Racial Disparities in Bipolar Disorder Treatment and Research: A Call to Action

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Abstract

Objectives:
Health disparities between individuals of African and European ancestry are well documented. The disparities in bipolar disorder may be driven by racial bias superimposed on established factors contributing to misdiagnosis including: evolving empirically-based diagnostic criteria (ICD, RDC, DSM), multiple symptom domains (i.e. mania, depression, psychosis), and multimodal medical and additional psychiatric comorbidity.

Methods:
For this paper, we reviewed the phenomenological differences between bipolar individuals of African and European ancestry in the context of diagnostic criteria and clinical factors that may contribute to a potential racial bias.

Results:
Published data shows that bipolar persons of African Ancestry, compared with bipolar persons of non-African Ancestry are more often misdiagnosed with a disease other than bipolar disorder (i.e. schizophrenia). Additionally, studies show that there are disparities in recruiting patients of African ancestry to participate in important genomic studies. This gap in biological research in this underrepresented minority may represent a missed opportunity to address potential racial differences in risk and course of bipolar illness.

Conclusion:
A concerted effort by the research community to increase inclusion of diverse persons in studies of bipolar disorder through community engagement may facilitate fully addressing these diagnostic and treatment disparities in bipolar individuals of African ancestry.

Key Words: Health/Racial Disparities, Minority Research Participation, Bipolar Disorder African Ancestry

Introduction

As the sixth leading cause of disability worldwide, the early onset and chronic nature of bipolar disorder underscores its cumulative illness burden and importance of early intervention and optimal disease management strategies. (1) (2) However, lack of access to and minimal utilization of healthcare coupled with low socioeconomic status continue to drive disease-related disability worldwide, including the United States (US). In comparison to the general US population, Americans with mental illness have decreased life expectancy; for people with severe mental disorders (i.e. schizophrenia, depression, and bipolar disorder), this life expectancy reduction ranges from 10-20 years.(3) (4)

There is a general recognition that the increased morbidity and mortality of people with serious mental illness may be magnified by racial disparities in access to, or provision of healthcare. African-American individuals with bipolar disorder, in comparison to White individuals with bipolar disorder, have been reported to have significantly higher rates of receiving an initial clinical diagnosis other than bipolar disorder; this misdiagnosis may impede treatment strategies that can directly address illness morbidity. (5, 6) (7)

The patient advocacy group Depression Bipolar Support Alliance (formerly known as the National Depressive & Manic Depressive Association) conducted membership surveys, both in 1994 and nearly ten years later, that continue to suggest lengthy delays (10 + years) in receiving an accurate diagnosis. (8) (9) Misdiagnosis has significant implications. A misdiagnosis of bipolar depression as unipolar major depressive

disorder with subsequent antidepressant treatment increases the likelihood of treatment non-response and/or antidepressant induced mania/mood destabilization, while a misdiagnosis of schizophrenia limits the opportunity for treatment with lithium and/or mood stabilizing anticonvulsants, as well as access to bipolar evidence-based psychotherapies. With these considerations in mind, we reviewed psychiatry disparity literature to gain a better understanding of racial diagnostic differences and explore methods for addressing this disparity, with focus on biological and genetic studies inclusive of individuals of African ancestry.

To accomplish this goal, we reviewed literature pertaining to diagnosis and treatment of bipolar disorder (either type I or type II) in people of African ancestry compared with people of non-African ancestry. Barriers to research inclusion and participation are also discussed, especially in the context of genetics research, underscoring the need and potential hazards of not addressing potential racial biases during diagnosis and treatment. We first present the literature chronologically to evaluate how recognition of this problem evolved over the last 50 years. We then explore the potential effects of misdiagnosis on outcome and prognosis, and posit genomic studies of bipolar disorder as a possible method of addressing this disparity.

Methods

Literature for this descriptive review was selected using key search terms to target studies describing diagnostic, treatment, and outcome differences between individuals of European and African ancestry, and research participation in biological research,

specifically genetic studies, among people of African and European ancestry. The cited literature came from PubMed and Google Scholar searches of the following key terms: Bipolar Disorder African Americans, Bipolar Disorder African Americans treatment, Bipolar Disorder African ancestry, Bipolar Disorder African Americans lithium, and Bipolar Disorder Blacks. To identify genetic studies, these key words were searched: Bipolar Disorder African Ancestry Genetics. A total of 28 publications were excluded from the initial search, and 20 more were excluded based on pertinent content; the details of which are shown in Figure 1.

We retained the language used in the original publications to describe various racial and ethnic identifications; for example, if a publication described patients of African ancestry as 'African American', the term 'African American' was used when discussing the publication. In addition, race and ethnicity are terms often used interchangeably. Oxford Dictionary defines ethnicity as "the fact or state of belonging to a social group that has a common national or cultural tradition", while defining race as "each of the major divisions of humankind, having distinct physical characteristics…a group of people sharing the same culture, history, language, etc; an ethnic group."(10)These definitions are very similar to each other and we therefore used it interchangeably and retain the language used (either race or ethnicity) in the cited studies.

Diagnostic Criteria Evolution and Historical Studies of Potential Racial Bias

Psychiatric diagnostic classification has been achieved globally through the World Health Organization (WHO) International Classification of Diseases (ICD), starting with

the ICD6 in 1948, and the Diagnostic and Statistical Manual (DSM), in the US with the American Psychiatric Association (APA). (11) Primarily based on dynamic formulation, manic-depressive "reaction" and "illness" were first classified in DSM I (1952) and DSM II (1968), respectively. Informed by earlier work from the Research Diagnostic Criteria (RDC) and DSM III (1980), empirically based, contemporary diagnostic categorization based on specific, descriptive, and reliable inclusion/exclusion criteria with inter-observer reliability and stability were introduced in DSM IIIR (1987). DSM IIIR marked a fundamental shift away from a predominantly psychodynamic theoretical influence toward a biomedical model. (12)

A second diagnostic debate, during this time of ICD and DSM classification revision, was whether psychosis in affective disorder represented a separate disease process from schizophrenia. (13) Internationally, more so than nationally in the US, there was a movement to adapt a broader concept or spectrum of affective psychosis. For example, a UK vs US comparative study by Cooper et al.,1972 found that despite similar clinical presentations, there was a significant difference in the diagnostic rates of schizophrenia (New York = 62%, London = 34%), psychotic depression (5X higher in London), and mania (12X higher in London). (14) The late entrance of lithium carbonate into the US pharmacopoeia in 1970 (US was the 50th country to admit lithium to the world marketplace) as well as further refinement of diagnostic criteria (DSM III, RDC, DSM IIIR) began to slowly shift the US diagnostic practice and started to address the misdiagnosis of bipolar disorder. (15) However, the misdiagnosis remains prevalent, especially in African American and African-Caribbean individuals. (5) (16) The evolution

of biomedical diagnostic criteria, increasing recognition of an affective spectrum concept including psychosis, and the first FDA approved medication for bipolar disorder introduced in the US more than 15 years after FDA approval of antipsychotic chlorpromazine (1954) and nearly 10 years after FDA approval of antidepressant amitriptyline (1961) are relevant historical events to better understand the African American bipolar patient experience. Additional clinical factors that may be associated with the misdiagnosis of bipolar disorder have included: stage of mania when seeking treatment, hospital setting where diagnosis is made, symptom presentation, and clinical interpretation of symptom presentation.

A case series of 3 African American people with psychotic bipolar disorder (2 male, 1 female) diagnosed as schizophrenic at a university hospital in New Jersey suggested that misdiagnosis was, in part, related to delays in seeking care. The investigators observed that hypomanic or manic behavior "may be more easily tolerated than it would be in a higher socioeconomic area" (versus the low socioeconomic area found in the study). (17) Classic Kraepelinian observations have suggested that as an episode of mania progresses, euphoria decreases and risk of psychosis increases. (18) Therefore, individuals with bipolar disorder who delay seeking treatment may be more likely to display psychotic symptoms once they present to medical center for a cross-sectional, non-longitudinal assessment. Of note, there have been no systematic studies of the contribution of treatment-seeking delay to misdiagnosis in bipolar individuals.

A 1983 medical record review compared rates of misdiagnosis among 76 bipolar individuals [Hispanic = 18 (23.4%), Black = 21 (27.3%), White = 37 (48.1%)] treated in an outpatient department of an inner-city New York hospital. A greater proportion of Black and Hispanic individuals with bipolar disorder were previously misdiagnosed with schizophrenia compared to White individuals (schizophrenia: 85.7% and 83.3% vs 51.4%; paranoid schizophrenia: 66.7% and 33.3% vs 18.9%; p<0.0005 and p<0.005; Black, Hispanic and White respectively). As none of the individuals had a history of clinical diagnoses of a nonaffective psychosis, ethnicity was concluded to be a significant factor in their misdiagnosis. (6) A larger 2004 study explored the relationship between ethnicity, symptom presentation, and diagnosis. African Americans were 4 times as likely to have a schizophrenia diagnosis when compared to otherwise similar White Americans (OR = 4.05, 95% CI: 3.91-4.19) (7) in analyses of the Veteran's Administration Medical Center National Psychosis Registry [n=134,523; 48,443 (36.9%) bipolar, 14,717 (10.9%) schizoaffective] that adjusted for potential demographic confounds. Furthermore, the lack of significant ethnic differences in positive and negative moderate symptom severity also suggests equivalent symptom burden but different clinical interpretation of diagnostic information. While these historical studies identify racial/ethnic bias as a contributor to misdiagnosis, more contemporary research (with enhanced study methodology) may suggest strategies to correct for these differences.

The Epidemiologic Catchment Area Study (ECA) was a landmark study that examined the utilization of a structured diagnostic interview suitable for administration by lay

interviewers in a community based setting. The diagnostic interview was administered to five sites of different sizes and resident characteristics (n=20,000; New Haven, CT, Baltimore, MD, St. Louis, MO, Durham, NC, and Los Angeles, CA). While the percentage of Black respondents at each site ranged from 4% to 34%, there was no significant difference in rates of bipolar disorder by race, suggesting the value of a highly-structured research diagnostic interview as a data source to reduce clinical interpretative differences among persons of different race and ethnicities. (19)

Critical investigations from the University of Cincinnati First-Episode Psychosis and Mania Projects not only used structured diagnostic interviews, as done in the ECA study, but also a multi-racial expert-consensus diagnostic panel of psychiatrists blind to ethnicity to reveal possible limitations, or biases, when clinical diagnoses are the sole source of patient data. (5) (20) The first project enrolled 100 people (46% African American and 54% Caucasian) from inpatient psychiatry services. The investigators evaluated the differences in clinical diagnoses made at the initial point of care (the Psychiatric Emergency Service) versus diagnoses made once patients were admitted to the inpatient unit where they underwent a research Structural Clinical Interview for DSM-III-R. African American bipolar individuals, in comparison to Caucasian bipolar individuals, were more likely to be diagnosed in the Emergency Department with non-affective psychosis in general (i.e. schizophrenia + psychosis NOS; 33% vs 13%, p=0.03) and in particular, with schizophrenia (20% in African American vs 7% in Whites; p=0.07). (5) In the second project, 195 African American and White individuals with at least 1 psychotic symptom were recruited between 1998 and 2001. Of these, 79 (39

African Americans and 40 White) received a bipolar disorder diagnosis by an expert-consensus blind to ethnicity. After controlling for demographic variables and comorbid drug use, African American men with bipolar disorder had significantly higher rates of clinical schizophrenia diagnoses (25% vs 7%, p=0.02) and higher rates of schizophrenia diagnosis by structured interview (29% vs 15%, p < 0.03) when compared to the other patient groups. Rates of first rank psychotic symptoms did not differ by ethnic groups, suggesting that the patient's race and sex were primary factors for schizophrenia diagnosis. (20) The use of an expert panel reviewing diagnostic criteria, in comparison to both clinical diagnosis and structured interview appeared to yield less misdiagnosis.

The evolution of bipolar disorder diagnostic criteria coincides with these inaugural efforts to understand differences in diagnosis between bipolar individuals of European and African ancestry. Reports suggest that these differences are mainly attributed to racial/ethnic bias and/or misattribution of psychotic symptoms. These historical and distinctive studies are key to understanding the development of this disparity and its impact on subsequent treatment. (Figure 2)

Treatment, Response, and Prognosis

A 2002 prospective longitudinal study reported that 24 African Americans with bipolar I disorder received antipsychotics at a greater percentage of follow up visits (44%/70 visits) than 34 Whites (40% /34 visits; p < 0.007). The prescription of typical antipsychotics in African American vs White bipolar individuals was significantly higher (38% AA vs 15%; p<0.05) (21). A larger 2003 cross-sectional study of 535 hospitalized

individuals with bipolar disorder confirmed this earlier observation as African Americans, in comparison to Whites, were prescribed antipsychotic medications at a higher rate (92% vs 62%); there was no difference, however, in the use of atypical vs typical antipsychotics. (22) While first-generation or typical antipsychotics are well known to be very effective in treating acute mania, they have a higher incidence (in comparison to FDA second generation or atypical antipsychotics) of mood destabilization (i.e. post manic depression) and extrapyramidal side effects including tardive dyskinesia. (23) Adverse effects such as these warrant strong efforts toward understanding the root cause of misdiagnosis and inevitable suboptimal treatment.

A study that examined 34 bipolar persons taking lithium carbonate demonstrated that African Americans had a mean lithium red blood cell (RBC)/plasma ratio [(n=12) 39.70 +/- 17.8] significantly higher than Whites [(n=22) 26.12 +/- 10.9, $p < 0.05$)]. The side effect burden was similarly higher in African Americans vs Whites even though the two groups did not significantly differ in mean daily dose (1131 mg/day vs 1159 mg/day) and average plasma level (0.58 +/- 0.27 vs 0.57 +/- 0.17; African American and Caucasian, respectively). The RBC measurement has been proposed to be a better measure of brain lithium level than conventional plasma levels and earlier research has suggested that African Americans, in comparison to Caucasians, have reduced efficiency in the RBC lithium sodium counter transport pathway. (24) (25) (26) Lower dose lithium proved to have positive results in a more recent study from 2015 that examined 283 bipolar patients who participated in a 6-month, randomized, double-blind, placebo-controlled trial of adjunctive low-dose lithium (600 mg) with optimized treatment

(LiTMUS). Compared to Whites, African Americans had greater reduction of depression symptoms (p=0.04) and improved quality of life (p=0.03). Although the study showed promising support for low-dose lithium in African Americans, larger sample sizes in future studies are necessary to confirm these significant findings. (27) Underutilization of mood stabilizers or suboptimal dosing of mood stabilizers may negatively affect disease progression.

Gonzalez, et al compared 1-year treatment outcomes from the U.S. Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) among African Americans, Hispanics, and Whites. African Americans (n=155) with psychotic symptoms at baseline, in comparison to non-Hispanic Whites (n=729) with psychotic symptoms at baseline, had a significantly lower response rate (50% reduction in Montogomery-Asberg Depression Rating Scale; MADRS) and recovery rate defined as remission of symptoms over the 1-year period (38% vs 53%; p<0.07). The investigators did note that symptom reports, during the clinical assessment, from some African Americans may have been misattributed to psychopathology instead of sociocultural background. For example, the authors proposed that a persecutory delusion classified as a psychotic symptom may have been more accurate to view as an anxiety symptom when sociocultural context was considered. (28) This misattribution could fuel unsuitable treatment recommendations (i.e. using antipsychotic vs anti-anxiety treatment). This study suggests that culturally competent treatment regimens in populations with different sociocultural background may help address racial bias and aid in yielding more appropriate treatment recommendations.

Consideration of sociocultural background may also be crucial regarding continuity of outpatient care. A 2005 Veterans Affairs (VA) National Patient Care Database study of veterans with bipolar disorder (n=2,316; African Americans = 303) revealed that African Americans were significantly less likely to have an outpatient follow-up visit within 90 days of their diagnosis compared to Whites (13% African Americans vs 87% Whites; p=0.009). The investigators suggested that the reduced likelihood of African Americans to receive adequate outpatient care compared to Whites may be due to lack of culturally competent providers, particularly in urban facilities. (29) A study from 2014 using the National Comorbidity Survey Replication (NSC-R; a U.S. study of mental health) further examined the difference in treatment of bipolar disorder between Black (n=30) and White (n=137) Americans. No Blacks received minimally adequate treatment (defined as use of a mood stabilizer alone or in combination with an antipsychotic) in the previous year, compared to 17% of Whites that did (p<0.05). Their findings suggest that, in general, people with bipolar disorder receive inadequate treatment that is then further confounded by race. (30)

Disparities in treatment regimens and subsequent lower quality outcomes warrant targeted treatment models aimed at improving outcomes and reducing health disparities. Specialized Care for Bipolar Disorder (SCBD) and Enhanced Clinical Intervention (ECI) are examples of such treatment regimens. The study that developed these treatment models sought to reduce health disparities in 3 groups often under-represented in clinical trials: the young and elderly, African Americans, and rural

residents with bipolar disorder. The ECI component was intensive case management adapted to the specific needs of each subpopulation focused on education about the mood disorder itself and treatment strategies. 463 bipolar individuals (68 African American, 385 Caucasian) were randomly assigned to SCBD alone or SCBD + ECI for up to 3 years. While the study results showed improvement in quality of life was greater in the SCBD+ECI group, there were no significant differences by race suggesting the benefit of culturally competent case management and standardized treatment protocols. (31) If personalized treatment protocols are to be developed, understanding the patient's sociocultural background is just as important as the diagnostic criteria of bipolar disorder in African Americans. (Table 1) Biologically-based definitions of bipolar disorder and psychotic symptoms are also valuable, but early in validation and development. Further advancement of clinically relevant biomarkers (through biological and/or genetic studies of the neurobiology of the disease) is an important step to addressing these disparities. (32)

Genomic Studies of Bipolar Disorder: Underrepresentation of Populations of African Ancestry

Understanding the genetic basis of bipolar disorder could greatly advance knowledge of its neurobiology and etiology. Bipolar disorder is a complex genetic disorder, with heritability estimated to be between 60-85%, indicating that a large proportion of disease risk is potentially attributed to inter-individual genetic variation. (33) Numerous studies have attempted to identify genetic factors contributing to risk of bipolar disorder to uncover the underlying pathophysiology and pathogenesis of the disease. While

genomic research could aid in resolving health disparities, others have argued that knowledge of genetic factors that contribute to illness or treatment outcomes will not itself reduce health disparities. Kashyap and colleagues note that although the role of genomics in health disparities is quite complex, it is critical to understand how genetic variation influences the health and well-being of at-risk communities to eliminate health disparities in the United States. (34) On the other hand, West, et al (35) argue that clarification of genetic contributors to disease etiology will not help to provide ways to address disparities, as they are rooted in social, material, and environmental conditions. Nevertheless, there is recognition that genetic studies should include diverse populations to enable identification of a wide range of genetic variation contributing to health outcomes and ensure that knowledge gained from these studies is applicable to all populations.

Numerous studies have been conducted to investigate the genetics of bipolar disorder, including many candidate gene studies, a growing number of genome-wide association studies (GWAS), and recently introduced whole exome and whole genome sequencing studies. These genetic association studies and the efforts of large international consortia, particularly the Psychiatric Genomics Consortium (PGC), have led to the discovery of several bipolar disorder risk variants with genome-wide significant evidence of association. (36) While these discoveries constitute important progress towards a better understanding of the neurobiology of the disease, the studies that produced these results were performed almost exclusively in populations of European ancestry. Very few studies of the genetics of bipolar disorder, and only one published GWAS, have

included samples of African ancestry. That GWAS included only 345 African American cases, a small number compared with the 1001 European American cases in the same study, providing inadequate power to detect genetic associations in the African American subset. (37) The small sample size of the published African American GWAS of bipolar disorder is in stark contrast to the large number of European ancestry cases that the PGC has accumulated (n = 9,784, to date), leading to the discovery of more than a dozen genetic variants contributing to bipolar disorder risk in European populations. (38) (Figure 3) Similarly, in reviewing GWASs of psychiatric pharmacogenomics, Murphy and McMahon noted that "non-European groups were underrepresented in these studies". (39)

The underrepresentation of individuals of African ancestry in genetic studies is a two-fold issue stemming both from the small numbers of African-ancestry participants, and the frequent exclusion of participating minorities from analyses to promote sample homogeneity and prevent confounding by population stratification. The low participation rate of African Americans in bipolar disorder genetic research speaks to the need to increase engagement of these populations in research; however, recruitment of African Americans for genetic research (and bipolar disorder studies more specifically) is challenging. (40) (Table 2) For example, the Mayo Clinic Bipolar Biobank has about 2,148 individuals enrolled, but only 3.7% are of African ancestry. (41) Even with policy initiatives from the National Institute of Mental Health (NIMH) aimed at increasing minority participation, results have been mixed. Nwulia et al (42) assessed participants in the US Bipolar Genome Study to identify concerns that influence individual

participation in psychiatric genetic studies, and found that there is an increased perception of harmful consequences among Blacks, when compared to Whites. The authors also reported that another main concern among Blacks when compared to Whites was racial discrimination (34% of AA were "very concerned" compared to 13% of Whites; $p < 0.0001$), and noted that there may be additional factors contributing to the decision to participate in research. To better understand what factors influence patient participation, Hartz et al (40) used a large, population-based sample from a genetic study of nicotine dependence (Collaborative Study on the Genetics of Nicotine Independence) to investigate differences between European American (n=705) and African American (n=352) participation. They examined three critical steps of study recruitment: establishment of initial contact, participation in screening, and recruitment into the genetic study (with blood draw). Surprisingly, the participation rate was lower in European Americans than in African Americans (57% vs 71%, $p < 0.0001$). This difference was because willingness to participate was not seen as a major barrier; once reached, minorities were more likely to participate. Locating minority participants and establishing contact were the key barriers, suggesting that recruitment efforts should focus on areas with high frequency of individuals of African ancestry.

Another recent study (43) assessed willingness to participate in a biobank, hypothesizing that willingness would be higher under more restrictive scenarios. Participants (n=13,000; AAs=1,483; White=6,521) were randomized to receive a survey in 1 of 3 hypothetical biobank scenarios; all scenarios were the same except for consent type and data sharing approach. In this study, African American participants expressed

lower levels of willingness to participate compared to Whites (56% vs 70%). However,

few studies have aimed to understand how to overcome barriers to study participation

and inclusion. The STEP-BD (The Systematic Treatment Enhancement Program for

Bipolar Disorder) created the Community Partner Program (CPP) to address the issue

of under-represented minorities in mental health research studies. When compared to

collaborating academic sites, community sites enrolled higher percentages of minority

participants (45.2% vs 15.3%, p <0.001). The inception of such programs is essential

and demonstrates that including community partners greatly enhances minority

involvement in research studies. Moreover, community-engaged participatory- based

research remains crucial to motivating individuals to consistently participate in research

activities. (44) These research activities are key to conducting impactful studies that will

enhance understanding of the biological and genetic basis of bipolar disorder, which

can possibly address previously observed symptomatic differences that lead to

misdiagnosis of bipolar African Americans.

Conclusion and Future Directions

This manuscript has reviewed the racial disparities in bipolar disorder diagnosis,

treatment, and research participation, emphasizing the need for increased efforts by the

scientific community to address these disparities. The reviewed literature suggests that

people of African ancestry with bipolar disorder (either type I or II) have higher rates of

misdiagnosis in comparison to people of non-African ancestry with bipolar disorder.

These disparities have developed and persisted despite diagnostic criteria revision from

a psychodynamic formulation to a biomedical model, increasing recognition of an

affective spectrum, and a bipolar pharmacopoeia, at least in the United States, developed 10-15 years later than treatments for schizophrenia and major depression.

This descriptive review has a number of limitations. While focused on biological research as a means to address health disparities, there needs to be recognition that many additional factors may contribute to a bipolar misdiagnosis and these factors may not be unique to patients of African ancestry. There are socioeconomic, cultural, and healthcare administrative aspects of access to and benefit from a bipolar diagnosis and treatment program that go beyond race and ethnicity. While this review focused on biological and genetic factors of bipolar disorder, other additional non- biological and historical factors may contribute to this health disparity. Systematic issues such as access to the healthcare system and historical mistrust may also play a role. The mechanisms and processes contributing to this important issue likely involves slavery, institutional racism, discrimination, poverty, and segregation. The focus on genomic and community based participatory research is meant to be an alternative approach to address these disparities and not reduce the importance of other contributing factors.

We proposed a plan of action to address these disparities that involves understanding the evolution of the problem, and identifying the contribution of associated clinical and biological risk factors of bipolar disorder, particularly through genomic studies. Targeted, biologically-based research focused on these differences has the potential to clarify the issues and effect change in the psychiatric care of minority populations. (44) However, low rates of research participation among minority populations compound the problem

because low numbers preclude comprehensive evaluation of potential biologic and cultural factors that may contribute to possible differences in clinical presentation and disease progression. Low research participation is best addressed through increased understanding of the barriers to engagement with minority communities as well as strong efforts from the scientific community to include minority persons in studies of bipolar disorder, especially genetic and other etiologic studies. (45) Examples of active engagement efforts include, but are not limited to: Community Based Participatory Research (CBPR) focused on patient and family education, working with faith based organizations to disseminate impactful and educational research findings, focused efforts to train more psychiatrists in cultural competency, and overall training of more psychiatrists of African ancestry. (46)

The complexities of the factors that contribute to misdiagnosis of bipolar disorder in individuals of African ancestry and minimal participation from minority samples are critical disparities that warrant attention and action from the scientific community and facilitators.

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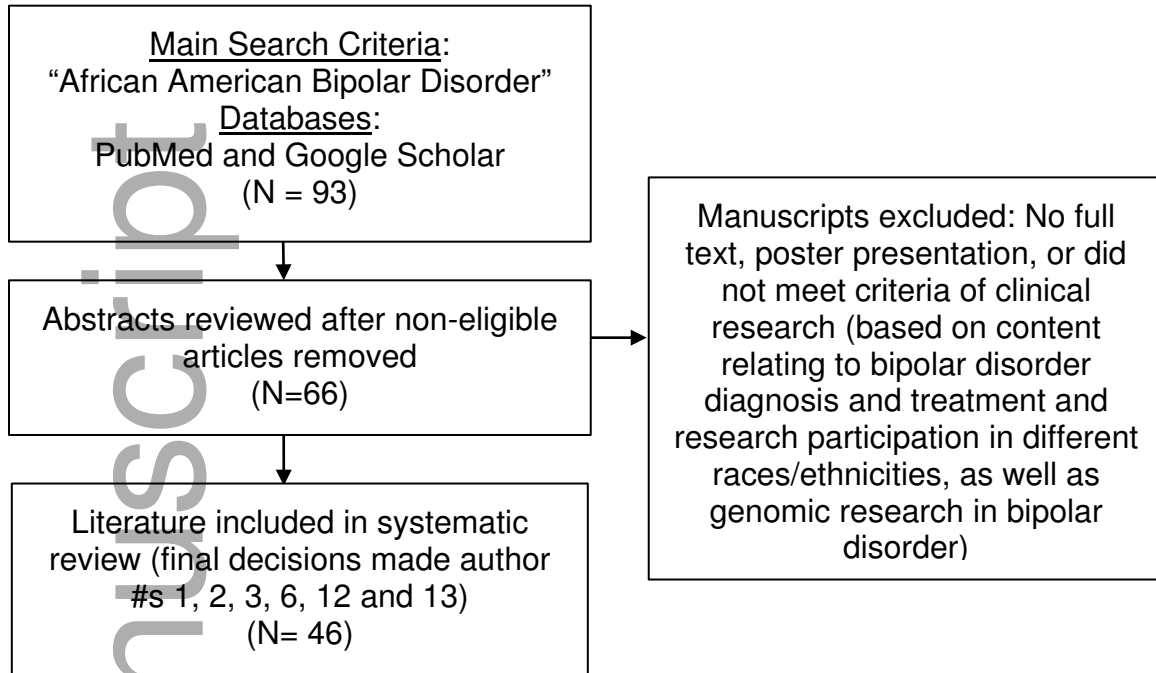
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Table 1. Studies Addressing Treatment and Drug Response in Bipolar Patients of African Ancestry

Study	Sample Size (N or % total)	Major Conclusions
Szarek, et al 2003 (22)	Total=535 Hospitalized Inpatients	Both AA and HIS were more likely to have antipsychotics prescribed (92% and 85%, respectively) compared with CA (62.2%).
Fleck, et al 2002 (21)	Total=58 Outpatients AA=24 (41.3%) CA=34 (58.6%)	AA received antipsychotics during a greater percentage of follow-up treatments compared with CA [mean=70 (44%) vs mean=34 (40%), p<0.007].
Fagiolini, et al 2009 (31)	Total N=463 AA=68 (14.7%) CA=385 (83.2%)	There was no significant difference found between participants of different race. However, adding ECI to SCBD showed benefits of greater QOL.
Gonzalez, et al 2010 (28)	Total = 1,858 AA = 155 (8.3%) CA = 1,551 (83.5%)	For depression response (measured by the MADRS), AA with psychotic symptoms at baseline had poorer outcomes compared with non-HIS CA with psychotic symptoms at baseline (total recovered/responded: AA=38 vs CA=241, p=0.339). (recovered/responded=50% improvement over baseline)
Kilbourne, et al 2005 (29)	Total BD I = 2,316 AA = 303 (13.1%)	AA patients were less likely to receive suitable outpatient care within 90 days of the index bipolar diagnosis compared with CA patients (202 vs 1,351, p=0.009)
Johnson, et al 2014 (30)	Total=167 AA=30 (18%) CA=137 (82%)	Minimally adequate treatment (defined as use of a mood stabilizer alone or in combination with an antipsychotic) was significantly different in AA vs CA (0% vs 17%, p<0.05).
Strickland, et al 1995 (24)	Total=34 AA=12 CA=22	There were higher lithium red blood cell/plasma ratios and side effects in AA vs CA (39.70±17.84 vs 26.12±10.95, p<0.05).
Gonzalez Arnold, et al 2015 (27)	Total=283 AA=47 (19.7%) CA=175 (61.8%) HIS=39 (13.8%) (Cohort included those with self-identified race)	AA on low dose lithium (600mg average dosage), compared with CA, had greater improvement on depression symptoms (p=0.04) and improved QOL scores (p=0.03).
AA, African American; CA, Caucasian; ECI, Enhanced Clinical Intervention; HIS, Hispanic; MADRS; The Montgomery-Åsberg Depression Rating Scale; QOL, Quality of Life; SCBD, Specialized Care for Bipolar Disorder		

**Table 2. Participation in Genetic Studies among Subjects of African Ancestry**

Study	Sample Size (N or % total)	Major Conclusions
Nwulia, et al 2011 (42)	Total = 1,253 AA = 188 (15%) CA = 1,065 (85%)	AA exhibited more concern for risks to procreation and (27% of AA were "very concerned" compared with 18% of CA; p<0.004) and racial discrimination (34% of AA were "very concerned" compared with 13% of CA; p<0.0001).
Hartz, et al 2011 (40)	Total N= 28, 658* AA=352 cases,152 controls EA=705 cases, 710 controls *Number screened by phone and filtered through inclusion/exclusion criteria	The participation rate was lower in EA than in AA (57% vs 71%, p<0.0001). Mistrust of medical research did not prove to be a barrier for minority participation. Critical barriers were locating minority subjects and establishing contact. Once reached, minorities were more likely to participate.
Kogan, et al 2009 (44)	Total=2,848 (4.1 % AA) Community sites: 157 (25.8 % AA) Academic sites: 2,691 (4.8 %AA)	Community sites had significantly higher minority enrollment than academic sites (45.2% vs 15.3%, p<.001)
Sanderson, et al 2017 (43)	Total=13,000 AA=1,483 (12%) CA=6,521 (51%)	AA participants expressed the lowest levels of willingness to participate compared to CA (56% vs 70%).
AA, African American; CA, Caucasian; EA, European Ancestry		

Figure 1: Flow Diagram for Literature Selection and Inclusion

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┌─────────────────────────────────┐
│      Main Search Criteria:      │
│ "African American Bipolar Disorder" │
│            Databases:            │
│    PubMed and Google Scholar     │
│            (N = 93)              │
└─────────────────────────────────┘
              │
              ▼
┌─────────────────────────────────┐      ┌─────────────────────────────────┐
│ Abstracts reviewed after non-eligible │      │   Manuscripts excluded: No full  │
│       articles removed           │─────▶│ text, poster presentation, or did │
│            (N=66)               │      │   not meet criteria of clinical   │
└─────────────────────────────────┘      │   research (based on content     │
              │                          │   relating to bipolar disorder    │
              ▼                          │   diagnosis and treatment and     │
┌─────────────────────────────────┐      │ research participation in different │
│ Literature included in systematic │      │      races/ethnicities, as well as │
│ review (final decisions made author │      │     genomic research in bipolar   │
│   #s 1, 2, 3, 6, 12 and 13)      │      │           disorder)              │
│            (N= 46)              │      └─────────────────────────────────┘
└─────────────────────────────────┘
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Figure 2. Timeline of Historical Clinical and Diagnostic Studies addressing Racial Differences & Potential Bias
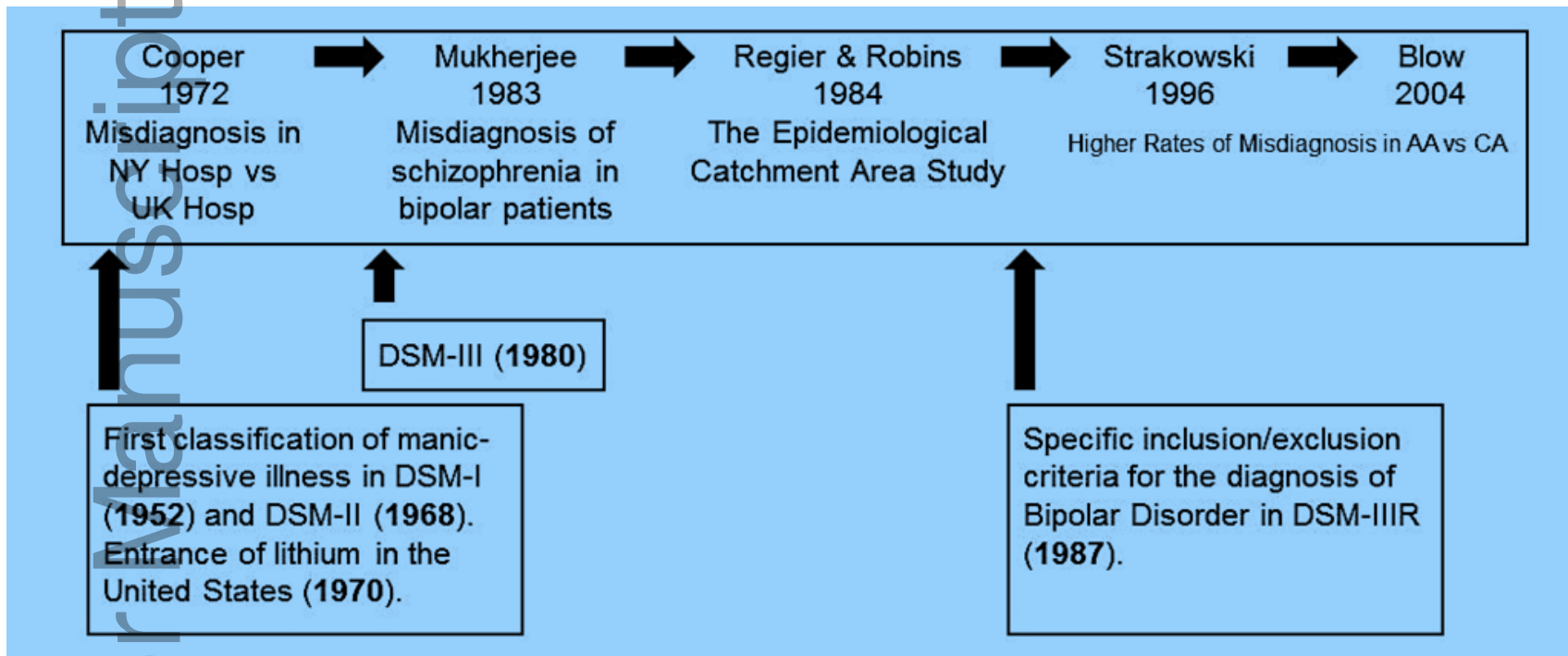
Figure 3. Sample Sizes of Largest AA & EA Bipolar Disorder Genome-Wide Association Study Published to Date