Key Words: mental health, bipolar disorder, healthcare disparities, ethnic and racial minorities, meta-analysis as topic, antimanic agents, antipsychotic agents, antidepressive agents, anticonvulsants, lithium compounds

Persistence of Lithium Underutilization in Patients of African Ancestry with Bipolar Disorder

By Monica J. Taylor–Desir, Jorge A. Sanchez–Ruiz, Eric J. Vallender, Balwinder Singh, Karen M. Meagher, Mark A. Frye

ABSTRACT ~ Bipolar disorder is a chronic disease that imposes a lifelong burden on those that suffer from it. Lithium is still considered both gold standard treatment and first-line maintenance treatment, and access to treatment with lithium is paramount to improving patient outcomes. However, access to adequate treatment is not only contingent on symptom recognition, accurate diagnosis, and individualization of treatment, but also affected by racial and ethnic disparities at each stage of patient experience. Individuals of African Ancestry with bipolar disorder are more frequently misdiagnosed with nonaffective psychoses, less likely to receive minimally adequate treatment or be prescribed lithium, and more likely to be prescribed antipsychotics. To compare prescription patterns in the treatment of bipolar disorder between individuals of African and European Ancestry, we conducted a pooled meta-analysis of four cohorts spanning different clinical settings, recruitment periods, and ascertainment methods, followed by sex-stratified analyses. We found that, overall, individuals of African Ancestry with bipolar disorder were significantly less likely to be prescribed lithium, and more likely to be prescribed first and second-generation antipsychotics during their lifetime, than those of European Ancestry. Furthermore, both men and women of African Ancestry were independently less likely to be prescribed lithium and more likely to be prescribed second generation antipsychotics than men and women of European Ancestry. However, women appeared to be more burdened by the significantly increased likelihood of first-generation antipsychotic prescription than men, for whom the association was marginally non-significant. This continued underutilization of lithium likely stems from the complex interaction of multiple biases. Psychopharmacology Bulletin. 2025;55(1):47-63.

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INTRODUCTION

Bipolar disorder is a chronic disease that imposes a lifelong burden on the individuals that suffer from it.¹ Its treatment typically entails both acute and maintenance pharmacotherapy for which lithium, first or second-generation antipsychotics, mood-stabilizing anticonvulsants, and antidepressants are often utilized.² Among these, lithium is still considered both gold standard treatment and first-line maintenance treatment by most international guidelines.³ Access to gold standard treatment is paramount to improving patient outcomes, given that untreated bipolar disorder is associated with a worse longitudinal course of illness.⁴

However, access to adequate treatment is contingent on symptom recognition, accurate diagnosis, and individualization of treatment. In addition, racial and ethnic disparities extend throughout the different stages of the patient experience (Figure 1), resulting in misdiagnosis, differences in treatment provision, and differential experiences of negative outcomes. Individuals of African Ancestry with bipolar disorder are more likely to be initially diagnosed with a non-affective psychosis, compared to those of European Ancestry.^{5–7} Furthermore, in contrast to individuals of European Ancestry, individuals of African Ancestry are less likely to receive minimally adequate treatment, less likely to be prescribed lithium, more likely to be prescribed antipsychotics, and more likely to endorse lower global functioning with treatment.^{8–11}

We have previously compared the patterns of bipolar disorder treatment between individuals of African Ancestry and European Ancestry across four distinct cohorts.^{9,12,13} Despite the diverse settings in which each of the cohorts were conducted, we observed distinct patterns of bipolar disorder treatment among individuals of African Ancestry. Therefore, we conducted this pooled meta-analysis to identify treatment patterns among individuals with bipolar disorder and to investigate treatment disparities between individuals of African ancestry and those of European Ancestry.

FIGURE 1

POINTS ALONG BD PATIENT JOURNEY KNOWN TO INVOLVE DISPARITIES



METHODS

Participants

We included data on lifetime medication use from three previous studies of disparities in the treatment of bipolar disorder between individuals of African and European Ancestry.^{9,12,13} For the National Institutes of Health (NIH) Genetic Association Information Network (GAIN) and the Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder (MCBB), the summary statistics included in this meta-analysis were obtained directly from the respective authors and match the data reported previously.^{9,12} For the University of Mississippi Medical Center (UMMC) and All of Us cohorts previously reported on by Tchikrizov et al. (2023), the summary statistics included in this meta-analysis represent more recent versions of the datasets than the ones reported previously (e.g. All of Us v7 versus All of Us v4), and are limited to individuals that self-identify as Black or White.

Genetic Association Information Network

GAIN summary statistics were obtained from the Akinhanmi et al. (2020) analysis, (dbGap accession number: phs000017.v3.p1). The GAIN initiative, established in 2006,¹⁴ conducted a GWAS of individuals of African and European Ancestry with bipolar disorder who were recruited across ten sites between 1990 and 2008.^{15,16} Per Akinhanmi et al. (2020), only individuals with bipolar disorder type I were included in this analysis. The Diagnostic Interview for Genetic Studies¹⁷ was used to ascertain bipolar disorder, collect demographic information, and lifetime use of medications.

Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder

We obtained summary statistics for the MCBB from the Taylor-Desir et al. (2023) analysis. The Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder was established in 2009 in collaboration with the Lindner Center of HOPE/University of Cincinnati and the University of Minnesota.¹⁸ Later, Universidad Autonoma de Nuevo Leon in Monterrey, Mexico, and Universidad de Los Andes in Santiago, Chile, joined the collaboration. Enrollment was conducted between 2009 and 2015, and included adults between 18 to 80 years of age with a diagnosis of bipolar disorder, type I or II, or schizoaffective disorder, bipolar type, as confirmed by the Structured Clinical Interview for DSM-IV-TR.¹⁹ Patients with active psychosis or suicidal ideation were excluded. At enrollment, clinicians ascertained participants' lifetime history of medications used for bipolar disorder, including lithium,

49

mood stabilizing anticonvulsants, antipsychotics, and antidepressants. Participants self-identified race and ethnicity.

University of Mississippi Medical Center

The UMMC cohort comprises all unique patients seen by the UMMC Department of Psychiatry and Human Behavior between January 1, 2013, and December 31, 2020. Summary statistics were obtained from UMMC at the time of writing.¹³ Bipolar disorder was ascertained through electronic health record matching using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code F31.x, which includes bipolar disorder type I and II. Using participant electronic health records, all available prescription data were searched for history of lithium, mood stabilizing anticonvulsants, antipsychotics, and antidepressants, regardless of formulation, dose, or route of administration. Race and ethnicity reflect self-identified data from electronic health records.

All of Us

Taylor–Desir et al.

50

The NIH All of Us Research Program is a prospective cohort study designed to enroll a diverse group of 1 million persons across the US. It is linked to more than 100 partner organizations and allows participants to consent to directly share their electronic health records with All of Us.²⁰ Participants may additionally consent to share digital health information, biospecimens, physical measurements, and surveybased information. Approved researchers are able to use the Researcher Workbench, a web-based interactive cloud-based computing environment, to explore and analyze the data. Among participants sharing their electronic health records with All of Us, bipolar disorder was ascertained through ICD-10-CM record matching using code F31.x, prescription data was searched for lithium, mood stabilizing anticonvulsants, antipsychotics, and antidepressants, and self-identified race and ethnicity were collected.¹³ The Åll of Us Registered Tier Dataset v7, available to authorized users through the Researcher Workbench, includes a total population of 413,457 individuals, 11,560 with a bipolar ICD code, and 9,130 who self-identify as Black (2,783) or White (6,347) and non-Hispanic.

Statistical Analysis

We pooled four cohorts previously reported on by our research group to examine the prescription patterns of individuals with bipolar disorder by meta-analyzing the lifetime prescription of lithium, mood stabilizing anticonvulsants, first generation antipsychotics, second generation antipsychotics, and antidepressants between individuals of African Ancestry and European Ancestry. First, among all participants, followed by sexstratified analysis. Between-study variance was estimated using the DerSimonian-Laird method.²¹ For dichotomous outcomes, we calculated the odds ratio (OR) along with a 95% confidence interval (CI) utilizing the Mantel-Haenszel random effects model. To evaluate the heterogeneity among the studies, the I² statistic was utilized, reflecting the proportion of variation due to random error. All analyses were conducted using R Statistical Software (v4.4.1; R Core Team 2024) using the meta R package²² for meta-analysis of binary outcome data with a predefined alpha level of 0.05 set for determining statistical significance. Due to the small number of studies, we decided not to evaluate publication bias for the meta-analysis.

RESULTS

In the conducted meta-analysis, which aggregated data from four distinct cohorts/studies encompassing a total of 14,668 participants, it was observed that among these participants, 4,304 were of self-reported African Ancestry and 10,384 of self-reported European Ancestry (Table 1). The analysis revealed statistically significant differences in prescription patterns by Ancestry group (Figure 2). Individuals of African Ancestry were less frequently prescribed lithium in comparison to their European Ancestry counterparts (OR [95% CI] = 0.64 [0.43 - 0.95];p = 0.03). Moreover, there was an increased likelihood of prescriptions for first-generation antipsychotics (OR [95% CI] = 1.62 [1.02 - 2.57]; p = 0.04) and second-generation antipsychotics (OR [95% CI] = 1.50 [1.20 - 1.89]; p < 0.01) among the African Ancestry group. It was also noted that the prescription rates for mood-stabilizing anticonvulsants and antidepressants did not significantly differ between the two ancestry groups. The studies exhibited considerable heterogeneity, with values ranging from 76% to 96%. Additionally, sex-stratified analyses within this study demonstrated consistent prescription patterns across both female and male participants (Table 2; Figure S1; Figure S2).

DISCUSSION

We meta-analyzed four cohorts of individuals with bipolar disorder to compare prescription patterns between individuals of African and European Ancestry. This study included cohorts spanning different clinical settings, recruitment periods, and ascertainment methods.

| 52 | |
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| Taylor-Desir et al. | |

| | DRTS INCLUDE |
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| TABLE 1 | CHARACTERISTICS OF THE COHC |

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| | | | AFRIC | CAN ANCESTRY | EUROF | PEAN ANCESTRY | | | | |
|--------|-----------------------------|--------------------|-----------------|---------------------|-----------------|----------------------|--------------|--------------------|-----------------|-----------------|
| | | | AGE. | | <u>AGE.</u> | | RECRUITMENT | | INCLUSION | EXCLUSION |
| COHORT | <u>STUDY</u> | SAMPLE SIZE | $MEAN \pm SD$ | SEX, N (%) | $MEAN \pm SD$ | SEX, N (%) | <u>YEARS</u> | ASCERTAINMENT | <u>CRITERIA</u> | <u>CRITERIA</u> |
| GAIN | Akinhanmi, | Total, N = 895 | 41.9 ± 10.2 | Female, 284 (68.4%) | 42.8 ± 13.4 | Female, 243 (50.6%) | 1990-2008 | Clinical interview | BDI | BDII, SCZA |
| | et al. 2020 ^[9] | AA, n = 415 | | Male, 131 (31.6%) | | Male, 237 (49.4%) | | DIGS 4 | | |
| | | EA, n = 480 | | | | | | | | |
| MCBDB | Taylor-Desir, | Total, $N = 1,960$ | 41.3 ± 11.9 | Female, 42 (64.6%) | 42.9 ± 14.9 | Female, 1165 (61.5%) | 2009–2015 | Clinical interview | BDI, | Suicidal |
| | et al. 2023 ^[12] | AA, n = 1,895 | | Male, 23 (35.4%) | | Male, 730 (38.5%) | | SCID for | BDII, | ideation |
| | | EA, n = 65 | | | | | | DSM-IV-TR | SCZA | Psychotic |
| | | | | | | | | | | symptoms |
| AoU | Tchikrizov, | Total, $N = 9,130$ | 51.5 ± 12.6 | Female, 1717 (62%) | 51.5 ± 14.7 | Female, 3954 (62%) | 2017–ongoing | Medical records | BDI, BDII | SCZA |
| | et al. 2023 ^[13] | AA, n = 2,783 | | Male, 999 (36%) | | Male, 2310 (36%) | | ICD-10-CM | | |
| | | EA, n = 6,347 | | | | | | F31.x | | |
| UMMC | Tchikrizov, | Total, $N = 2,703$ | 37.8 ± 13.5 | Female, 589 (57%) | 43.0 ± 14.7 | Female, 1027 (62%) | 2013-2020 | Medical records | BDI, BDII | SCZA |
| | et al. 2023 ^[13] | AA, n = 1,041 | | Male, 452 (43%) | | Male, 635 (38%) | | ICD-10-CM | | |
| | | EA, n = 1,662 | | | | | | F31.x | | |
| | | | | | | | | | | |

Medicine Biobank for Bipolar Disorder Biobank; AoU, All of Us Research Program; UMMC, University of Mississippi Medical Center; SD, standard deviation; n, participant count; DIGS, Diagnostic Interview for Genetic Studies; SCID, Structured Clinical Interview for DSM-IV-TR; ICD-10-CM, International Classification of Diseases, version 10, clinical Abbreviations: Ad, self-reported African Ancestry; EA, self-reported European Ancestry; GAIN, Genetic Association Information Network; MCBDB, Mayo Clinic Individualized modification; BD, bipolar disorder; SCZA, schizoaffective disorder.

FIGURE 2

Forest Plot of Bipolar Disorder Treatment Patterns among Individuals with African or European Ancestry

| Study or | AA | | EA | | | Odds Ratio for AA vs. EA | |
|---------------------|---------------------------|------------------------|---------------------|-----------|-------------------|--------------------------|-------------------|
| Subgroup | Events | Total | Events | Total | OR [95% CI] | MH, Random, 95% Cl | |
| Lithium | | | | | | | |
| GAIN | 218 | 415 | 356 | 480 | 0.39 [0.29, 0.51] | | |
| MCBDB | 30 | 65 | 641 | 1895 | 1.68 [1.02, 2.76] | | |
| All of Us | 311 | 2783 | 1086 | 6347 | 0.61 [0.53, 0.70] | | |
| UMMC | 71 | 1041 | 204 | 1662 | 0.52 [0.39, 0.69] | | |
| Total (95% CI) | | 4304 | | 10384 | 0.64 [0.43, 0.95] | - | |
| Heterogeneity: Ta | $u^2 = 0.139$ | ; Chi ² = 2 | 6.69, df = 3 | (P < 0.01 |); $I^2 = 89\%$ | | |
| Test for overall ef | fect: Z = -2 | .22 (P = 0 | .03) | | | | |
| Eirst constation | antinew | hotics | | | | | |
| | 107 | 229 | 224 | 200 | 1 02 [0 76 1 27] | | |
| MCRDR | 8 | 550 65 | 106 | 1805 | 2 37 [1 10 5 00] | | |
| | 1200 | 2783 | 2383 | 6347 | 2.37 [1.10, 5.09] | | |
| | 655 | 2703 | 2303 | 1662 | 2 53 [2 16 2 07] | | |
| | 055 | 1041 | 007 | 1002 | 2.55 [2.10, 2.97] | | |
| | $u^2 = 0.100$ | 4221 | 1 00 df - 2 | IU292 | 1.02 [1.02, 2.57] | | |
| Test for overall ef | u = 0.190 fect: Z = 2. | 04 (P = 0) | 1.08, af = 3 04) | (P < 0.01 |); 1 = 95% | | |
| | | | , | | | | |
| Second generat | tion antip | sychotic | S | | | | 2 |
| GAIN | 326 | 415 | 350 | 480 | 1.36 [1.00, 1.85] | <u> </u> | <u>ک</u> |
| MCBDB | 21 | 65 | 408 | 1895 | 1.74 [1.02, 2.96] | | wlor-Desir et al. |
| All of Us | 1807 | 2783 | 3752 | 6347 | 1.28 [1.17, 1.40] | | J |
| UMMC | 827 | 1041 | 1126 | 1662 | 1.84 [1.53, 2.21] | | |
| Total (95% CI) | • | 4304 | | 10384 | 1.50 [1.20, 1.89] | ◆ | |
| Heterogeneity: Ta | $u^2 = 0.037$ | ; $Chi^2 = 1$ | 2.81, df = 3 | (P < 0.01 |); $I^2 = 77\%$ | | |
| Test for overall en | ieci. Z = 3. | 49 (P < 0. | 01) | | | | |
| Mood stabilizin | g anticon | vulsants | | | | | |
| GAIN | 288 | 415 | 383 | 480 | 0.57 [0.42, 0.78] | | |
| MCBDB | 37 | 65 | 807 | 1895 | 1.78 [1.08, 2.94] | | |
| All of Us | 860 | 2783 | 2864 | 6347 | 0.54 [0.49, 0.60] | - | |
| UMMC | 370 | 1041 | 559 | 1662 | 1.09 [0.92, 1.28] | | |
| Total (95% CI) | | 4304 | | 10384 | 0.85 [0.53, 1.38] | | |
| Heterogeneity: Ta | $u^2 = 0.216$ | ; Chi ² = 6 | 3.42, df = 3 | (P < 0.01 |); $I^2 = 96\%$ | | |
| Test for overall ef | fect: Z = -0 | .65 (P = 0 | .52) | | | | |
| Antidepressant | • | | | | | | |
| GAIN | 353 | 375 | 421 | 461 | 1 52 [0 89 2 61] | | |
| MCBDB | 26 | 65 | 677 | 1895 | 1 20 [0 72 1 99] | | |
| All of Lis | 1985 | 2783 | 4683 | 6347 | 0.88 [0.80, 0.98] | | |
| UMMC | 544 | 1041 | 1115 | 1662 | 0.54 [0.46 0.63] | ₽ 1 | |
| Total (95% CI) | 344 | 4264 | 1110 | 10365 | 0 90 [0 61 1 33] | | |
| Heterogeneity: Ta | $u^2 = 0.125$ | $Chi^2 = 3$ | 591 df = 3 | (P < 0.01 | $1^{2} = 92\%$ | | |
| Test for overall ef | fect: Z = -0 | .52 (P = 0 | .60) | 0.01 | ,, i = 02 /0 | | |
| | | | | | Г | | |
| | | | | | 0.3 | 2 0.5 1 2 5 | |
| | | | <i>a</i> . . | | | | |

Abbreviations: AA, self-reported African Ancestry; EA, self-reported European Ancestry; GAIN, Genetic Association Information Network; MCBDB, Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder Biobank; UMMC, University of Mississippi Medical Center; OR, odds ratio; CI, confidence interval; MH, Mantel-Haenszel.

Overall, individuals of African Ancestry with bipolar disorder were significantly less likely to be prescribed lithium, and more likely to be prescribed first and second generation antipsychotics during their course of illness, compared to those of European Ancestry. Furthermore, both

TABLE 2

| A. PHARMACOTHERAPY PRESCRIPTION PATTERNS AMONG MALE INDIVIDUALS WITH BD | | | | | | | | |
|---|-----------------|---------------------|-----------------------------|---------|--|--|--|--|
| MEDICATIONS | STUDIES | PARTICIPANTS | <u>OR (95% CI)</u> | P-VALUE | | | | |
| Lithium | 4 | 5518 | 0.47 [0.39, 0.56] | < 0.01 | | | | |
| FGA | 4 | 5437 | 1.79 [0.99, 3.25] | 0.05 | | | | |
| SGA | 4 | 5518 | 1.51 [1.09, 2.10] | 0.01 | | | | |
| MSAC | 4 | 5518 | 0.91 [0.49, 1.70] | 0.77 | | | | |
| Antidepressants | 4 | 5490 | 0.84 [0.58, 1.20] | 0.34 | | | | |
| B. PHARMACO | THERAPY PRESCRI | PTION PATTERNS AM | ONG FEMALE INDIVIDUALS WITH | BD | | | | |
| MEDICATIONS | STUDIES | PARTICIPANTS | <u>OR (95% CI)</u> | P-VALUE | | | | |
| Lithium | 4 | 9020 | 0.64 [0.43, 0.95] | 0.03 | | | | |
| FGA | 4 | 8932 | 2.33 [1.20, 4.54] | 0.01 | | | | |
| SGA | 4 | 9020 | 1.44 [1.16, 1.80] | < 0.01 | | | | |
| MSAC | 4 | 9020 | 0.74 [0.49, 1.12] | 0.16 | | | | |
| Antidepressants | 4 | 8989 | 0.83 [0.57, 1.23] | 0.36 | | | | |

Sex-Stratified Analysis of Individuals of African Ancestry Compared to European Ancestry

Abbreviations: BD, bipolar disorder; OR, odds ratio; CI, confidence interval; FGA, first generation antipsychotics; SGA, second generation antipsychotics; MSAC, mood-stabilizing anticonvulsants.

54

Taylor-Desir et al.

men and women of African Ancestry were independently less likely to be prescribed lithium and more likely to be prescribed second generation antipsychotics, yet women of African Ancestry appeared to be more burdened by the significantly increased likelihood of first generation antipsychotic prescription than men, for whom the association was marginally non-significant.

As reflected by a recent report from the National Academies of Science, Engineering, and Medicine, it is crucial to carefully distinguish socially-constructed population descriptors such as ancestry, race, and ethnicity from genetic ancestry.²³ This metaanalysis is complicated by prior data collection of "self-reported African Ancestry," which merits unpacking as self-reported ancestry should not be conflated with genetic ancestry markers, and is also distinct from self-reported race and ethnicity. Ancestry, a socially-constructed population descriptor, denotes "a person's origin or descent, lineage, 'roots,' or heritage, including kinship."23 and was previously utilized by two of the studies we have included in the present meta-analysis. However, in our discussion of the literature, we have retained the language used in the original publications to describe racial and ethnic groups. Disentangling these population characteristics is especially relevant to advancing understanding of psychiatric health disparities. The longstanding underrepresentation of groups that have been marginalized is a barrier to rigorous and generalizable psychiatric research.^{24,25} Additionally, the forces of stigma and racial discrimination carry specific and intersecting burdens

for patients and families struggling with mental health disorders.^{26,27} To advance a comprehensive analysis of causal factors driving bipolar disorder health disparities, this discussion carefully delineates population descriptors as described throughout this metaanalysis and related findings in the literature. The current findings are thereby more carefully situated in complex and persistent prescription treatment disparities over twenty years.^{11,28}

Treatment differences similar to the ones observed in our metaanalysis have been reported by studies with smaller sample sizes comparing self-reported Black individuals to those of other races and ethnicities.²⁹ Meanwhile, Gonzalez Arnold et al. (2015), demonstrated that African Americans prescribed low dose lithium improved more over the course of their study than White individuals in depressive symptoms and quality of life. The authors conclude that although specific medication or psychological treatment responses may differ, when treatment plans or services are designed to provide high quality care, racial and ethnic minority group outcomes can be similar to those of White individuals.³⁰ Similarly, both a specialized care model and a tailored psychosocial intervention independently improved treatment outcomes for individuals with bipolar disorder irrespective of race and residence, highlighting that high quality care is equally effective across racial and ethnic groups.³¹

Among the cohorts included in this meta-analysis, GAIN (Genetic Association Information Network) is the oldest cohort, having initiated recruitment in 1990. More importantly, data from this cohort was utilized to conduct the first GWAS of bipolar disorder among individuals of African Ancestry only 15 years ago.³² In contrast, All of Us started recruitment 27 years later, in 2017.²⁰ And while disparities in the care of individuals of African Ancestry with bipolar disorder have been the subject of multiple scientific reports, including the studies pooled in this meta-analysis,^{5–13} the differences in prescription patterns between individuals of African Ancestry and those of European Ancestry have not resolved when comparing the oldest and the most recent cohort included here. This continued underutilization of lithium most likely stems from the complex interaction of many different factors, rather than a single bias.

Whether intentional or unintentional, bias can arise from prejudice and discrimination in the identification of symptoms, diagnosis, provision of care, structural or systemic barriers to accessing care, and distrust of the medical establishment with or without hesitancy to seek treatment. Within the provision of care, prejudice–having "differential assumptions about the abilities, motives, and intentions of others according to their race"³³–may result in symptom misattribution and an inability to recognize an individual's need for a specific treatment,

while discrimination–"differential actions toward others according to their race"³³–may present in biased prescribing practices.

On the other hand, social determinants of health as well as structural or systemic barriers, often in the form of institutionalized racism-that is, racism that has been "codified in our institutions of custom, practice, and law"³⁴—present individuals with an inherent disadvantage, limiting their opportunity to receive adequate health care. Geographic and transportation barriers, such as those experienced by residents of areas with limited transportation,³⁵ may impair an individual's ability to visit a specialized clinic or laboratory. Socioeconomic barriers, such as those experienced by people who are not securely housed, individuals experiencing poverty, or those with pre-existing debt and/or medical bills,^{36–38} can result in the inability for individuals to pay for care or receive it without incurring debt, or the selection of cheaper treatments. Education barriers, such as those experienced by people with low health literacy, which is disproportionately higher among African Americans,³⁹ can limit an individual's ability to navigate the health care and health insurance systems to understand coverage and costs, or hinder their ability to participate in shared-decision making. Yet, these barriers do not exist in isolation, and constantly interact with each other. As an example, the effect of racial residential segregation has been compounded through time, driving health care inequalities, mediated by differential opportunities and exposures within neighborhoods, differential health care infrastructure and provider supply, and differential utilization of health care,⁴⁰ and can be observed in Blackserving hospitals scoring worse in most patient safety indicators than non-Black-serving hospitals.⁴¹

Treatment and outcome disparities for bipolar disorder must also be situated in the clinical burdens and acceptability of treatment. An international survey of prescribers indicated the general decline in the use of lithium related to patients' negative beliefs/attitudes towards lithium, and intoxication risk. Physicians were less likely to prescribe lithium in developing economy countries.³ Shared-decision making between physician and patient can offer patients support in determining treatments that are most effective and acceptable, however, studies have yet to examine specific attitudes of and shared decision-making conversations with African Americans with bipolar disorder. Previous studies have reported that Black patients have identified barriers to shared decision including: lack of knowledge of their diagnosis, clinician mistrust, decision disagreement with clinicians, poor engagement with clinicians, and invalidation of patient experiences by clinicians.⁴²

This study has several important limitations that should be considered. First, this meta-analysis is primarily limited by the number of

studies included, as it was a narrative review that combined data from four large cohorts and did not systematically search the literature for other cohorts. Second, there was important variability in the inclusion criteria and methods of ascertaining bipolar disorder across the four cohorts included. Notwithstanding, this meta-analysis represents the largest report on racial disparities in pharmacotherapy for bipolar disorder. Third, our study reports on lifetime lithium data, yet none of the cohorts provide information on the reasons for non-initiation of lithium, whether this was due to patient preference or prescriber concerns. Additionally, there is potential for recall bias in cases where data was self-reported by patients. Fourth, one must consider the use of ICD codes to ascertain bipolar disorders in some cohorts as a limitation, given the inherent challenges of relying solely on ICD codes for diagnostic accuracy. Finally, data on prescriptions, such as that which was included in our study, does not equate to data on medication adherence, as the presence of a medication in an individual's medical records does not necessarily confirm that the individual initiated or continued the treatment. 🍨

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References

- 1. Leboyer M, Kupfer DJ. Bipolar Disorder: New Perspectives in Health Care and Prevention. *J Clin Psychiatry*. 2010;71(12):1689–1695. doi:10.4088/JCP.10m06347yel
- Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disorders*. 2018;20(2):97–170. doi:10.1111/bdi.12609
- 3. Hidalgo-Mazzei D, Mantingh T, Pérez De Mendiola X, et al. Clinicians' preferences and attitudes towards the use of lithium in the maintenance treatment of bipolar disorders around the world: a survey from the ISBD Lithium task force. *Int J Bipolar Disord*. 2023;11(1):20. doi:10.1186/s40345-023-00301-y
- Fico G, Anmella G, Gomez-Ramiro M, et al. Duration of untreated illness and bipolar disorder: time for a new definition? Results from a cross-sectional study. *Journal of Affective Disorders*. 2021;294:513–520. doi:10.1016/j.jad.2021.07.062
- Blow FC, Zeber JE, McCarthy JF, Valenstein M, Gillon L, Bingham CR. Ethnicity and diagnostic patterns in veterans with psychoses. *Soc Psychiatry Psychiatr Epidemiol*. 2004;39(10):841–851. doi:10.1007/ s00127-004-0824-7
- Haeri S, Williams J, Kopeykina I, et al. Disparities in Diagnosis of Bipolar Disorder in Individuals of African and European Descent: A Review. *Journal of Psychiatric Practice*. 2011;17(6):394–403. doi:10.1097/01.pra.0000407962.49851.ef
- Strakowski SM, McElroy SL, Keck PE, West SA. Racial influence on diagnosis in psychotic mania. J Affect Disord. 1996;39(2):157–162. doi:10.1016/0165-0327(96)00028-6
- 8. Akinhanmi MO, Biernacka JM, Strakowski SM, et al. Racial disparities in bipolar disorder treatment and research: a call to action. *Bipolar Disorders*. 2018;20(6):506–514. doi:10.1111/bdi.12638
- Akinhanmi MO, El-Amin S, Balls-Berry JE, et al. Decreased core symptoms of mania and utilization of lithium/mood stabilizing anticonvulsants in U.S. bipolar I patients of African vs European ancestry. *Journal of Affective Disorders*. 2020;260:361–365. doi:10.1016/j.jad.2019.09.022
- Gonzalez JM, Bowden CL, Berman N, et al. One-Year Treatment Outcomes of African-American and Hispanic Patients With Bipolar I or II Disorder in STEP-BD. PS. 2010;61(2):164–172. doi:10.1176/ ps.2010.61.2.164
- Johnson KR, Johnson SL. Inadequate Treatment of Black Americans With Bipolar Disorder. PS. 2014;65(2):255–258. doi:10.1176/appi.ps.201200590
- 12. Taylor-Desir MJ, Balls-Berry JE, McElroy SL, et al. Comparison of Demographic and Clinical Features of Bipolar Disorder in Persons of African and European Ancestry. *J Racial and Ethnic Health Disparities*. 2023;10(1):367–372. doi:10.1007/s40615-022-01228-3

- Tchikrizov V, Ladner ME, Caples FV, et al. Health disparities in the treatment of bipolar disorder. Personalized Medicine in Psychiatry. 2023;37–38:100101. doi:10.1016/j.pmip.2023.100101
- The GAIN Collaborative Research Group. New models of collaboration in genome-wide association studies: the Genetic Association Information Network. *Nat Genet*. 2007;39(9):1045–1051. doi:10.1038/ng2127
- Dick DM, Foroud T, Flury L, et al. Genomewide Linkage Analyses of Bipolar Disorder: A New Sample of 250 Pedigrees from the National Institute of Mental Health Genetics Initiative. *The American Journal of Human Genetics*. 2003;73(1):107–114. doi:10.1086/376562
- Nurnberger JI, DePaulo JR, Gershon ES, et al. Genomic survey of bipolar illness in the NIMH genetics initiative pedigrees: A preliminary report. *Am J Med Genet*. 1997;74(3):227–237. doi:10.1002/ (SICI)1096-8628(19970531)74:3<227::AID-AJMG1>3.0.CO;2-N
- Nurnberger JI. Diagnostic Interview for Genetic Studies: Rationale, Unique Features, and Training. Arch Gen Psychiatry. 1994;51(11):849. doi:10.1001/archpsyc.1994.03950110009002
- Frye MA, McElroy SL, Fuentes M, et al. Development of a bipolar disorder biobank: differential phenotyping for subsequent biomarker analyses. *International Journal of Bipolar Disorders*. 2015;3(1):14. doi:10.1186/s40345-015-0030-4
- First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition with Psychotic Screen (SCID-VP W/ PSY SCREEN). Biometrics Research, New York State Psychiatric Institute; 2002.
- The All of Us Research Program Investigators. The "All of Us" Research Program. N Engl J Med. 2019;381(7):668–676. doi:10.1056/NEJMsr1809937
- DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986;7(3):177–188. doi:10.1016/0197-2456(86)90046-2
- 22. Schwarzer G. meta: General Package for Meta-Analysis. Published online February 8, 2006:7. doi:10.32614/CRAN.package.meta
- 23. National Academies of Sciences, Engineering, and Medicine. Using Population Descriptors in Genetics and Genomics Research: A New Framework for an Evolving Field. The National Academies Press; 2023:26902. doi:10.17226/26902
- Pedersen SL, Lindstrom R, Powe PM, Louie K, Escobar-Viera C. Lack of Representation in Psychiatric Research: A Data-Driven Example From Scientific Articles Published in 2019 and 2020 in the *American Journal of Psychiatry*. AJP. 2022;179(5):388–392. doi:10.1176/appi.ajp.21070758
- 25. U.S. Department of Health and Human Services. Mental Health: Culture, Race, and Ethnicity: A Supplement to Mental Health: A Report of the Surgeon General. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services; 2001. Accessed September 4, 2024. http://www.ncbi.nlm.nih.gov/books/NBK44243/
- Van Der Voort TYG, Goossens PJJ, Van Der Bijl JJ. Burden, coping and needs for support of caregivers for patients with a bipolar disorder: a systematic review. *Psychiatric Ment Health Nurs*. 2007;14(7):679-687. doi:10.1111/j.1365-2850.2007.01158.x
- Warwick H, Mansell W, Porter C, Tai S. 'What people diagnosed with bipolar disorder experience as distressing': A meta-synthesis of qualitative research. *Journal of Affective Disorders*. 2019;248:108–130. doi:10.1016/j.jad.2019.01.024
- 28. Kupfer DJ, Frank E, Grochocinski VJ, Houck PR, Brown C. African-American participants in a bipolar disorder registry: clinical and treatment characteristics. *Bipolar Disorders*. 2005;7(1):82–88. doi:10.1111/j.1399-5618.2004.00163.x
- 29. Li K, Richards E, Goes FS. Racial differences in the major clinical symptom domains of bipolar disorder. *Int J Bipolar Disord*. 2023;11(1):17. doi:10.1186/s40345-023-00299-3
- 30. Gonzalez Arnold J, Salcedo S, Ketter TA, et al. An exploratory study of responses to low-dose lithium in African Americans and Hispanics. *Journal of Affective Disorders*. 2015;178:224–228. doi:10.1016/j.jad.2015.02.035
- Fagiolini A, Frank E, Axelson DA, et al. Enhancing outcomes in patients with bipolar disorder: results from the Bipolar Disorder Center for Pennsylvanians Study. *Bipolar Disord*. 2009;11(4):382–390. doi:10.1111/j.1399-5618.2009.00700.x
- Smith EN, Bloss CS, Badner JA, et al. Genome-wide association study of bipolar disorder in European American and African American individuals. *Mol Psychiatry*. 2009;14(8):755–763. doi:10.1038/ mp.2009.43
- Jones CP. Levels of racism: a theoretic framework and a gardener's tale. Am J Public Health. 2000;90(8):1212–1215. doi:10.2105/ajph.90.8.1212
- 34. Jones CP. Confronting Institutionalized Racism. Phylon. 2002;50(1/2):7. doi:10.2307/4149999
- 35. Sánchez TW, Stolz R, Ma JS. Moving to Equity: Addressing Inequitable Effects of Transportation Policies on Minorities. The Civil Rights Project at Harvard University; 2003:68.

60

- Bailey ZD, Feldman JM, Bassett MT. How Structural Racism Works—Racist Policies as a Root Cause of U.S. Racial Health Inequities. Malina D, ed. N Engl J Med. 2021;384(8):768–773. doi:10.1056/ NEJMms2025396
- Olivet J, Wilkey C, Richard M, et al. Racial Inequity and Homelessness: Findings from the SPARC Study. The ANNALS of the American Academy of Political and Social Science. 2021;693(1):82–100. doi:10.1177/0002716221991040
- Shim RS. Dismantling Structural Racism in Psychiatry: A Path to Mental Health Equity. AJP. 2021;178(7):592–598. doi:10.1176/appi.ajp.2021.21060558
- Muvuka B, Combs RM, Ayangeakaa SD, Ali NM, Wendel ML, Jackson T. Health Literacy in African-American Communities: Barriers and Strategies. *HLRP: Health Literacy Research and Practice*. 2020;4(3). doi:10.3928/24748307-20200617-01
- White K, Haas JS, Williams DR. Elucidating the Role of Place in Health Care Disparities: The Example of Racial/Ethnic Residential Segregation. *Health Services Research*. 2012;47(3pt2):1278–1299. doi:10.1111/j.1475-6773.2012.01410.x
- Ly DP, Lopez L, Isaac T, Jha AK. How Do Black-Serving Hospitals Perform on Patient Safety Indicators?: Implications for National Public Reporting and Pay-for-Performance. *Medical Care*. 2010;48(12):1133–1137. doi:10.1097/MLR.0b013e3181f81c7e
- 42. Mhaimeed N, Mhaimeed O, et al. Shared decision making with black patients: A scoping review. *Patient Education and Counseling*. 2023;110:107646. doi:10.1016/j.pec.2023.107646
- University Of Mississippi Medical Center CFI. Patient Cohort Explorer (PCE). Published online 2020. doi:10.6084/M9.FIGSHARE.12252737.V2

SUPPLEMENTARY MATERIAL

FIGURE S1

Forest Plot of Bipolar Disorder Treatment Patterns among Female Individuals with African or European Ancestry



Abbreviations: AA, self-reported African Ancestry; EA, self-reported European Ancestry; GAIN, Genetic Association Information Network; MCBDB, Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder Biobank; UMMC, University of Mississippi Medical Center; OR, odds ratio; CI, confidence interval; MH, Mantel-Haenszel.

62

FIGURE S2

Forest Plot of Bipolar Disorder Treatment Patterns among Male Individuals with African or European Ancestry



Abbreviations: AA, self-reported African Ancestry; EA, self-reported European Ancestry; GAIN, Genetic Association Information Network; MCBDB, Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder Biobank; UMMC, University of Mississippi Medical Center; OR, odds ratio; CI, confidence interval; MH, Mantel-Haenszel.