 and Table 5 show treatment of patients with schizophrenia by race and gender respectively. In the *All of Us* dataset, 1,396 individuals with schizophrenia (73.7%) had been treated with an antipsychotic, 666 individuals (35.1%) had received haloperidol, 878 individuals (46.3%) an FGA, and 1,269 individuals (67.0%) an SGA, but in none of these groups did Black participants with schizophrenia show different treatment patterns than white patients (RR haloperidol = 0.95, RR FGA = 0.93, RR SGA = 0.97, RR any antipsychotic = 0.95). At the UMMC Department of Psychiatry and Human Behavior, 2,148 (95.2%) patients diagnosed with schizophrenia were prescribed an antipsychotic. While significant racial disparities were observed, they were of a much smaller magnitude than observed for bipolar disorder. These same patterns held for the 1,705 individuals (75.6%) receiving haloperidol (RR = 1.11), 1,741 individuals (77.2%) treated with any FGA (RR = 1.08), or the 1,914 individuals (84.8%) treated with an SGA (RR = 1.06). The gender disparities observed for treatment of bipolar disorder with antipsychotics were similarly attenuated or eliminated entirely for schizophrenia.

Table 2
Racial disparities in the treatment of patients with bipolar disorder in the *All of Us* Dataset v4 and at the University of Mississippi Medical Center.

		Race (Black vs. white) *All of Us*	UMMC
Lithium	pooled across gender	0.66 (0.57–0.76) ****	0.56 (0.43–0.72) ****
	males only	0.47 (0.36–0.61) ****	0.46 (0.30–0.69)***
	females only	0.79 (0.66–0.94)**	0.63 (0.46–0.88)**
Antipsychotics			
Haloperidol	pooled across gender	1.34 (1.21–1.49) ****	1.61 (1.49–1.74) ****
	males only	1.37 (1.17–1.60) ****	1.60 (1.45–1.77) ****
	females only	1.32 (1.15–1.52) ****	1.56 (1.39–1.76) ****
Any First Generation Antipsychotic	pooled across gender	1.18 (1.10–1.27) ****	1.57 (1.45–1.69) ****
	males only	1.29 (1.14–1.45) ****	1.58 (1.44–1.74) ****
	females only	1.12 (1.03–1.23)**	1.50 (1.34–1.68) ****
Any Second Generation Antipsychotic	pooled across gender	1.01 (0.96–1.05)	1.17 (1.12–1.23) ****
	males only	0.99 (0.91–1.07)	1.22 (1.14–1.31) ****
	females only	1.02 (0.96–1.08)	1.14 (1.07–1.21) ****
Any Antipsychotic	pooled across gender	1.01 (0.97–1.05)	1.15 (1.11–1.18) ****
	males only	0.99 (0.93–1.07)	1.20 (1.15–1.26) ****
	females only	1.01 (0.97–1.06)	1.10 (1.05–1.15) ****
Anticonvulsants			
Lamotrigine	pooled across gender	0.43 (0.38–0.49) ****	0.28 (0.20–0.38) ****
	males only	0.26 (0.20–0.36) ****	0.14 (0.06–0.33) ****
	females only	0.49 (0.43–0.57) ****	0.34 (0.24–0.47) ****
Carbamazepine	pooled across gender	0.51 (0.41–0.64) ****	0.97 (0.60–1.59)
	males only	0.40 (0.26–0.60) ****	1.88 (0.80–4.42)
	females only	0.57 (0.44–0.75) ****	0.71 (0.37–1.34)
Valproate	pooled across gender	0.95 (0.85–1.07)	1.68 (1.47–1.93) ****
	males only	0.99 (0.83–1.17)	1.61 (1.34–1.92) ****
	females only	0.93 (0.80–1.08)	1.67 (1.36–2.05) ****
Any Anticonvulsant	pooled across gender	0.65 (0.61–0.71) ****	1.06 (0.95–1.18)
	males only	0.65 (0.57–0.74) ****	1.28 (1.09–1.49)**
	females only	0.66 (0.60–0.72) ****	0.90 (0.77–1.04)
Antidepressants			
Any Antidepressant	pooled across gender	0.91 (0.87–0.94) ****	0.78 (0.73–0.83) ****
	males only	0.89 (0.83–0.96)**	0.78 (0.69–0.87) ****
	females only	0.91 (0.87–0.95) ****	0.79 (0.73–0.86) ****

We hypothesized that some of the differences observed in the UMMC population compared to the *All of Us* dataset, particularly in haloperidol and valproate usage, was the result of chemical restraint in the inpatient setting. To test this in the UMMC dataset, we compared the rate of PRN medication administration with an EHR indication of "Agitation" in patients diagnosed with bipolar disorder to those diagnosed with schizophrenia. 513 patients with bipolar disorder (17.3%) received a central nervous system agent for this reason compared to 775 patients diagnosed with schizophrenia (32.9%). While significantly more Black patients received PRN Agitation medications than white patients for both those diagnosed with bipolar disorder and schizophrenia, as with the antipsychotics the magnitude of this difference was substantially less in the schizophrenia group (relative risk ratio for bipolar disorder = 2.01 (1.72–2.35, 95% CI), schizophrenia = 1.27 (1.11–1.45), both $p < 0.0001$).

Discussion

In both the *All of Us* and UMMC data, race significantly correlated with differences in treatment with lithium. As had been the case historically [10], Black patients with bipolar disorder were less likely to be treated with lithium than white patients. Among the anticonvulsant mood stabilizers, lamotrigine and carbamazepine were both more commonly prescribed to white patients with bipolar disorder than Black patients. Valproate, on the other hand, saw no differences between racial groups in the *All of Us* dataset and was more commonly seen in Black patients with bipolar disorder at UMMC. We hypothesize that this difference reflects the use of valproate as an anti-agitation treatment in inpatient settings coupled with known disparities surrounding use of chemical restraint [35–37]. Interestingly, the same patterns in anticonvulsant use emerge as gender disparities with females more likely to receive lamotrigine and males more likely to receive valproate regardless of data set.

The use of antidepressants was consistently less prevalent in Black populations and in males in both datasets. Despite unclear evidence of effectiveness in bipolar depression and concerns about treatment-induced affective switching into mania, antidepressant medications continue to be used clinically as monotherapy and in combination with mood-stabilizing medications for bipolar disorder [38]. The reduced rates of use of these therapeutics in the Black populations and male populations of these datasets may reflect a lower incidence of diagnosis of the depressive phase of the illness, higher prevalence of patients

Table 3
Gender disparities in the treatment of patients with bipolar disorder in the *All of Us* Dataset v4 and at the University of Mississippi Medical Center.

		Gender (male vs. female)	
		All of Us	UMMC
Lithium	pooled	1.07	0.99
	across race	(0.94–1.21)	(0.79–1.24)
	Black only	0.72	0.80
		(0.54–0.95)*	(0.50–1.27)
	white only	1.20	1.11
		(1.04–1.39)*	(0.85–1.44)
Antipsychotics			
Haloperidol	pooled	1.28	1.43
	across race	(1.15–1.42)****	(1.32–1.55)****
	Black only	1.31	1.41
		(1.12–1.54)***	(1.29–1.55)****
	white only	1.27	1.38
		(1.10–1.45)***	(1.23–1.56)****
Any First Generation Antipsychotic	pooled	0.87	1.42
	across race	(0.81–0.94)***	(1.32–1.53)****
	Black only	0.95	1.42
		(0.85–1.06)	(1.30–1.56)****
	white only	0.83	1.35
		(0.75–0.91)****	(1.20–1.52)****
Any Second Generation Antipsychotic	pooled	0.96	1.02
	across race	(0.92–1.00)	(0.98–1.07)
	Black only	0.94	1.06
		(0.87–1.02)	(0.99–1.12)
	white only	0.97	0.99
		(0.91–1.02)	(0.92–1.06)
Any Antipsychotic	pooled	0.92	1.06
	across race	(0.88–0.96)****	(1.02–1.10)**
	Black only	0.91	1.11
		(0.85–0.97)**	(1.06–1.15)****
	white only	0.93	1.01
		(0.88–0.97)**	(0.96–1.07)
Anticonvulsants			
Lamotrigine	pooled	0.64	0.40
	across race	(0.58–0.72)****	(0.31–0.52)****
	Black only	0.38	0.20
		(0.28–0.51)****	(0.09–0.47)***
	white only	0.70	0.47
		(0.63–0.79)****	(0.36–0.62)****
Carbamazepine	pooled	0.90	0.69
	across race	(0.74–1.09)	(0.42–1.16)
	Black only	0.67	1.20
		(0.42–1.05)	(0.55–2.61)
	white only	0.96	0.45
		(0.78–1.18)	(0.22–0.94)*
Valproate	pooled	1.25	1.70
	across race	(1.12–1.39)****	(1.48–1.95)****
	Black only	1.31	1.62
		(1.08–1.58)**	(1.35–1.95)****
	white only	1.23	1.69
		(1.08–1.40)**	(1.38–2.07)****
Any Anticonvulsant	pooled	0.88	1.11
	across race	(0.83–0.95)**	(1.00–1.23)
	Black only	0.87	1.36
		(0.76–1.01)	(1.16–1.60)***
	white only	0.88	0.96
		(0.82–0.95)**	(0.83–1.10)
Antidepressants			
Any Antidepressant	pooled	0.88	0.86
	across race	(0.85–0.91)****	(0.81–0.92)****
	Black only	0.87	0.86
		(0.81–0.93)****	(0.76–0.97)***
	white only	0.89	0.87
		(0.85–0.93)****	(0.81–0.94)*

Table 4
Racial disparities in the treatment of patients with schizophrenia in the *All of Us* Dataset v4 and at the University of Mississippi Medical Center.

		Race (Black vs. white)	
		All of Us	UMMC
Antipsychotics			
Haloperidol	pooled across	0.95	1.11
	gender	(0.84–1.07)	(1.05–1.17)***
	males only	0.87	1.08
		(0.74–1.02)	(1.01–1.15)*
	females only	1.08	1.13
		(0.88–1.32)	(1.02–1.26)*
Any First Generation Antipsychotic	pooled across	0.93	1.08
	gender	(0.84–1.02)	(1.03–1.14)**
	males only	0.89	1.07
		(0.78–1.01)	(1.01–1.14)*
	females only	0.98	1.09
		(0.84–1.13)	(0.99–1.20)
Any Second Generation Antipsychotic	pooled across	0.97	1.06
	gender	(0.91–1.04)	(1.02–1.11)**
	males only	0.92	1.05
		(0.84–1.00)*	(1.00–1.11)
	females only	1.05	1.07
		(0.95–1.16)	(1.00–1.15)*
Any Antipsychotic	pooled across	0.95	1.05
	gender	(0.90–1.01)	(1.02–1.07)***
	males only	0.91	1.04
		(0.85–0.98)*	(1.01–1.07)**
	females only	1.01	1.05
		(0.93–1.09)	(1.00–1.09)*

Table 5
Gender disparities in the treatment of patients with schizophrenia in the *All of Us* Dataset v4 and at the University of Mississippi Medical Center.

		Gender (male vs. female)	
		All of Us	UMMC
Antipsychotics			
Haloperidol	pooled	0.98	1.14 (1.08–1.20)
	across race	(0.87–1.11)	****
	Black only	0.91	1.11 (1.05–1.18)
		(0.77–1.06)	***
	white only	1.12	1.17 (1.05–1.30)
		(0.90–1.38)	**
Any First Generation Antipsychotic	pooled	0.91	1.12 (1.06–1.17)
	across race	(0.82–1.00)	****
	Black only	0.87	1.11 (1.05–1.17)
		(0.77–0.99)*	***
	white only	0.96	1.13 (1.02–1.24)
		(0.82–1.12)	*
Any Second Generation Antipsychotic	pooled	0.92	1.00 (0.97–1.04)
	across race	(0.86–0.98)**	
	Black only	0.87	0.99 (0.96–1.04)
		(0.80–0.94)***	
	white only	0.99	1.01 (0.94–1.09)
		(0.90–1.10)	
Any Antipsychotic	pooled	0.92	1.04 (1.02–1.06)
	across race	(0.88–0.98)**	***
	Black only	0.89	1.03 (1.01–1.06)
		(0.83–0.95)***	**
	white only	0.98	1.04 (0.99–1.09)
		(0.90–1.07)	

treated for the manic phase in the samples, or greater concern for treatment-induced switching in these populations, possibly due to greater burden of disease. But while it is formally possible that these differences in clinical presentation are reflective of underlying biological differences in disease, it seems more likely that they reflect systemic differences in access to treatment and help-seeking behaviors perhaps in combination with clinician bias during application of differential diagnosis.

Unlike lithium, mood stabilizing anticonvulsant medications, and antidepressants, FGA and haloperidol use was much more common in Black patient populations in both the *All of Us* and UMMC datasets. This pattern also held, if greatly diminished, at UMMC for SGA and antipsychotics generally, but was not present for these categories in the *All of Us* data. Haloperidol use was also consistently greater in males compared to females, but the use of other antipsychotics was gender neutral. The greater use of antipsychotic medications in Black populations is in line with previous findings [11,13]. The differences

observed between the various sample populations, we believe, is representative of differences in patient mix. Greater prescription rates in the use of FGAs and SGAs at UMMC compared to the *All of Us* sample likely results from differences in the course of illness during which patients are encountered. UMMC patients are more likely to be in the acute phase of illness, with greater burden of manic symptoms. Similar to valproate, haloperidol has become a primary agent in the default order set for agitation [39] and racial and gender disparities in clinical response may manifest here as well. These findings may demonstrate that degrees of disparities in treatment, if not the disparity itself, are at least partially setting-dependent.

For patients with schizophrenia, in contrast to the bipolar disorder patterns, haloperidol, FGA, and SGA use differed between race and gender to a much lesser extent in both the *All of Us* and UMMC datasets. Disparities in haloperidol and FGA use were diminished for UMMC patients with schizophrenia compared to bipolar disorder and were largely absent for the *All of Us* participants. This pattern largely held for SGAs as well, although there was also no significant difference in use of these agents for treatment of patients with bipolar disorder in the *All of Us* population. In all medications examined available for the treatment of both disorders, disparities between races and genders were more prominent in the bipolar group than schizophrenia. This larger degree of discrepancies identified is suggestive of a possible cause and underscores the importance of appropriate and timely diagnosis of bipolar disorder, particularly in Black and male populations.

Despite equal true prevalence of schizophrenia and affective psychoses between racial groups, clinical and even structured interviews result in greater rates of diagnosis of the former in Black patients and higher rates of diagnosis of the latter in white individuals [40,41]. Black patients with bipolar disorder are less likely to present with depression, when presenting with acute mania are less likely to endorse euphoria, and are more likely to report persecutory delusions and hallucinations than white counterparts [15].

In the treatment of bipolar disorder, race was a significant factor in increasing the risk of not receiving lithium, greatly disfavoring Black patients, with even greater differences observed than reported in prior literature [10]. Previous findings of greater haloperidol use among Black individuals and males with bipolar disorder were likewise repeated in this study. Of note, despite a long history of higher FGA use in Black populations than in white populations [11], this difference was substantially attenuated or not seen in patients with schizophrenia diagnoses.

As a cross-sectional study, associations are necessarily correlative and no causal inference can be made. We examined very heterogeneous populations with potentially different psychopathologies. Further, while previous studies [10] and the *All of Us* sample are largely or completely outpatient, UMMC serves a large proportion of inpatients, who may require more urgent treatment and may skew towards more acute presentations, particularly mania and psychosis. The difference in the nature of sample populations may explain some of the broad differences in rates of medication use reported, particularly those most commonly used for chemical restraint in an inpatient setting. With regards to diagnosis, we could not establish that patients diagnosed with bipolar disorder had not been assigned a schizophrenia diagnosis previously or vice versa. We were also unable to further investigate information regarding side effects, compliance, discontinuation of treatment, or causes of discontinuation.

The data presented here demonstrate the persistence of racial disparities in the treatment of bipolar disorder. These findings are largely consistent both from a nationwide community sample collected through the *All of Us* Research Program and from an unbiased assessment of all patients locally at the University of Mississippi Medical Center Department of Psychiatry and Human Behavior. In both datasets, lithium was more commonly prescribed to white patients than Black patients. In both populations, anticonvulsant use for the treatment of bipolar disorder was more common in white populations and in females for lamotrigine and carbamazepine, but opposite for valproate. Also in both populations white patients and females with bipolar disorder were more likely to be treated with antidepressants. At UMMC, Black patients with bipolar disorder were more likely to receive antipsychotics across all subclasses, while in the *All of Us* data this same disparity was only observed for haloperidol and other first generation antipsychotics. Notably, these prescription differences in antipsychotics were greatly blunted or even reversed in patients diagnosed with schizophrenia. The fact that these disparities persist across sites and contexts even to the present day demonstrate their pervasiveness. It also suggests that the disparities are the result of systemic factors rather than idiosyncrasies of individual providers or the setting in which they operate.

While the overall picture presented by this data is convincing, there are notable limitations. While the age profiles of the various subgroups did not systematically vary, we lack information concerning age of onset of disease or age at first treatment. We also lack information about previous hospitalizations or the specific contexts in which the patients encountered different classes of medication. It is possible, and perhaps likely, that some of these treatment differences, particularly in antipsychotic prescriptions, may reflect differences in presentation and/or misdiagnosis, but these rationales are less convincing for differences seen in other classes of medication. More generally, the present data exists in aggregate limiting the ability to dissociate specific factors or interactions. This additional level of analysis, particularly with better phenotyping measures and more detailed clinical case reports, will be important for better understanding the root causes of these disparities beyond simply their persistence across populations.

While we cannot eliminate bias within the hospital doors, we hypothesize that this is driven largely by structural racism in broader social factors including access to care and community support structures that in turn lead to racial disparities among the individuals arriving at the hospital for mental health services. Additionally, there are likely social and cultural mores that influence both treatment seeking behavior and clinical treatment itself for males compared to females. The first step in addressing these disparities is observing that they exist and that they continue to persist broadly across a variety of clinical settings. Structured interviewing for bipolar diagnoses and more complete accounting of symptoms, at presentation and across the course of illness, are likely to improve the understanding of the origins of these racial disparities and provide a foundation to meaningfully reduce them. Addressing these disparities will be imperative for supporting our patients with bipolar disease and understanding how the community of mental health providers and advocates can develop and improve services to a diverse population.

CRediT authorship contribution statement

Vladimir Tchikrizov: Methodology, Formal analysis, Writing – original draft. **Mark E. Ladner:** Conceptualization, Supervision. **Felicia V. Caples:** Conceptualization. **Mitzi Morris:** Resources. **Hailey Spillers:** Resources. **Christina D. Jordan:** Resources, Writing – review & editing. **Joyce E. Balls-Berry:** Conceptualization. **Monica J. Taylor-Desir:** Conceptualization. **Mark A. Frye:** Conceptualization, Writing – review & editing. **Eric J. Vallender:** Conceptualization, Methodology, Formal analysis, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmip.2023.100101.

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