Exploring Biologic Predictors of Response Disparities to Atypical Antipsychotics among Blacks: A Quasi-Systematic Review

Rebecca N. Jerome, MLIS, MPH[1]; Jill M. Pulley, MBA[1]; Nila A. Sathe, MA, MLIS[2,3]; Shanthi Krishnaswami, MBBS, MPH,[2]; Alyssa B. Dickerson, BS[1]; Katherine J. Worley, MLIS[1,2]; Consuelo H. Wilkins, MD, MSCI[4]

Purpose: Management of schizophrenia among Blacks in the United States is affected by persistent disparities. This review explored response to atypical antipsychotics among Blacks compared with other groups to assess systematic variation that may contribute to disparities.

Methods: We conducted a quasi-systematic review of studies reporting response to atypical antipsychotics among Blacks compared with other groups, including effects of genetic variation.

Results: Of 48 identified research articles, 29 assessed differences in outcomes without inclusion of genetic variation and 20 explored effects of genetic variation; of note: one article included both types of data. Analysis of the 29 papers with clinical outcomes only suggests that while data on efficacy and risk of movement disorders were heterogeneous, findings indicate increased risk of metabolic effects and neutropenia among Blacks. Of the 20 articles exploring effects of genetic variation, allelic or genotypic variations involving several genes were associated with altered efficacy or safety among Blacks but not Whites, including risk of decreased response involving variation in *DRD4* and *DRD1*, and improved efficacy associated with variants in *DRD2*, *COMT*, and *RGS4*. Others showed significant improvement in treatment response only among Whites, including variation in *DTNBP1*, *DRD4*, and *GNB3*.

Conclusions: The current analysis can help tailor management among Blacks using an atypical antipsychotic. Heterogeneity in genetic variation effects and response allele frequency suggests that pharmacogenetics approaches for atypical antipsychotics will need to explicitly incorporate race and ethnicity. *Ethn Dis*. 2020;30(Suppl 1):229-240; doi:10.18865/ed.30.S1.229

Introduction

Diagnosis and management of mental health conditions among Blacks in the United States remains complex and affected by significant disparities, particularly in those with more severe disease. Blacks may be 2-5 times more likely to be diagnosed with schizophrenia as compared with Whites[1]; further, research indicates differences in prescribing, including overuse of lower efficacy, higher-risk first generation antipsychotics in this group.[2] In addition to these striking disparities in disease management, any unrecognized systematic variations in response to atypical antipsychotic therapy could be significantly contributing to disparities among Blacks living with schizophrenia.

While the growing body of pharmacogenomics research has significant potential for guiding treatment decisions, the persistent heterogeneity of observed treatment responses in many clinical situations suggests that additional genetic and other biologic factors may contribute to the success, or failure, of a given treatment approach in individuals of different racial and ethnic backgrounds. Notable patterns of altered safety and efficacy in Blacks, for example, as compared with other demographic groups include: a *CCR5* genotype associated with response to highly active antiretroviral therapy, further modified by strength of African ancestry,[3] and an altered risk profile in Black severe heart

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[1] Vanderbilt Institute for Clinical and Translational Research, Vanderbilt University Medical Center, Nashville, TN
[2] Vanderbilt Evidence-Based Practice Center, Institute for Medicine and Public Health, Vanderbilt University Medical Center, Nashville, TN
[3] Vanderbilt Department of Health Policy, Institute for Medicine and Public Health, Vanderbilt University Medical Center, Nashville, TN
[4] Department of Medicine, Vanderbilt University Medical Center and Department of Internal Medicine, Meharry Medical College, Nashville, TN

Address correspondence to Rebecca N. Jerome, MLIS, MPH; Vanderbilt Institute for Clinical and Translational Research; Vanderbilt University Medical Center; 2525 West End Ave., suite 600; Nashville TN 37203; rebecca.jerome@vumc.org

failure patients receiving spironolactone.[4] Such differences may significantly contribute to ongoing health disparities, particularly as they relate to potential decreased therapeutic efficacy or increased risk of side effects.

The published literature, as a body of existing data, represents an important opportunity for employing analytic approaches to understanding safety and efficacy patterns that may further inform clinical practice and future research related to the care of individuals of different racial and ethnic backgrounds. To begin to explore potential biologic factors that may affect response to atypical antipsychotic agents, including potential differences in safety and efficacy, we used a quasi-systematic literature review approach. The goals of this analysis included: 1) to inform treatment planning when feasible and appropriate; and 2) to enrich hypothesis formation for future research to develop deeper understanding of the biologic explanations underpinning some of these results.

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Methods

Information Sources and Eligibility Criteria

This pilot review employed data aggregated by IMS Institute for Healthcare Informatics to identify the most prescribed brand name and generic drugs in the United States,[5] prioritizing agents with FDA-approved indications for treatment of conditions with known health or treatment response disparities[6] affecting Blacks. For this review, we used this information as well as clinical input and focused on the atypical antipsychotics, commonly used to treat schizophrenia and related disorders. Our quasi-systematic review protocol, PRISMA diagram, and detailed evidence extraction files are archived at https://rocket.app.vumc.org/index.php?doc_id=21299.

We searched MEDLINE via PubMed for articles published from January 2000 to November 2016 using a combination of controlled vocabulary and key terms related to atypical antipsychotics, African ancestry, and genetic or drug response variation. We selected the year 2000, when the first draft of the human genome was completed, as a starting date given that the majority of evidence related to our pharmacogenomics objective would be published after this time.[7] To ensure that our analysis incorporated the most current literature, we completed a final manual search of citations in PubMed published from November 2016 through August 2019. We did not include EMBASE searches due to exploration indicating that this resource was duplicative of the citations retrieved using PubMed. In parallel, we developed inclusion criteria in consultation with team experts and informed by our preliminary review of response variability information.

We sought studies assessing any differential response to drugs of interest and those identifying genetic polymorphisms related to drug response variability or modification. We included: 1) empirical studies of any design and pooled trial analyses, systematic reviews, and meta-analyses addressing variation in effectiveness or safety of atypical antipsychotics among Blacks compared with another racial/ethnic group; and 2) original research studies evaluating genetic variations that may affect drug response in Blacks compared with other ethnic groups. We limited inclusion to English language studies. Four reviewers (RJ, SK, NS, KW) independently screened titles/abstracts and the full text of studies using predetermined criteria, with discrepancies between reviewers resolved through discussion to reach consensus.

Data Extraction and Analysis

We extracted study design, key study population characteristics, methodologic characteristics (study design), and outcome data on constructs of interest (race/ethnicity, al-

lelic variations, efficacy measures, safety data) from eligible studies. To accommodate the heterogeneous terminology used among studies to refer to subgroups by race and ethnicity, we use the term Black throughout this analysis to refer to any subgroup defined within studies as Black, African, African American, or of African ancestry, and use the term White to refer to subgroups defined within studies as White, Caucasian, European American, or of European ancestry. Other less commonly compared groups in this literature are described using the definition used in the original studies (eg, Mexican, Puerto Rican, Latin American, Asian).

We synthesized studies qualitatively and report descriptive statistics in summary tables. As this was a pilot review, we did not formally assess the methodologic quality of studies. To assess relative population frequency of variants with significant allelic or genotypic effects on efficacy and/or safety, we explored minor allele frequency (MAF) among the subgroups using SNP prevalence data in gnomAD.[8]

Results

Article Selection and Overview

Of the 3158 articles retrieved by our searches, 48 papers describing antipsychotics outcome data met inclusion criteria. While our search focused on atypical antipsychotic agents, we summarize data regarding typical antipsychotics when also present in an included study.

Studies focusing on adult participants predominated in this literature. Whites were the most common group compared with Blacks, with only a few studies analyzing a Hispanic or Latin American group for comparison. Most studies categorized race and ethnicity based on participant self-report or did not share their approach for categorizing race and ethnicity; a limited number of analyses incorporated genetic ancestry markers. Almost all articles focused on antipsychotic therapy for treatment of disorders on the schizophrenia spectrum; a limited number described other uses, such as management of agitation in the pediatric psychiatric unit setting.

Antipsychotics: General Efficacy or Safety Effects by Race/Ethnicity

We identified 29 articles assessing potential differences in efficacy and/or safety of atypical antipsychotic agents in Blacks as compared with other racial or ethnic groups, including those studies exploring subgroup effects within clinical data without analysis of genomic variant effects. These studies included a range of approaches for defining the Black subgroup, including self-report in three,[9–11] self-report plus participant-reported race/ethnicity of biologic parents and grandparents in two,[12,13] and the medical record or a registry/database in six;[14–19] an approach was not reported in 17 articles[20–36] and one meta-analysis used existing categorization from included studies.[37] One study using self-reported Black race also included estimation of geographic ancestry using the STRUCTURE software.[12]

Efficacy

Ten studies analyzed potential differences in efficacy outcomes associ-

Table 1. Atypical antipsychotic studies reporting efficacy outcomes (without genetic data)

Author, year	Design	Black N/Total N	Condition(s)[a]; Drug(s)[b]	Efficacy among Blacks[c]
Arnold 2013[9]	RCT	506/1398	Sz; O,Q,R,Z,P	↑
Chan 2013[12]	Pooled trials	30/237	Sz; C,O,R,H	=
Loebel 2013[35]	RCT	95/524	Sz; L,Q	=
Meltzer 2011[36]	RCT	160/548	Sz; L,O	=
Stauffer 2010[20]	Pooled trials	375/980	Sz,Sp,Sa; O	=
Lawson 2009[10]	Pooled trials	267/955	Sz; Z,H	=
Barzman 2007[14]	Case series	33/69	Ag; Z	=
Patel 2006[22]	Case series	38/105	Szspec; R	↑
Ciliberto 2005[21]	RCT, post-hoc	174/439	Sz,Sz; R	= Total PANSS, θ 2 subscales
Emsley 2002[23]	RCT, post hoc	50/129	Sz,Sp; NS	↑

Key: ↑ increased efficacy; ↓ decreased efficacy; = similar efficacy among groups; θ efficacy found in another group but not found among Blacks; RCT, randomized controlled trial; post hoc, secondary analysis of trial data.
a. Sa, schizoaffective disorder; Sp, schizophreniform disorder; Sz, schizophrenia; Szspec, schizophrenia spectrum disorders.
b. C, clozapine; H, haloperidol; L, lurasidone; NS, specific agents not detailed; O, olanzapine; P, perphenazine; Q ,quetiapine; R, risperidone; Z, zuprasidone.
c. Compared with other racial and/or ethnic groups.

ated with antipsychotic therapy in Blacks as compared with other racial or ethnic groups (Table 1).[9,10,12,14,20–23,35,36] Three pooled analyses of antipsychotics trial data found equal clinical efficacy of these agents in Blacks as compared with other groups.[10,12,20] ANCOVA subgroup analyses of two randomized controlled trials (RCTs) of atypical antipsychotics found no significant treatment interactions with race and ethnicity.[35,36] A fourth pooled analysis of trial data from South Africa found improved efficacy of antipsychotic therapies in Black and mixed descent participants as compared with White participants (P=.002 for group difference in incidence of > 40% reduction in Positive and Negative Syndrome Scale (PANSS) total scores).[23]

In a secondary analysis of Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial data by Arnold et al, investigators found that White adults discontinued olanzapine and risperidone for lack of efficacy at higher rates than Black or Hispanic participants (P=.04), while Hispanic participants discontinued perphenazine and ziprasidone for lack of efficacy at higher rates than Whites or Blacks (P≤05).[9] In another secondary analysis of RCT data, Ciliberto et al found no effect of race on total PANSS scores in risperidone-treated adults; however, White participants improved on all five PANSS subscales while Blacks improved on only three, failing to show improvements in disorganized thought and uncontrolled hostility/excitement.[21]

The two retrospective case series included children and adolescents and found differing results. Patel et al found greater improvement in challenging behaviors during risperidone therapy among Black as

Table 2. Atypical antipsychotic studies reporting safety outcomes (without genetic data)

Author, year	Design	Black/Total N	Condition(s)[a]; Drug(s)[b]	Safety among Blacks[c]				
				DC	MV	N	MT	B
Demler 2016[33]	Case series	NR/193	Sz; C			↓		
Kane 2014[30]	RCT	223/340	Sz; A				↓	
Su 2014[11]	Case control	135/492	Spsy,Ba,Sa, D;Mult		↓			
Arnold 2013[9]	RCT	506/1398	Sz; O,Q,R,Z,P	=	↑			
Chan 2013[12]	Pooled trials	30/237	Sz; C,O,R,H		=		↓	
Maher 2013[18]	Case series	28/88	Sz,Sa; C			↓		
Nowrouzi 2013[31]	Pooled studies	56/139	Sz; C,O,R,H				↓	
Muller 2012[13]	Pooled studies	58/186	Sz,Sa; C,O,R,H				↓	
Stauffer 2010[20]	Pooled trials	375/980	Sz,Sp,Sa; O	=	=		↓	
Krakowski 2009[27]	RCT, post hoc	56/93	Sz,Sa; C,O,H				↓	
Lawson 2009[10]	Pooled trials	267/955	Sz; Z,H		↓		=	
Lipkovich 2009[29]	Pooled trials	399/3826	Szspec,Bp,Br;O				↓	
Rahman 2009[19]	Case series	25/133	NR;Q			↓		
Ormerod 2008[37]	Meta-analysis	287/844	Ps,D; Mult		=		=	
de Leon 2007[26]	RCT, post hoc	7/50	Sz,Sa; C				↓	
Kelly 2007[17]	Case series	588/1875	Sz,Sa; C			↓		
Nihalani 2007[25]	Case series	NR/49	Sz,Sa,Dd, Bp; C				↓	
Wonodi 2007[32]	Case series	62/114	NR; Mult		↓			
Ciliberto 2005[21]	RCT, post-hoc	174/439	Sz,Sa; R		=		=	
Henderson 2005[28]	Case series	6/96	Sz,Sa; C				↓	
Howes 2005[34]	Cross sectional	55/102	NR;Mult					↓
Lambert 2005[15]	Registry	3111/18182	Sz; O,C,R,Q				↓	
Lambert 2005[16]	Registry	2174/12637	Sz; O,C				↓	
Rosenheck 2000[24]	RCT, post hoc	125/423	Sz; C,H				↓	

Key: ↑ increased safety; ↓ decreased safety; = similar safety among groups; RCT, randomized controlled trial; post hoc, secondary analysis of trial data; DC, all cause discontinuation; MV, movement disorders; MT, metabolic dysfunction; N, neutropenia; BN, bone mineral density changes.
a. Ba, bipolar affective disorder; Bp, bipolar disorder; Br, borderline personality disorder Dd, delusional disorder; D, depression; NR, not reported; Ps, psychosis; Sa, schizoaffective disorder; Sp, schizophreniform disorder; Spsy, schizophrenia psychosis; Sz, schizophrenia; Szspec, schizophrenia spectrum disorders.
b. A, aripiprazole; C, clozapine; H, haloperidol; Multi, multiple atypical antipsychotics; NS, specific agents not detailed; O, olanzapine; Q, quetiapine; R, risperidone; Z, zuprasidone.
c. Compared with other racial and/or ethnic groups.

compared with Hispanic adolescents with schizophrenia,[22] while Barzman et al found no effect of ethnicity on ziprasidone efficacy for management of agitation in the pediatric psychiatric unit setting.[14]

Safety

Potential differences in various antipsychotics-related safety outcomes among Blacks as compared with other groups were identified in 23 articles (Table 2); adverse events included metabolic effects (16 articles),[10,12,13,15,16,20,21,24–31,37] movement disorders (8 articles),[9,11,12,20,21,32,37,38] neutropenia (4 articles),[17–19,33] bone mineral density (1 article),[34] and general side effects (1 article).[21]

Results of analyses exploring the risk of metabolic adverse effects among Blacks exposed to atypical antipsychotic agents were varied but seem to indicate a general trend toward increased risk of metabolic side effects in this group as compared with other groups. Eight analyses indicated increased risk of weight gain in Blacks using various antipsychotic agents, including two pooled analyses of olanzapine trial data,[20,29] two secondary analyses of individual clozapine RCTs,[26,39] one RCT of aripiprazole,[30] two pooled analysis of studies involving multiple antipsychotics,[13,31] and one secondary analysis of an RCT including multiple antipsychotic agents.[27] Yet, three additional studies found no effect of race on this outcome; studies included a risperidone trial,[21] a pooled analysis of ziprasidone RCTs,[10] and a meta-analysis of data on multiple antipsychotics.[37] Increased risk of new-onset diabetes and/or increased serum glucose was also observed among Blacks in an olanzapine registry study[15] and a clozapine case series[28]; increased risk of diabetic ketoacidosis among Blacks was also noted in one case series.[25] However, three analyses failed to find a significant effect of race on glucose and/or diabetes, including two pooled analyses of ziprasidone and olanzapine RCT data[10,20] and a meta-analysis of multiple antipsychotics.[37] Two studies also found Blacks to be at greater risk of increased lipid levels during antipsychotic therapy as compared with other groups, including a registry study of olanzapine[16] and a secondary analysis of an RCT including multiple antipsychotics,[27] though two additional studies failed to find a significant effect of race on lipids in patients treated with olanzapine[20] or ziprasidone,[10] respectively.

Among the eight articles examining variation in risk for antipsychotic-associated movement disorders by race and ethnicity, results were heterogeneous. Three analyses found no significant effect of race and ethnicity on incidence of movement adverse events (AEs) among adults, including a pooled analysis of RCTs of olanzapine,[20] a secondary analysis of a risperidone RCT,[21] and a pooled analysis of RCTs involving multiple antipsychotic agents.[12] Three studies indicated increased risk of movement AEs in Blacks as compared with other groups, including a pooled analysis of adult data from ziprasidone RCTs,[10] a case control study including multiple antipsychotics in adult participants,[11] and a pediatric case series including multiple antipsychotics.[32] Conversely, two studies found reduced risk of movement AEs among Black adults as compared with adults from other subgroups; these included a pooled analysis of haloperidol RCT data[10] and a secondary analysis of an RCT including multiple antipsychotic agents.[9]

Four retrospective case series assessed neutropenia during antipsychotic therapy in Blacks as compared with other groups, three examining clozapine[17,18,33] and one assessing quetiapine.[19] Two of these papers included adults[17,33] and two focused on children/adolescents.[18,19] All four analyses indicated increased risk of various neutropenia-related events among Blacks as compared with others; these risk signals varied and included higher incidence of moderate neutropenia/leukopenia/granulocytopenia,[19,33] higher incidence of discontinuation due to leukopenia,[17] and increased risk of neutropenia.[18]

One study in the UK assessed bone mineral density (BMD) in patients taking various antipsychotics, finding no evidence of reduced BMD among White participants and Black women at the total spine, total hip, and femoral neck, while Black men showed reduced BMD at total spine but not at the hip or femoral neck.[34] Finally, the one article assessing overall incidence of side effects in patients receiving risperidone found no significant effect of race and ethnicity on this general outcome.[21]

Antipsychotics: Genetic Variants and Response

Building upon the subgroup effects detected in studies limited to subgroup analyses of clinical data, we next assessed the 20 articles assessing effects of interaction between genomic variation and race on response to

antipsychotic therapy (Tables 3 and 4), with analyzed outcomes including efficacy (12 articles),[40–51] incidence of any adverse effects (1 article),[52] risk of weight gain (5 articles),[13,53–56] risk of movement disorders (3 articles),[52,57,58] and drowsiness (1 article).[54] These studies included a range of approaches for defining the Black subgroup, including self-report in three,[49,57,58] self-report plus participant-reported race/ethnicity of biologic parents and grandparents in three,[13,55,56] principal component analysis comparing participants with 1000 Genome Phase 1 data,[50,51] and estimation of geographic ancestry using the STRUCTURE program[41]; the approach for defining the Black subgroup was not reported in 11 articles.[40,42–48,52–54]

Genetic Variants and Efficacy of Antipsychotic Therapies

Twelve articles yielded data examining possible genetic modifiers of response to antipsychotic therapy in Blacks as compared with other groups (Table 3). One study identified a *GRM3* genotype associated with significantly improved response to atypical antipsychotic treatment in both Whites and Blacks;[48] the response-associated allele is more prevalent among Blacks as compared with Whites.[8]

A number of detected effects were associated with influence on efficacy in Blacks without significant effects in Whites. Of these, nonresponse or lower response to treatment was associated with a 120 bp tandem repeat in *DRD4*,[42] a G(n) mononucleotide repeat in *DRD4*,[42(p4)] and a *DRD1* genotype[45]; the variant in the *DRD1* genotype is also more than twice as prevalent among Blacks as compared with Whites.[8] *STXBP5L* was found to be a key locus in association with lurasidone response among Blacks but not Whites in a GWAS of pooled data three trials, while *CTNNA2* variation was associated with reduced lurasidone response in both groups (though separate variants in Blacks compared with Whites).[51] Another GWAS, involving two of these lurasidone trials, failed to find any variants of genome-wide significance.[50]

Potential pharmacogenetic markers associated with improved efficacy of atypical antipsychotics among Blacks without a similar association among Whites included two *DRD2* variants,[46] one *DRD2* genotype,[47] two *DRD2* haplotypes,[46,47] a *COMT* genotype,[48] and three variants in *RGS4*.[49] In terms of pharmacogenetic markers predicting improved response to specific therapeutics in Blacks but not Whites, a *DTBNP1* SNP was associated with better clozapine response,[41] a *DTNBP1* genotype associated with improved haloperidol response,[41] and a *RGS4* genotype associated with duration of treatment continuation as well as specific agent efficacy.[49] Several of these variants also differ in prevalence between subgroups; as compared with Whites, the response-associated allele for significant SNPs was at least 10% more prevalent among Blacks for two variants, at least 10% less prevalent for five variants, and roughly similar for two variants.[8]

Several genetic markers were significantly associated with treatment response in White but not Black participants, including improved treatment response associated with diplotype and haplotype effects in *DTNBP1*,[41] a 48 bp repeat in *DRD4*,[42] and a *GNB3* genotype.[40]

Finally, one study found a *DRD1* haplotype predicting lower treatment response among Whites, while a different haplotype in this gene was associated with improved treatment response among Blacks.[45]

Genetic Variants and Safety of Antipsychotic Therapies

We identified eight studies that included analysis of the potential impact of genetic variation on adverse effects of atypical antipsychotic use among Blacks as compared with other subgroups (Table 4).[13,52–58] One secondary analysis of RCT data examined treatment discontinuation due to adverse drug reaction, finding that this outcome correlated significantly with lower activity variants in the *FMO3* gene among Blacks treated with olanzapine (P=.01); no similar effect of these variants was observed in the overall cohort or the White subgroup.[52] One of these variants has similar prevalence between Blacks and Whites, while the other is more than 10% less prevalent among Blacks.[8]

Of the four analyses assessing potential genetic variants modifying antipsychotic-associated weight gain, one study indicated increased risk of a *DRD2* variant on weight gain among both Whites and Blacks, though the variant is much less prevalent among Blacks.[13] Three analyses found significant weight gain risk alleles in Whites that failed to have a significant effect among Blacks, including variants in *ADRA2A* (both allele and genotype effects),[53] *FMO3*,[54] *DRD2*,[13] and *TaqIA*.[13] Three of these risk alleles are less prevalent among Blacks and one is of similar prevalence between

Table 3. Atypical antipsychotic studies: genetic associations with efficacy outcomes

Author, year	Design	Black/Total N	Condition(s)[a] Drug(s)[b]	Variants and relative directionality of effect on efficacy among Blacks[c]
Li 2018[50]	Pooled trials	219/587	Sz; L	↑ (*STXBP5L* variants);↓Eff (*CTNNA2* SNP)
Li 2018[51]	Pooled trials	195/429	Sz; L	= (multiple genes and SNPs)
Hwang 2012, 2011, 2010, 2007, 2006, 2005[42–47]	Pooled studies	98/426	Sz; C,O,R,H	↓ (120-bp repeat and $(G)_n$ repeat, *DRD4*); θ (48-bp repeat, *DRD4*; *DRD1* haplotype); ↑ (*DRD1* genotype and haplotype; SNPs and haplotypes, *DRD2*)
Fijal 2009[48]	RCT, post hoc	78/153	Sz,Sa; R	↑ PANSS negative symptom change (*COMT* SNP); = PANSS total score change (*GRM3* SNP); θ PANSS positive symptom change (*GRM3* SNP)
Zuo 2009[41]	RCT	54/181	Sz; H,C	θ (*DTNBP1* haplotype, diplotype); ↑ (clozapine; *DTNBP1* SNP); ↑ (haloperidol; *DTNBP1* SNP)
Campbell 2008[49]	RCT, post hoc	198/678	Sz;P,Z,O,R,Q	↑ (*RGS4* SNP)
Muller 2005[40]	Pooled cohorts	57/145	Sz; C,H,O,R	θ (*GNB3* SNP)

Key: ↑ increased efficacy; ↓ decreased efficacy; =equal efficacy; θ genetic effect on efficacy found in another group not found among Blacks; bp, base pair; PANSS, Positive and Negative Syndrome Scale; RCT, randomized controlled trial; SNP, single nucleotide polymorphism.
a. Sa, schizoaffective disorder; Sz, schizophrenia.
b. A, aripiprazole; C, clozapine; H, haloperidol; L, lurasidone; O, olanzapine; P, perphenazine; Q, quetiapine; R, risperidone; Z, zuprasidone.
c. Compared with other racial and/or ethnic groups.

Blacks and Whites.[8] One study found significantly increased weight gain/appetite among Latin Americans carrying the p.Glu308Gly (rs2266780) *FMO3* variant, not observed among Blacks or other subgroups;[54] this variant is more common among Latin Americans as compared with Blacks.[8]

One study found significantly increased risk of weight gain in association with a *DRD3* allele[13] among Black participants with no significant effect in Whites; the *DRD3* allele is also almost two times more prevalent among Blacks. Intriguingly, one study found opposite directionality of effect on weight gain for a variant in *CCKBR*, identifying increased risk of weight gain with this allele in Blacks but decreased risk of weight gain among Whites[55]; the risk allele is also >20% less prevalent among Blacks as compared with Whites.[8] This same dataset did not find any effect of *INSIG2* alleles in either group.[56]

Of the three articles exploring multiple antipsychotic agents and potential genetic modifiers of risk of antipsychotic-induced movement disorders, one study failed to find

Table 4. Atypical antipsychotic studies: genetic associations with safety outcomes

Author, year	Design	Black/Total N	Condition(s)[a] Drug(s)[b]	Outcome type and relative directionality of effect among Blacks[c]
Greenbaum 2012[57]	Cross-sectional	111/178	Sz; R,O,C	=movement disorders (*ZFPM2* SNP)
Muller 2012[13]	Pooled studies	58/186	Sz,Sa; C,O,R,H	=weight gain (*DRD2* SNP); θ different variants affecting weight gain in Blacks and Whites (*DRD2* and *DRD3* SNPs)
Tiwari 2010[55]	RCT	57/217	Sz; C,O	↓metabolic dysfunction (*CCKBR* SNP)
Tiwari 2010[56]	RCT	54/154	Sz, C,O	=metabolic dysfunction (*INSIG2* SNP)
Greenbaum 2009[58]	Cross-sectional	115/184	Sz; R,O,C	=movement disorders (*RGS2* SNPs)
Sickert 2009[53]	Pooled studies	54/129	Sz; C,O,R,H	θ metabolic dysfunction (*ADRA2A* SNP)
Cashman 2008[54]	Pooled cohorts	240/844	Sz; O	θ metabolic changes; drowsiness (*FMO3* SNPs)
Grossman 2008[52]	RCT, post hoc	211/708	Sz; O,Q,R,Z,P	↓discontinuation due to ADR (*FMO3* SNPs)

Key: ↑ increased safety; ↓ decreased safety; = similar safety among groups; θ genetic effect on safety found in another group not found among Blacks; RCT randomized controlled trial; SNP single nucleotide variant.
a. Sz, schizophrenia.
b. C, clozapine; H, haloperidol; O, olanzapine; P, perphenazine; Q, quetiapine; R, risperidone; Z, zurasidone.
c. Compared with other racial and/or ethnic groups.

significant associations in either Blacks or Whites, including *CYP2D6* or *CYP1A2**1F effects on risk of tardive dyskinesia.[52] Two studies focused on antipsychotic-induced parkinsonism (AIP) and found both an AIP susceptibility allele (G allele of intronic variant g.105503826C>G (rs12678719) in *ZFPM2*) and a protective allele (G allele of g.192812042C>G (rs4606) in the 3' untranslated region of *RGS2*); both variants had significant effects in both the Black subgroup and the overall cohort,[57,58] with one being similar prevalence between Blacks and Whites and one >2 times more prevalent among Blacks.[8]

One study assessed the potential contribution of *FMO3* variants to risk of drowsiness during olanzapine therapy; p.Val257Met was associated with risk in the Latin American subgroup (P=.042) but not among Blacks, Whites, or Asians.[54]

Discussion

This quasi-systematic review mined the literature to assess potential disparities in efficacy- and safety-related characteristics in Blacks compared with other racial or ethnic groups in response to use of atypical antipsychotic agents. We found notable differences in efficacy and safety outcomes between Blacks and other groups for this type of agent. In addition to variability in treatment response, our review detected signals related to increased risk of safety issues in Blacks, such as metabolic issues including weight gain and treatment-associated diabetes, and movement-related adverse effects. While increased risks of these side effects with use of an atypical antipsychotic agent are generally well-known and also acknowledged to be relevant issues in the care of Black patients, disparately increased risks in this subgroup do not appear to be prominently noted in the biomedical literature and may have important clinical implications.

Qualitative analysis of the data also indicates increased risk of neutropenia in Blacks as compared with Whites; given that 25%-50% of Blacks are affected by benign ethnic neutropenia (BEN) and mandatory clozapine monitoring includes specific reference ranges and requirements for this group,[59] baseline and periodic laboratory testing may present a particularly key component of safety monitoring in Blacks using an atypical antipsychotic. However, a 2016 systematic review of patients with BEN treated with clozapine indicated no signs of impaired phagocytosis and infection parameters (frequency, severity, outcome) similar to those without BEN; these authors suggested that a neutrophil count >1,000/mm^3 is safe for initiation or resumption of clozapine therapy.[60] Awareness of these issues can inform clinicians' approach to monitoring and concomitant interventions in Blacks taking atypical antipsychotics.

…our review detected signals related to increased risk of safety issues in Blacks, such as metabolic issues including weight gain and treatment-associated diabetes, and movement-related adverse effects.

Pharmacogenomics analyses illuminated potential genetic contributors to the effects noted above; for example, the same allele associated with decreased risk of weight gain in Whites was associated with increased weight gain among Blacks using antipsychotic therapy.[55] Investigators note that this finding may represent a "flip flop" phenomenon, potentially caused by altered linkage disequilibrium between the causal locus and the variants analyzed or underlying variation in frequency of the causal locus in the two populations.[55] Further, in two additional studies, the variants associated with increased efficacy among Blacks and Whites differed, with unique variants in each group, suggesting that different polymorphisms contributing to efficacy in these groups.[40,48] While potentially an issue of underpowered samples, a number of variants with significant effects among Whites failed to exhibit significant effects among Blacks.

We also observed notable variability in the underlying population frequency of alleles with significant effects among included studies. Blacks' exposure to some significant alleles, as measured by MAF reported in gnomAD,[8] is higher by an absolute 10% or more as compared with Whites, while Blacks' exposure to other re-

sponse alleles is lower by 10% or more. This underlying variability in allele carriage was observed in both treatment response- and adverse effect- associated variants. These observations strongly suggest that future pharmacogenomics studies and strategies will need to be intentionally diverse as well as explicitly incorporate consideration of race and ethnicity, rather than simply extrapolating results from Whites to other subgroups.

Study Limitations

Several limitations apply to this pilot review. Included articles exploring racial disparities in safety and efficacy of atypical antipsychotics, as well as genetic modifiers, are affected by relatively low sample sizes especially within subgroups, suggesting that their power to detect the full spectrum of predictors of efficacy and safety among Blacks is somewhat limited. Our search focused on studies analyzing the efficacy or safety of atypical antipsychotics by race and ethnicity; though we identified a number of RCT analyses, there may be additional subgroup analyses in the larger atypical antipsychotic literature that our search and review approach did not capture. As this was a quasi-systematic review, the current approach did not incorporate some systematic review steps that may help mitigate bias, such as risk of bias scoring. Also of note, a significant subset of the studies analyzing atypical antipsychotic effects included multiple reuse and recombination of the same datasets, with unknown impact on risk of false positive signals in the associated analyses. Heterogeneity of atypical antipsychotic agents considered among various studies also precluded quantitative analysis of results beyond the pooled analyses included in this review; additionally, many articles did not detail their approach for defining the Black subgroup of participants, introducing the possibility of further variability that is difficult to estimate. The limited amount of pediatric data also precludes substantive conclusions regarding implications for care of children and adolescents. Further, while analyses of the effects of SNPs and, to a lesser extent haplotypes, seem to predominate in this literature, other related signals such as protein-protein interactions and epigenetics may also hold great promise as the literature evolves. Finally, though this review focused on response disparities among Blacks, we note incidental findings of variability in treatment response and adverse effect among Hispanic and Latino patients reported in some studies, suggesting that additional systematic assessment would be valuable in supporting tailoring of atypical antipsychotic therapy in this subgroup as well.

Conclusions

This review demonstrates an approach for synthesizing existing data to illuminate differential treatment efficacy and safety signals among Blacks as compared with other subgroups. The current analysis can help inform clinician tailoring of patient education and monitoring among Blacks using an atypical antipsychotic agent, including framing a plan for surveillance for neutropenia and potential metabolic issues.

Given the variability in allelic, genotypic, and haplotype-associated effects observed in studies evaluating the effects of this potential modifiers on safety and efficacy of the atypical antipsychotics, this literature further suggests that any pharmacogenetics-based strategies for tailoring selection of a therapeutic will need to explicitly incorporate consideration of race and ethnicity, as different variation characteristics appear to influence treatment efficacy and safety in Blacks as compared with other groups. The wide differences observed in minor allele frequency for some variants, further suggest that the need for development and validation of pharmacogenetic strategies informed by race and ethnicity will be an essential component of future strategies to ensure safety and efficacy of atypical antipsychotic therapy in individual patients.

Future research into hypotheses informed by the signals identified in this review will allow us to better understand biologic underpinnings of variable safety and efficacy of antipsychotics among Blacks, including the import of these effects within each individual's treatment plan. Such approaches, when applied to appropriately powered datasets, will allow us to continue to advance the ability of precision medicine to truly be applied clinically across the rich diversity of our patient population.

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Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Jerome, Pulley, Sathe, Dickerson, Worley, Wilkins; Acquisition of data: Jerome, Pulley, Sathe, Krishnaswami, Dickerson, Worley, Wilkins; Data analysis and interpretation: Jerome, Pulley, Sathe, Krishnaswami, Dickerson, Worley, Wilkins; Manuscript draft: Jerome, Pulley, Sathe, Dickerson, Worley, Wilkins; Acquisition of funding: Jerome, Pulley, Sathe, Worley, Wilkins; Administrative: Jerome, Pulley, Sathe, Krishnaswami, Dickerson, Worley, Wilkins; Supervision: Jerome, Pulley, Sathe, Worley, Wilkins

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