Racial Disparities in Mood Stabilizer Prescribing in Mania in Nonpsychotic, Hospitalized Patients With Bipolar I Disorder

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Abstract

Objective: To investigate racial disparities in the first-time prescription of mood stabilizers for first-episode mania in nonpsychotic, hospitalized patients with bipolar I disorder, specifically comparing the rates of lithium and valproic acid prescription between non-Hispanic Black and non-Hispanic White patients.

Methods: A retrospective cohort study was conducted using the TriNetX database. We included eligible hospitalized non-Hispanic Black and non-Hispanic White patients newly diagnosed with bipolar I disorder without psychotic features between January 1, 2014, and December 31, 2023. Propensity score matching was employed to create balanced comparison populations of non-Hispanic Black and non-Hispanic White patients, controlling for factors that may influence medication selection. A measure of association analysis was performed to calculate and compare the fraction of patients with either lithium or valproic acid use in both cohorts. Odds ratios were assessed.

Results: The study included 1,582 patients (N = 791 per cohort). After propensity matching, baseline characteristics were well balanced. Lithium was prescribed to 24% of White patients compared to 15% of Black patients (odds ratio [OR] 1.82, 95% CI, 1.41–2.35, $P < .05$). Conversely, valproic acid was prescribed to 20% of Black patients compared to 12% of White patients (OR 0.53 95% CI, 0.40–0.71, $P < .05$).

Conclusions: Significant disparities in the prescription rates of valproic acid and lithium were observed, with Black patients more likely to receive valproic acid and less likely to receive lithium compared to their White counterparts. Efforts to address these inequities should involve addressing structural, patient-related, and clinician-related factors that may contribute to our findings.

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Bipolar disorder is a complex, chronic psychiatric disease impacting the lives of over 48 million people worldwide including 5 million Americans.[1] Treatment strategies for bipolar disorder are often aimed at addressing active symptoms and preventing recurrence of symptoms in the future and consist of treatment with mood stabilizers or antipsychotics. The cornerstone of inpatient management of bipolar disorder is often guided by the current phase of illness (manic or depressed) and the presence, or absence, of psychotic symptoms. Multiple agents including lithium, valproic acid (VPA) derivatives, and most atypical antipsychotics and haloperidol are considered first-line treatments for acute mania lending to a large variability in the initial choice of agent when prescribing.[2] Dual therapy of combination lithium or VPA with certain antipsychotics is also considered first-line.[2] Lithium may be preferred in patients with a family history of appropriate response, patients in euphoric mania, patients with suicidality, women of childbearing age due to a risk of teratogenicity, or those with hepatic dysfunction or other contraindications to VPA use.[2] VPA may be preferred in patients with irritable mania, with renal dysfunction, or in the setting of potential drug-drug interactions.[2] While evidence-based treatment guidelines provide guidance for overall treatment, medication selection can also be influenced by various factors such as cost, formulary availability, formulation, patient characteristics and preference, and prescriber preference.

Available literature suggests that disparities exist in the diagnosis and treatment of bipolar disorder.[3] Depp and colleagues[4] found that Black patients with bipolar I

Clinical Points

- Racial disparities in lithium and valproic acid derivative prescribing for acute mania have not been elucidated.
- Black patients are more likely to be prescribed valproic acid derivatives whereas white patients are more likely to be prescribed lithium.
- Given their similar efficacy, prescribers should be aware of factors that could influence medication choice between these agents.

and II disorder received disproportionately higher rates of antipsychotics compared with White patients. Gonzalez and colleagues[5] found no difference in lithium discontinuation rates when comparing Black and White cohorts with bipolar disorder receiving low-dose lithium adjunct to personalized, guideline-based pharmacologic treatment. Observational data also suggest that Black patients in any phase of bipolar disorder are less likely to receive lithium than White patients.[3,6,7] Much of the available literature evaluates medication use in bipolar disorder in aggregate, without stratifying treatment differences in different phases of treatment or specifiers such as the presence of psychosis, the setting, or medication-specific factors that could influence choice. Furthermore, most literature is not well-controlled to account for medication selection influenced by prior medication trials or comorbid conditions.

This study aims to investigate racial disparities in the prescription of mood stabilizers for Black and White patients with a new diagnosis of bipolar I disorder without psychotic features hospitalized for an acute manic episode and being treated with lithium or VPA. Given the paucity of data and the presence of anecdotal evidence suggesting a potential disparity, we hypothesize that Black patients are prescribed VPA derivatives at a higher rate than lithium in this population.

METHODS

Study Design and Data Source

This was a retrospective study utilizing a US cohort of 64 Health Care Organizations grouped into a network within the TriNetX database called the US Collaborative Network. TriNetX is a global federated health research network providing de-identified access to retrospective electronic medical records across health care organizations. Diagnosis, laboratory measures, medications, and hospitalization data are available for 73 million patients in the US and 88 million patients globally through this platform.

Cohort Selection

Patients included met the following inclusion criteria between January 1, 2014, and December 31, 2023: age greater than 18 years, non-Hispanic Black/African American, or non-Hispanic White, experienced an inpatient hospitalization with a new diagnosis of bipolar I disorder and currently manic without psychotic features (*ICD-10*: F30.1, F31.1). To avoid prescribing bias, patients with a history of receiving lithium or a VPA derivative prior to the index date of hospitalization were excluded. Patients with a diagnosis of schizophrenia, schizotypal, delusional, and other nonmood psychotic disorders (F20-29) within 14 days of the index hospitalization were excluded to ensure diagnostic clarity.

Outcomes

Patients initiated on any formulation of lithium or a VPA derivative within 3 days of the index hospitalization were assessed. Use in non-Hispanic Black/African American and non-Hispanic White patients was then compared to evaluate differences in prescribing rates. To better understand concomitant antipsychotic use, similar analysis was performed grouping antipsychotics into the following categories: first-generation antipsychotics (FGAs) and atypical or second-generation antipsychotics. All medications commercially available in the United States from these subclasses were included in the analysis.

Propensity Score Matching

To create balanced comparison populations, propensity score matching was performed in a 1:1 ratio stratified by race considering each patient's medical history over the previous year. Matching criteria included 23 different features intended to control for confounding risk factors that might predispose a patient to receiving lithium or VPA derivatives. These criteria included relevant demographic information such as age, sex, and pregnancy status. Additionally, comorbid conditions influencing medication selection were utilized including liver disease (*ICD* code K 70–77), pancreatitis (*ICD* code K85), kidney disorders (*ICD* code N17–N19), thyroid conditions (*ICD* code E00–E07), and epilepsy (*ICD* code G40). Lastly, medications impacting lithium metabolism including diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), or nonsteroidal anti-inflammatory inhibitors (NSAIDs), among others, were matched to account for a preference to prescribe VPA derivatives.

Statistical Analysis

To ensure the matched patient cohorts are balanced, a standardized mean difference (SMD) less than 0.1 were considered adequately matched for each matching feature utilized.[8] A measure of association analysis was performed to calculate and compare the fraction of patients with either lithium or VPA use. Odds ratios were calculated comparing the frequency of the use of each

medication between the 2 cohorts. Reported *P* values less than .05 were considered significant for each comparison.

Cohort selection, population matching, and measure of association analyses were performed within the TriNetX analytics platform. Information collected within the platform for cohort creation and matching was queried with relevant *ICD* diagnostic codes and RXNorm medication codes.

RESULTS

With the initial TriNetX search, we identified 3,653 non-Hispanic White patients and 800 non-Hispanic Black patients meeting inclusion/exclusion criteria (Figure 1). After propensity score matching, 2 cohorts of 791 patients each were created for subsequent analyses balanced for all matching criteria implemented (SMD less than 0.1). The mean age was 38 years old, and the population was composed of more females than males (60%). Cohorts were matched to include patients with a similar prevalence of comorbid conditions that could impact medication choice, including liver disease and renal impairment, and to account for certain drug interactions. The maximum standardized difference of matched cohorts was 0.09, suggesting a good balance on measured characteristics.

Overall, both cohorts exhibited a low prevalence of liver disease (3%), chronic kidney disease, and acute kidney failure (5%–7%, respectively). Few patients were concomitantly receiving diuretics, ACEIs, or ARBs; however, 20% of each cohort was receiving NSAIDs. Fifty percent of patients in each cohort had a noted record of active substance use. See Table 1 for a detailed description of cohort demographics, at baseline and after matching.

Mood stabilizer monotherapy was infrequently prescribed presumably due to the coprescription of antipsychotic therapy to treat mania. However, White patients were significantly less likely to receive a VPA derivative relative to Black patients (OR 0.53 [95% CI, 0.40–0.71], $P < .05$), with approximately 12% of White patients (N = 93) and 20% of Black patients in (N = 158) being prescribed a VPA derivative for treatment of acute mania (Table 2). Additionally, White patients were significantly more likely to be prescribed lithium (OR 1.82 [95% CI, 1.41–2.34], $P < .05$), with 24% of White patients (N = 187) prescribed lithium compared to 15% of Black patients (N = 115).

Among those prescribed antipsychotics, black patients were more likely to be prescribed FGAs adjunct to lithium or VPA derivatives (42%) compared to White patients (32%). Adjunct atypical antipsychotic prescribing was similar between cohorts at 72% and 75% among White and Black patients, respectively.

DISCUSSION

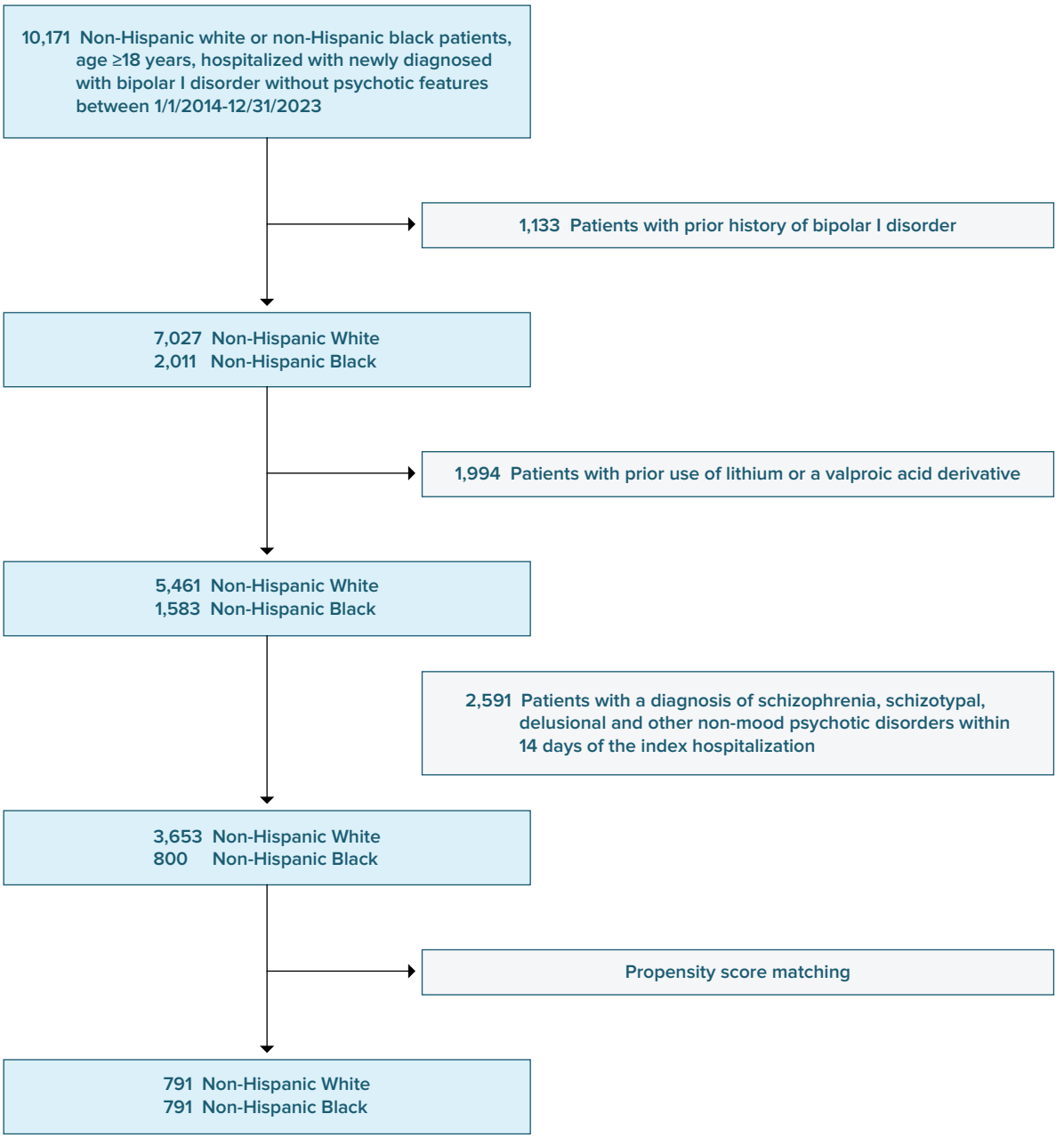
In this retrospective database study using propensity-score matching and evaluating inpatients prescribed mood stabilizers for first-episode, acute mania without psychotic features, Black patients were more likely than White patients to receive VPA derivatives and were less likely to receive lithium. This study provides new information on the initial choice of traditional mood stabilizers when selecting monotherapy for this patient population, stratified by subgroup. These findings confirm the hypothesis that Black patients are prescribed VPA derivatives at a higher rate than lithium for bipolar mania and suggest a disparity that requires further examination. Additionally, this study corroborates previously reported disparities in antipsychotic prescribing, showing that FGAs are prescribed at higher rates for Black patients compared to White patients.

In the United States, the fight for health equity has spanned several decades. Health equity describes a desired state in health care where all people have a fair opportunity to attain their highest level of health.[9] The racial disparity in bipolar disorder treatment observed in our study is one of several disparities that impede the fulfillment of health equity in the United States. We describe below medication, structural, patient-related, and clinician-related factors that may explain our findings.

Medication-Related Factors

Lithium and VPA are equal in efficacy for acute mania and are both recommended first-line by the most recent guidelines released by the Canadian Network for Mood and Anxiety Treatments (CANMAT) for bipolar disorder.[2] When comparing medication characteristics, both medications are low cost and generic, allowing for similar access to the medication irrespective of a patient's insurance status. Both are typically dosed 1–2 times per day, so neither would disproportionately impact adherence due to dosing frequency. Adverse effects occur with both medications but impact different organ systems. VPA derivatives are more sedating than lithium and may be preferred in patients with poor sleep secondary to mania or in those with agitation.[9,10] Both require therapeutic drug monitoring, though lithium has a narrower therapeutic index and greater potential for drug interactions and toxicity with supratherapeutic levels. VPA has greater evidence of teratogenicity and is often preferred second to lithium in women of childbearing age who could become pregnant. Lithium may also be preferred in a patient with suicidality. Conversely, VPA may be preferred in elderly patients, given less of a risk of toxicity. By using propensity-score matched cohorts, differences in prescribing secondary to these medication characteristics have been greatly reduced. Given the similarity in efficacy for both

Figure 1.
Flowchart of Cohort Creation



medications, their administration and cost, and the adjustment for patient characteristics that could influence prescribing, the prescribing disparity between lithium and VPA between Whites and Blacks requires further examination.

Structural Factors

Factors such as racism, discrimination, poverty, and nonrepresentation in research are structural barriers that impact health outcomes for minoritized communities including mental health. Consider the ripple effect of redlining, a practice historically used to segregate residential neighborhoods by race; this policy created a differential in the available opportunities for education, employment, and optimal health across the United States. While the practice of redlining was legally banned in 1968, its harmful consequences continue. Majority Black neighborhoods were deemed undesirable, and the potential of financial investment into such neighborhoods was lost. This translated to a loss of

Table 1.

Baseline Characteristics of Both Cohorts, Before and After Propensity Score Matching

	Initial populations					Propensity score matched populations				
	Cohort 1, white (n = 3,653)		Cohort 2, black (n = 800)		*P* value	Cohort 1, white (n = 791)		Cohort 2, black (n = 791)		*P* value
	n	%	N	%		n	%	n	%	
Age (y), mean (SD)	44 (16.2)		38 (15.1)		<.001	38 (14.5)		38 (15)		.48
Female[a]	1947	53.3	479	59.9	.001	485	61.3	472	59.7	.5
Male[a]	1706	46.7	321	40.1	.001	306	38.7	319	40.3	.5
Diagnosis (ICD code, if applicable)[a]										
Diseases of liver (K70-K77)	172	4.7	24	3	.033	20	2.5	24	3	.5
Persons encountering health services in circumstances related to reproduction (Z30-39)	150	4.1	55	6.9	.001	45	5.7	52	6.6	.45
Acute kidney failure (N17)	274	7.5	60	7.5	.99	40	5.1	56	7.1	.09
Chronic kidney disease (N18)	192	5.3	50	6.3	.26	33	4.2	46	5.8	.13
Acute kidney failure and chronic kidney disease (N17-N19)	378	10.3	83	10.4	.98	58	7.3	78	9.9	.07
Volume depletion (E86)	223	6.1	36	4.5	.079	26	3.3	34	4.3	.29
Disorders of thyroid gland (E00-E07)	493	13.5	52	6.5	<.001	53	6.7	52	6.6	.92
Epilepsy and recurrent seizures (G40)	140	3.8	28	3.5	.66	18	2.3	27	3.4	.07
Other cardiac arrhythmias (I49)	215	5.9	32	4	.04	22	2.8	32	4	.17
Atrial fibrillation and flutter (I48)	123	3.4	20	2.5	.21	13	1.6	20	2.5	.22
Heart failure (I50)	153	4.2	40	5	.31	23	2.9	38	4.8	.05
Persons with potential health hazards related to socioeconomic and psychosocial circumstances (Z55-Z65)	746	20.4	136	17	.03	130	16.4	135	17.1	.74
Schizophrenia, schizotypal, delusional, and other nonmood psychotic disorders (F20-F29)	135	3.7	46	5.8	.09	30	3.8	41	5.2	.18
Anxiety, dissociative, stress-related, somatoform, and other nonpsychotic mental disorders (F40-48)	1717	47	253	31.6	<.001	236	29.8	251	31.7	.41
Mental and behavioral disorders due to psychoactive substance use (F10-F19)	2,113	57.8	395	49.4	<.001	383	48.3	393	49.7	.58
Medication[a,b]										
Loop diuretics (CV 702)	185	5.1	46	5.8	.43	37	4.7	43	5.4	.49
Thiazides/related diuretics (CV701)	137	3.8	44	5.5	.02	33	4.2	41	5.2	.34
ACE inhibitors (CV 800)	233	6.4	55	6.9	.61	37	4.7	53	6.7	.08
Angiotensin II receptor inhibitors (CV 805)	105	2.9	31	3.9	.14	24	3	26	3.3	.77
Nonsteroidal anti-inflammatory analgesics (CN104)	841	23	177	22.1	.59	160	20.2	173	21.9	.423

[a]Values are % (n) unless otherwise stated.
[b]Utilized RxNorm VA medication class.

Table 2.

Lithium and Valproic Acid Derivative Use in White vs Black Patients

	Cohort 1, white (n = 791)		Cohort 2, black (n = 791)		Odds ratio (95% CI)
	N	%	n	%	
Valproic acid derivatives	93	11.8	158	20	0.53 (0.40–0.71)[a]
Lithium	187	23.6	115	14.5	1.82 (1.41–2.35)[a]

[a]*P* < .05.

economic growth and lower availability of overall health resources, including mental health education and resources.[10] Historical abuse and structural racism in medical research have largely led to medical distrust and low representation of Black Americans in clinical trials. Given this distrust, it is possible that minoritized communities often may not communicate mental health symptoms, or tolerability of medication therapy to providers. Without clear data on medication safety and efficacy in this population, providers are left to use their individual judgement on therapeutic agents that fit best for Black patients, often without evidence.[11] While we understand that these factors are not implicitly a direct cause of our findings, we believe that considerations of structural factors, both historical and current, are imperative to the strive toward health equity.

Patient-Related Factors

Mental health stigma in minoritized communities remains a barrier to optimal mental health care. African Americans are less likely to seek out mental health care largely due to the fear of stigmatization and disease perception. Further, African American patients report higher rates of negative experiences with health care providers, lending to the possibility of lower follow-up rates.[11] Given lithium's narrow therapeutic index and greater potential for toxicity, this could influence the selection of VPA derivatives over lithium in this community.

Clinician-Related Factors

Providers may activate a set of beliefs, assumptions, and biases about a patient's identity at the onset of a clinical encounter, oftentimes without realizing.[12] These perceptions influence prescribing and could result in prescribing disparities, such as what was observed in our study. Since lithium, VPA derivatives, and antipsychotics are all considered first-line treatments for bipolar mania, there is a significant possibility that prescriber choices, influenced by perceptions not grounded in evidence, could impact the selection of these agents. Some of these factors have been mentioned above; however, implicit and explicit biases could also be present and contribute to the prescribing disparity we have observed. VPA is occasionally prescribed off-label to manage aggression in conditions like schizophrenia and schizoaffective disorder.[13] Anecdotally, it may sometimes be preferred in manic patients exhibiting aggressive behaviors based on an extrapolation of these data and its sedating properties. The results of this analysis raise important questions about potential differences in the perception of aggression in Black versus White patients with mania. It is possible that Black patients are more frequently perceived as aggressive, which may contribute to the higher rates of VPA prescribing observed in this cohort. This calls for a closer examination of how racial perceptions of clinicians shape patient care and outcomes.

In 2021, the American Psychiatric Association described racial discrimination embedded within psychiatry as a notable contributor to reduced quality of care for Black, Indigenous, and people of color (BIPOC) populations and the perpetuation of dangerous stereotypes.[14] It is well established that clinician attitudes and biases significantly impact patient quality of care and may contribute to overall health disparities.[15] The prescribing disparities in our findings may reflect a conglomerate of these factors. As such, we believe that addressing these inequities will require an intentional, multimodal approach.

We recommend continued efforts toward confronting racial stereotypes and biases disseminated through inaccurate race-based medical education. We recognize that race is a social construct, and therefore we submit that curricula should actively combat race-based diagnostic bias, race-based clinical guidelines, and identifying disparities without proper historical or social determinant context. We advocate for the inclusion of cultural competence and cultural humility in medical school and residency training curricula across the nation. These should include knowledge of evidence-based ethnopsychopharmacology. It is paramount that we produce future providers who recognize the importance of addressing implicit and explicit biases during patient care. Of these future providers, steps must be taken to include providers from underrepresented backgrounds.

Underrepresentation in the health care workforce is of great concern. Black psychiatrists make up merely 2% of the psychiatry physician workforce.[16] It is well documented that due to historical trauma, African American patients often feel a greater sense of distrust toward health care. This sense of distrust is often greatly improved when under the care of a provider from a similar racial-ethnic background.[17] Minoritized patients who experience racial similitude with their providers also report easier communication and greater satisfaction with treatment overall.[18] We recommend increased support for the recruitment and retention of well-trained diverse mental health providers to meet this need and best provide patient-centered care. Increasing representation in mental health provider workforce would mitigate the issue of provider biases and prejudice.

Strengths and Limitations

Our study has several strengths including the large sample size and the use of propensity-scored matching to account for patient characteristics that could confound results. By narrowing the population to nonpsychotic inpatients prescribed mood stabilizers, we were able to capture a population that would not have prior mood stabilizer medication trials that could influence prescribing.

Several limitations exist. First, we were not able to capture the severity of mania in patients included or evaluate individual symptoms that could impact medication choice. Second, we did not have any information on prescriber demographics or education. Despite the limitations associated with retrospective database analysis, such as incomplete data capture, coding variability, and the absence of potential confounders, including lifestyle factors, socioeconomic status, and patient preferences, our study utilized a large national database, enhancing the generalizability of our findings to broader populations.

CONCLUSION

This analysis demonstrates a prescribing disparity in lithium and VPA derivative prescription between nonpsychotic mania among hospitalized White and Black patients with bipolar I disorder. Despite a balanced distribution of patient characteristics that might influence medication choice, significant disparities in the prescription rates of VPA derivatives and lithium were observed, with Black patients more likely to receive VPA derivatives and less likely to receive lithium compared to their White counterparts. This prescribing inequity highlights broader issues in health care access and delivery. Efforts to address these inequities should involve tackling systemic racism, confronting clinician

biases, ensuring prescriber education addresses mental health inequity, and improving diversity in the health care workforce.

The data accessed for this project are available through the platform TriNetX: https://live.trinetx.com.

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