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ORIGINAL REPORT

Persistence of racial disparities in prescription of first-generation antipsychotics in the USA

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ABSTRACT

Purpose The aim of this study was to estimate the prevalence of first-generation antipsychotics (FGA) prescribed for treatment of psychiatric and neurological conditions and use of benztropine to reduce extrapyramidal side effects (EPS) by patient race/ethnicity in a nationally representative sample of adult outpatient visits.

Methods The study sample included all outpatient visits ($N = 8154$) among patients aged 18–69 years where a prescription for one or more antipsychotics was recorded across 6 years of the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey (2005–2010). Use of FGA was compared by race/ethnicity using multiple logistic regression models accounting for patient and clinical characteristics stratified by neighborhood poverty rate. Frequency of EPS was determined by use of benztropine to reduce or prevent EPS.

Results Black patients were significantly more likely than White patients to use FGA (odds ratio = 1.48, $p = 0.040$) accounting for psychiatric and neurological diagnoses, treatment setting, metabolic factors, neighborhood poverty, and payer source. Black patients were more than twice as likely as White patients to receive higher-potency FGA (haloperidol or fluphenazine), particularly in higher-poverty areas (odds ratio = 2.50, $p < 0.001$). Use of FGA, higher among Black than White patients, was positively associated with use of benztropine to reduce EPS.

Conclusions Racial disparities in the pharmacological treatment of severe mental disorders persist 30 years after the introduction of second-generation antipsychotics. The relatively high frequency of FGA of use among Black patients compared with White patients despite more Food and Drug Administration-approved indications and lower EPS risk for second-generation antipsychotics requires additional research. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—antipsychotics; racial disparities; prescribing patterns; pharmacoepidemiology

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INTRODUCTION

In the USA, Black patients are less likely than White patients to receive adequate treatment for severe mental health disorders across several measures including access to care, expenditures following initiation of treatment, and multiple quality indicators.[1–3] Among those receiving care, previous studies have reported racial disparities in the use of antipsychotics, with consistent evidence of higher rates of prescribing older first-generation antipsychotics (FGA) among Black patients compared with White patients.[4–9] There is some evidence that racial disparities in prescribing FGA may be more pronounced in community-based settings than in hospital settings.[10] Persistence of racial disparities in use of FGA 30 years after the introduction of second-generation antipsychotics (SGA) needs to be viewed in the context of current efficacy and side-effect data for these two classes of antipsychotic medication.[11–13] The newer SGA (e.g., aripiprazole, olanzapine, and quetiapine) have a broader array of Food and Drug Administration (FDA)-approved indications, including use in treatment of depression, mania, and irritability due to autism. However, these newer SGA medications generally have a greater propensity to cause metabolic side effects, including risk

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of new-onset diabetes.[14] FGA prescribing does not indicate inappropriate care, especially for those with higher metabolic side-effect risk, but has greater risk of extrapyramidal symptoms (EPS) than SGA. Among SGAs, preferential use of medications with higher risk of metabolic side effects (i.e., olanzapine or risperidone versus aripiprazole or ziprasidone) can also cause disparities in health outcomes such as diabetes or metabolic syndrome. We sought to determine if racial differences persist in prescription of FGA using a nationally representative sample of outpatient visits despite expiration of most patents for SGA and more favorable neurological side-effect profiles than FGA.

Side effects of antipsychotics include involuntary tremor or Parkinsonism, with the highest risk of EPS associated with FGA.[15] FGA has also been associated with long-term health risks including increased overall mortality,[16–18] hip fractures,[19] and falls[19] independent of physical and psychiatric comorbidities. Pneumonia,[20,21] metabolic disorders,[22] cardiovascular disease,[23,24] and heart attacks[25,26] have also been associated with long-term use of antipsychotics, although results across classes have been mixed, with metabolic side effects most common among SGA.[14] The SGA emerged in the 1980s, first with clozapine, with the promise of equal or improved efficacy, decreased EPS, and better adherence.[27,28] A series of additional SGA were approved over the following three decades, generally with evidence of equal effectiveness and lower rates of EPS than FGA.[29–32] Use of clozapine is now rare, used primarily for treatment-resistant psychosis and to reduce suicide risk,[33] requiring the most extensive monitoring due to potentially fatal side effects.[34]

Antipsychotics are most often indicated for schizophrenia and the acute manic phase of bipolar disorder, but "off-label" uses include obsessive-compulsive and refractory depression, with some SGA approved for major depressive disorder beginning with aripiprazole in late 2007.[35] Off-label use of SGA has increased for the treatment of agitation in Alzheimer's disease, Parkinson's disease, and childhood-onset development disorders.[36–39] The use of clozapine, the first SGA, may be contraindicated based on low white blood cell counts, requiring routine blood monitoring, a problem more common among Black patients.[40] Although SGA are better tolerated, on average, than their FGA counterparts in terms of EPS, the SGA have been associated with weight gain, postural hypotension, sedation, diabetes, and more frequent sexual side effects than FGA.[41–44] More recently, use of SGA has been associated with increased mortality among dementia patients resulting in a black box FDA warning.[45]

The selective marketing of FGA by pharmaceutical companies to treat Black men in the 1970s, particularly haloperidol, has been previously documented.[46] There is evidence of greater use of FGA among Black men persisting at least into the early 2000s.[47–49] Previous studies have found that Black patients are also more likely than White patients to receive long-acting injections,[50] which may involve higher doses and worse EPS but benefits in terms of treatment adherence.[51]

This study sought to determine if racial disparities in prescribing FGA persisted into the period of 2005–2010, controlling for diagnoses, payer source, income level, and other potential confounders. The primary hypothesis was that Black patients continue to disproportionately receive FGA regardless of psychiatric diagnosis, comorbidities, metabolic factors, treatment setting, and payer source. We then determined if use of FGA was associated with increased EPS among Black patients compared with White patients based on use of benzotropine. A secondary hypothesis was that a racial difference in use of FGA would be more prominent in low-income settings.

METHODS

Subjects

The study sample consists of all patients ages 18–69 years receiving any antipsychotic medication across 6 years (2005–2010) of the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from a combined pool of 246 616 total patient visits to primary care, mental health, and hospital outpatient facilities. The NAMCS is a national, multistage probability sample of patient visits at physician practices including psychiatric outpatient visits within 112 primary sampling units.[52] The NHAMCS is a national probability sample of ambulatory visits made to non-federal, general, and short-stay hospitals in the USA conducted by the Centers for Disease Control and Prevention and National Center for Health Statistics (NCHS).[53] The survey has been conducted annually since 1992. The basic sampling unit is the physician–patient encounter or visit. Telephone visits, house calls, and visits made in non-office hospital settings or institutions (e.g., nursing homes) and non-medical administrative visits were excluded. Designated staff or field representatives completed a patient record form for each sampled visit based on information obtained from the medical record. Data collected included patient demographics, reasons for visit, diagnoses, chronic conditions, medications, provider type, and disposition including hospitalization. A pooled sample of 6 years was required to

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achieve a sufficient sample size ($n \sim 8000$) to detect modest differences (>2%) in use of FGA between Black and White patients taking into account survey design effects and an estimated overall FGA prevalence of 10–15%.

Measures

Diagnoses of psychiatric and neurological conditions, up to three recorded per visit, were determined based on ICD-9-CM three-digit codes including specific psychoses (schizophrenia, bipolar disorder, and organic psychoses), depression, anxiety disorders, personality disorders, neurodegenerative disorders, hyperkinetic or conduct disorders, alcohol dependence, drug dependence or abuse, and other non-psychotic psychiatric disorders. Reasons for each patient visit were categorized as being primarily related to mental health, neurological symptoms, or physical health. Visits involving psychiatric care, mental health counseling, or care provided by a mental health provider were also determined. Metabolic factors including hypertension, obesity, diabetes, and dyslipidemia were also recorded for each patient.

Drug characteristics were assigned using Multum's Lexicon Drug Database (2006–2010) and the FDA's National Drug Code Directory (2005). FGA included brand-named and generic equivalents of chlorpromazine, haloperidol, fluphenazine, loxapine, mesoridazine, methotrimeprazine, molindone, perphenazine, thioridazine, thiothixene, and trifluoperazine, while SGA included aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Haloperidol and fluphenazine were further categorized as higher-potency FGA. Concurrent use of benztropine, used to offset drug-induced EPS, was determined to estimate the burden of EPS.

Hospitalization, treatment at a hospital outpatient versus community setting, total medications, and use of multiple antipsychotics were used as proxies of psychiatric severity. The use of multiple antipsychotic prescriptions simultaneously, while relatively rare and controversial for treating psychoses,[54,55] is associated with symptom severity and treatment resistance in schizophrenia.[46] Race, sex, and age were based on clinician reports. Neighborhood poverty level was determined by patient zip code linked to US census data. Payer source was based on the expected source of payment, with multiple sources of payment allowed.

Statistical analysis

Data were analyzed using the sampled visit weight adjusted by NCHS for survey non-response. Because of the complex sample design, sampling errors were estimated using Stata 11.0. Bivariate associations between specific diagnoses and use of FGA were assessed using chi-square tests. Adjusted Wald tests were used to test crude overall differences in proportions of patients receiving specific antipsychotic medications, comparing non-Hispanic Black (hereafter, Black) patients with non-Hispanic White (hereafter, White) patients. Multiple logistic regression models were used to predict prescription of a FGA adjusted for patient diagnoses, primary reason for visit, provider type, setting, neighborhood poverty rate, payer source, proxies for severity, metabolic factors, age, and sex. Parallel multiple logistic regression models were used to assess racial differences in use of benztropine. To test for differences by neighborhood poverty level, stratified models were compared at both above and below 10% poverty.

RESULTS

Of 246 616 unique outpatient visits in the combined NHAMCS/NAMCS dataset among adults aged 18–69 years, a total of 8194 or 2.1% (1.9–2.2) involved a patient currently or newly prescribed with an antipsychotic medication. The distributions of demographic characterteristics among those receiving antipsychotic medications are shown in Table 1. Among patients

Table 1. Demographic characteristics of patients using any antipsychotic medication at the time of office visit ($N = 8197$), National Hospital Ambulatory Medical Care Survey and National Ambulatory Medical Care Survey (2005–2011)

	N (unweighted)	% (weighted)
Race		
White	5423	76.0
Black	1768	14.4
Hispanic	648	6.0
Other	355	3.6
Sex		
Female	4609	59.7
Male	3585	40.3
Visit location		
Large metro, city	2615	29.2
Large metro, suburb	1701	21.5
Medium-sized metro	1158	23.0
Small metro	404	6.7
Rural/non-metro	787	16.4
Other/missing	195	3.2
Neighborhood poverty rate		
<5%	966	15.9
5 to <10%	1748	27.9
10 to <20%	2150	33.0
> = 20%	1704	17.8
Missing/unknown	292	4.4

Basic demographics of patients using or newly receiving an antipsychotic medication among all patient visits in the pooled National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Surveys 2005–2010.

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prescribed with any antipsychotic, 10.6% (9.1–12.0) were prescribed with FGA, while 92.4% (91.2–93.6) were prescribed with SGA. A small proportion of patients were prescribed with both FGA and SGA (3.0% [2.3–3.8]), while 10.5% (9.2–12.0) received multiple antipsychotics. Most prescriptions for antipsychotics were continuing (90.8% [89.4–92.2]) as opposed to newly prescribed, with no differences between FGA (92.1% [88.3–95.8]) and SGA (90.8% [89.3–92.3]) overall. However, 16.0% (5.7–26.4) of prescriptions for FGA were newly prescribed among Black patients compared with 7.2% (3.3–11.0) among White patients with no differences by race in the proportions of newly prescribed SGA (8.7% vs 9.5%).

The most common psychiatric and neurological diagnoses among patients receiving antipsychotic medications are shown in Table 2. Schizophrenia, bipolar disorder, and other psychotic disorders were all positively associated with use of FGA, while a childhood-onset developmental disorder, hyperkinetic or conduct disorder, and neurodegenerative or other central nervous system disorder were negatively associated with use of FGA. Black patients prescribed with an antipsychotic (27.8% [22.5–33.1%]) were significantly more likely than White patients (12.6%, 95%CI [10.9–14.3]) to have a current diagnosis of schizophrenia ($F[1, 2427] = 31.20$, $p < 0.001$). By contrast, over a quarter of White patients (26.4% [24.1–28.7]) prescribed with an antipsychotic medication were diagnosed with bipolar disorder compared with 15% (9.9–20.0) of Black patients ($F[1, 2427] = 16.7$, $p < 0.001$).

Among patients receiving any antipsychotic drug (Table 3), Black patients (14.6% [10.9–18.3%]) were disproportionately represented among those prescribed with FGA compared with White (9.3% [7.8–10.7%]) patients. These racial differences were most pronounced for the haloperidol–fluphenazine (HAL-FLU) group of higher-potency FGA antipsychotics, with Black patients (9.8%) more than twice as likely to receive HAL-FLU compared with White patients (4.2%) (crude odds ratio (OR) = 2.6 [1.83–3.69], $p < 0.001$). Use of HAL-FLU among those prescribed with antipsychotics was particularly elevated among Black patients in higher-poverty areas (crude OR = 3.3 [2.04–5.23], $p < 0.001$). After accounting for all other factors in multiple logistic regression models, these racial differences in HAL-FLU prescribing remained statistically significant overall (adjusted OR = 1.65 [1.15–2.37], $p = 0.003$) and in higher-poverty areas (adjusted OR = 2.38 [1.42–4.00], $p = 0.001$).

Overall, Black patients were more than twice as likely as White patients (crude OR = 1.97 [1.41–2.72], $p < 0.001$) to be prescribed with an FGA. This higher use of FGA among Black patients was only partially attenuated (adjusted OR = 1.48 [1.02–2.15], $p = 0.040$) by differences in psychiatric diagnosis and neurological comorbidities, setting factors, proxies for severity

Table 2. Prevalence of psychiatric and neurological disorders among all adult patients prescribed with an antipsychotic medication, by race/ethnicity and total ($N = 8194$)

Diagnoses (ICD-9-CM codes)	White ($n = 5423$)	Black ($n = 1768$)	Total ($N = 8194$)
	% (95%CI)	% (95%CI)	% (95%CI)
Bipolar disorder (296.0–296.99 exc. 296.2–296.36)	26.4 (24.1–28.7)	15.4*** (9.9–20.9)	23.9 (21.6–26.2)
Schizophrenia (295.0–295.95)	13.1 (11.4–14.8)	28.5*** (23.1–33.9)	15.5 (13.5–17.4)
Anxiety disorders (300.0–300.9)	14.5 (12.4–16.7)	6.5*** (3.7–9.4)	13.4 (11.3–15.5)
Major depression[a] (296.2–296.36)	11.3 (9.9–12.7)	9.9 (6.5–13.2)	11.5 (10.0–12.9)
Other depressive disorder[b] (311)	7.1 (5.6–8.6)	7.9 (3.9–11.8)	7.6 (6.2–8.9)
Drug dependence/substance abuse (304–305.93)	5.1 (3.7–6.6)	6.7 (3.8–9.5)	5.5 (4.1–6.9)
Hyperkinetic/conduct disorder (312–312.9, 314–314.9)	4.2 (3.1–5.2)	2.2* (0.6–3.7)	3.5 (2.7–4.4)
Other non-organic psychosis (298.0–298.9)	2.2 (1.3–3.1)	2.2 (0.6–3.8)	2.3 (1.6–3.0)
Personality disorder (301–301.9)	3.3 (2.4–4.2)	0.9*** (0.1–1.9)	2.8 (2.1–3.4)
Intellectual/developmental disorder[c] (299.0–299.91,315.0–319)	2.2 (1.4–3.0)	1.6 (0.7–2.4)	2.0 (1.4–2.7)
Alcohol dependence (303–309.3)	1.6 (1.1–2.2)	1.4 (0.6–2.2)	1.5 (1.0–2.0)
Organic psychosis (290.0–290.9)	1.1 (0.7–1.6)	0.8 (0.3–1.5)	1.1 (0.7–1.5)
Neurodegenerative disorders (331.0–333.9)	0.8 (0.4–1.3)	1.0 (0.0–2.4)	0.8 (0.4–1.2)
Other psychiatric disorders (306.0–310.9, 313.0–313.9, 315.0–316.9)	5.6 (4.6–6.7)	2.6** (1.3–3.9)	5.1 (4.2–6.0)
Other central nervous system disorder (340–349.9)	2.6 (1.7–3.4)	1.6 (0.7–2.6)	2.4 (1.6–3.1)

Prevalence of specific psychiatric and neurological disorders based on ICD-9-CM among patients receiving an antipsychotic medication in the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey 2005–2010 with adjusted Wald tests of differences in proportions comparing Black with White patients.

[a]Includes only diagnosed depression and not depressive symptoms noted at visit.

[b]Includes childhood-onset developmental disorders including autism spectrum disorders and mild to severe intellectual disabilities.

[c]Includes adult-onset neurodegenerative disorders including Alzheimer's disease and Parkinson's disease.

*$p < 0.05$.

**$p < 0.01$,

***$p < 0.001$.

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Table 3. Antipsychotic prescriptions by generic name among patients currently or newly prescribed with any antipsychotic medication, by race/ethnicity ($N = 8194$)

Antipsychotic	White patients ($n = 5243$)		Black patients ($n = 1768$)		Total[a] ($n = 8194$)	
	%	95%CI	%	95%CI	%	95%CI
First generation (FGA)						
Haloperidol	2.7	(2.0–3.5)	5.7	(3.2–8.1)*	3.2	(2.4–4.0)
Fluphenazine	1.5	(0.9–2.1)	4.4	(2.6–6.3)**	1.9	(1.3–2.5)
Chlorpromazine	1.5	(0.9–2.1)	1.8	(0.1–3.5)	1.4	(0.9–1.9)
Perphenazine	1.4	(0.7–1.9)	1.0	(0.1–1.9)	1.3	(0.8–1.8)
Others (8)	2.2	(1.5–2.9)	1.8	(0.6–3.1)	2.0	(1.5–2.6)
FGA, total	9.3	(7.8–10.7)	14.6	(10.9–18.3)**	9.8	(8.5–11.1)
Second generation (SGA)						
Quetiapine	34.6	(32.3–36.8)	30.2	(25.6–34.7)	34.5	(32.3–36.7)
Risperidone	21.8	(19.8–23.7)	26.8	(22.2–31.5) *	22.5	(20.7–24.3)
Olanzapine	14.7	(12.9–16.5)	16.8	(13.8–19.8)	14.9	(13.4–16.5)
Aripiprazole	19.0	(16.9–21.0)	14.5	(10.7–18.4) *	18.2	(16.3–20.0)
Ziprasidone	6.7	(5.5–8.0)	8.1	(5.1–11.1)	6.9	(5.8–8.1)
Clozapine	3.0	(2.1–4.0)	0.6	(0.2–1.0) ***	1.2	(0.2–2.2)
SGA, total	92.8	(91.5–94.3)	90.0	(87.0–93.0)	92.6	(91.5–93.7)
Both FGA and SGA	2.1	(1.5–2.6)	4.6	(2.5–6.8) **	2.4	(1.8–3.1)

Proportion of patients receiving specific antipsychotic medications in the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey 2005–2010 by race/ethnicity with adjusted Wald tests of differences in proportions comparing Black patients with White patients.
[a]Total includes Hispanic ($n = 648$) and other race/ethnicity ($n = 355$).
[b]Percentages are weighted using sampling weight.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

(hospitalization and multiple antipsychotics), patient demographics, metabolic factors, neighborhood poverty, and payer source (Table 4). Conversely, Black patients were significantly less likely than White patients to receive SGA (results not shown) across all outpatient visits (crude OR = 0.56 [0.36–0.86], $p = 0.009$) although this difference in use of SGA was not statistically significant after adjustment for all other factors (adjusted OR = 0.67 [0.43–1.05], $p = 0.079$).

Clozapine was the least commonly prescribed SGA, with Black patients (0.6% [0.2–1.0%]) significantly less likely than White patients (2.9% [2.0–3.8%]) to receive clozapine. Quetiapine, the most prevalent of all antipsychotics with lowest rate of EPS, was still on a US patent during the study period, making it more expensive than other comparable medications, with non-significantly higher prevalence of prescribing among White patients. Use of aripiprazole, still on patent, was also significantly higher among White than Black patients. Risperidone and olanzapine, available as generics, were most commonly used among Black patients, those living in high-poverty neighborhoods and Medicaid users (not shown). Thus, even among those using SGA, Black patients disproportionately received older medications compared with White patients, including risperidone with worse EPS than other SGA. Use of multiple antipsychotics was no more common among Black patients than White patients.

Black patients (12.1%) prescribed with antipsychotics were more than twice as likely as White patients (5.5%) to have a concurrent prescription of benztropine for EPS side effects (crude OR = 2.35 [1.6–3.4], $p < 0.001$). This difference by race remained statistically significant after adjustment in multivariate models (adjusted OR = 1.68 [1.13–2.48], $p = 0.010$). Most of this difference was for FGA, with one-third of Black patients receiving an FGA also receiving benztropine (Table 5). By comparison, only 3.6% of Black patients receiving only SGA had concurrent use of benztropine. Among those prescribed with SGAs, higher use of benztropine was evident among patients prescribed with risperidone (8.7% [6.1–11.2], adjusted OR = 3.1 [2.0–4.8], $p < 0.001$), with significantly higher frequency of use of risperidone among Black than White patients.

DISCUSSION

This study found evidence of disproportionate use of FGA among Black patients compared with White patients three decades after the introduction of SGA with equal efficacy and lower extrapyramidal side effects. An increased burden of EPS in FGA compared with SGA, and disproportionate risk of EPS among Black patients, was indicated by increased use of benztropine prescriptions to counter drug-induced EPS. Black patients were also significantly more likely than White

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patients to have a diagnosis of schizophrenia, consistent with previous studies.[56,57] There was some evidence that racial disparities in prescribing FGA were more pronounced in low-income settings. Finally, within classes of therapeutics, Black patients on FGA were more likely to receive higher-potency antipsychotics than White patients, while those prescribed with SGA were more likely to receive generics with higher risk of EPS than White patients. There is no previous evidence that Black patients require higher doses than White patients in terms of treatment response.[58]

In addition to the cross-sectional study design, there are several limitations worth noting. Patients receiving

Table 4. Predictors of prescription of first-generation antipsychotics (FGA) among patients receiving any antipsychotic medications ($n = 8194$) based on multiple logistic regression

	Antipsychotic users ($N = 8194$)		
Patient and clinical factors	Odds ratio	(95%CI)	*p*-value
Patient demographics			
Race/ethnicity[a]			
Black	1.48	(1.02–2.15)	0.040
Hispanic	0.61	(0.23–1.62)	0.326
Other	1.11	(0.54–2.27)	0.876
Male	1.26	(0.93–1.69)	0.129
Age	1.02	(1.00–1.03)	0.010
Visit location[b]			
Large metro, city	0.88	(0.59–1.31)	0.518
Large metro, suburb	0.82	(0.50–1.36)	0.518
Medium metro	0.84	(0.51–1.38)	0.790
Small metro	0.55	(0.25–1.22)	0.142
Neighborhood poverty rate[c]			
5–9%	0.68	(0.39–1.18)	0.169
10–19%	0.91	(0.52–1.59)	0.748
> = 20%	0.94	(0.49–1.79)	0.847
Diagnoses[d]			
Schizophrenia	2.17	(1.51–3.14)	<0.001
Bipolar disorder	0.77	(0.47–1.26)	0.297
Organic psychosis	0.63	(0.18–2.18)	0.465
Other psychosis	1.69	(0.92–3.07)	0.089
Depression	0.48	(0.35–0.65)	<0.001
Anxiety	0.39	(0.21–0.71)	0.002
Personality disorder	1.14	(0.63–2.06)	0.668
Other psychiatric disorder	1.11	(0.60–2.04)	0.750
Neurodegenerative disorder	0.09	(0.02–0.35)	<0.001
Other central nervous system disorder	0.19	(0.08–0.46)	<0.001
Development disorder	1.40	(0.69–2.27)	0.356
Hyperkinetic/conduct	0.16	(0.06–0.46)	0.001
Alcohol dependence	0.97	(0.41–2.27)	0.945
Substance abuse	0.78	(0.48–1.27)	0.324
Metabolic factors[e]			
Obesity	0.97	(0.67–1.39)	0.847
Hypertension	1.40	(0.90–2.17)	0.136
Diabetes	1.29	(0.78–2.11)	0.316
Dyslipidemia	0.23	(0.09–5.75)	0.002
Severity			
Hospitalized	6.67	(3.54–12.6)	<0.001
Multiple antipsychotics[f]	3.90	(2.63–5.80)	<0.001
New prescription	1.04	(0.65–1.66)	0.865
Hospital outpatient[g]	0.91	(0.70–1.18)	0.477
Total medications	1.01	(0.92–1.10)	0.845
Primary complaint[h]			
Psychiatric	1.02	(0.77–1.36)	0.875
Neurological	1.71	(0.88–3.33)	0.115
Visit type[i]			
Psychiatric	0.88	(0.61–1.26)	0.875
Other mental health	0.78	(0.54–1.12)	0.115
Provider type[j]			
Mental health	1.01	(0.65–1.58)	0.939

(*Continues*)

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Table 4. (Continued)

Patient and clinical factors	Antipsychotic users ($N = 8194$)		
	Odds ratio	(95%CI)	p-value
Payment method[k]			
Medicare	1.15	(0.85–1.57)	0.381
Medicaid	0.97	(0.67–1.40)	0.856
Self-pay	1.29	(0.79–2.13)	0.313
No charge	0.86	(0.41–1.79)	0.681
Other	0.64	(0.35–1.19)	0.163

Multiple logistic regression models showing predictors of FGA prescriptions among those receiving any antipsychotic medication in the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) 2005–2010.
[a]Reference group is White patients.
[b]Reference setting is area outside an Metropolitan Statistical Area (MSA).
[c]Reference is <5% poverty.
[d]Diagnoses based on ICD-9-CM coding, up to three diagnoses per visit.
[e]Metabolic factors based on ICD-9-CM coding and/or additional chronic conditions recorded at each visit. For obesity, body mass index > 30 and/or obesity recorded as chronic condition.
[f]Includes multiple FGA, multiple second-generation antipsychotics (SGA), or FGA + SGA.
[g]Setting type based on survey used (NHAMCS or NAMCS) with NAMCS visits as reference group.
[h]Based on primary reason for visit as recorded at time of office visit, with non-psychiatric or non-neurological as the reference category.
[i]Visit types recorded on the original survey as involving psychiatric services or other mental counseling with all other visits as reference group.
[j]Indicator variable that a mental health professional was seen during the office visit regardless of visit-type designation.
[k]Expected sources of payment as indicated on original survey. Multiple types of visits were possible, with private insurance as the reference group.

Table 5. Estimated burden of extrapyramidal side effects based on use of benztropine, by race and antipsychotic medication ($N = 8194$)

	White ($n = 5432$)		Black ($n = 1768$)		Total ($N = 8194$)	
Prescription for benztropine % (95%CI)						
Antipsychotic medication						
FGA[a]	23.2	(17.3–29.1)	33.3	(21.5–44.7)	25.2	(20.1–30.3)
Haloperidol–fluphenazine	36.6	(26.5–46.7)	43.6	(30.5–56.6)	37.8	(30.7–44.8)
Other FGA[b]	9.2	(4.1–14.2)	10.5	(0.1–20.8)	9.2	(5.0–13.3)
SGA (only)[c]	3.6	(2.7–4.5)	7.7	(4.2–11.1)*	4.3	(3.3–5.2)
Risperidone	8.2	(5.5–11.1)	11.3	(3.6–19.1)	8.7	(6.1–11.2)
Quetiapine	1.4	(0.5–2.1)	6.9	(1.3–12.4)	2.2	(1.1–3.3)
Olanzapine	2.9	(1.2–4.6)	7.9	(1.8–14.0)	3.9	(1.9–5.8)
Aripiprazole	4.6	(1.9–7.2)	4.8	(0.1–10.2)	4.6	(2.3–6.8)
Other SGA[d]	4.6	(1.9–7.4)	9.2	(1.5–16.9)	5.3	(2.8–7.7)
Multiple SGA	4.9	(2.1–7.7)	15.8	(5.9–25.7) *	6.3	(3.4–9.2)
Totals	5.5	(4.5–6.5)	12.1	(8.4–15.7)***	6.5	(5.3–7.6)

SGA, second-generation antipsychotics; FGA, first-generation antipsychotics.
Concurrent prescription of benztropine, used to reduce extrapyramidal symptoms side effects, among patients receiving specific antipsychotic medications comparing Black with White patients in the combined National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey 2005–2010. Tests of association based on adjusted Wald tests comparing Black with White patients.
[a]Includes prescription of multiple antipsychotics including an SGA.
[b]Includes chlorpromazine and perphenazine.
[c]Excludes concurrent prescription of an FGA.
[d]Includes ziprasidone and clozapine.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

antipsychotic medications represented both prevalent and incident cases, making it difficult to determine the progression of prescriptions following diagnosis. Although the study used several proxies for severity including hospitalization and use of multiple antipsychotics, there was no direct measure of severity or adherence across psychiatric disorders that may account for systematic treatment differences. Only three diagnoses were recorded at each visit, limiting the ability to fully account for all psychiatric comorbidities. Further, the study was not sufficiently powered to use five-digit ICD-9-CM diagnoses and relied on broader three-digit ICD-9-CM categories. Patients receiving regular care were likely over-represented in the study relative to those who have only sporadic contact with healthcare providers. Further, patients who received care in institutional settings or among non-traditional providers were excluded. Because the

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primary focus was on persistence of disparities between Black and White patients, the study was not sufficiently powered to address potential disparities among other race/ethnicity groups. Although this study accounted for neighborhood poverty and payer source, there was not a direct measure of individual-level socioeconomic status.

Regardless of any systematic diagnostic or prescribing bias,[59,60] the higher costs of SGA would have continued to favor the use of FGA and generics over SGA and brand-named drugs in higher-poverty settings, which were also disproportionately Black patients. However, with patents for SGA expiring, this explanation for the persistence of racial disparities in prescribing of FGA becomes increasingly implausible. It was not possible to consider factors such as differential patient demand for brand-named versus generic drugs by race. In assessing use of benztropine for EPS, it was not possible to distinguish prophylactic uses from prescriptions based on the presence of symptoms, so greater use of benztropine may reflect prescribing guidelines related to risk of EPS rather than elevated EPS among Black patients.[61]

One factor that may contribute to the persistence of racial disparities in prescribing FGA was the 2004 American Diabetes Association (ADA)-American Psychiatric Association (APA) consensus statement on metabolic side effects and monitoring, with SGA having greater potential for metabolic side effects than FGA. Because Black patients have higher rates of obesity, diabetes, and hypertension than White patients,[62] these factors may influence prescribing in favor of FGA to avoid weight gain and metabolic problems. A related problem is that prescribers may perceive Black or lower-income patients as less likely to adhere to lab monitoring guidelines or are less aggressive in monitoring of Black patients.[63] Indeed, Black patients were less likely than White patients in the current study to receive clozapine, consistent with its relative difficulty of use, requiring ongoing blood monitoring. Given the small percentage of patients prescribed with clozapine overall, however, this difference cannot account for the observed differences in FGA versus SGA. The higher use of olanzapine and risperidone among Black patients compared with White patients is not consistent with greater concerns over metabolic monitoring for SGA, however, as these drugs have worse metabolic profiles than newer SGA. Although the study accounted for diabetes, hypertension, obesity, and dyslipidemia as a proxy for metabolic concerns, there may be residual confounding by perceived higher risk of metabolic complications among Black patients.

Also relevant to this time period were the emerging results of the National Institute of Mental Health-funded Clinical Antipsychotic Trials of Intervention Effectiveness study, which brought into question the overall superiority of SGA over FGA,[64,65] although this uncertainty regarding the benefits of SGA did not result in different prescribing of FGA.[66] The relatively high proportion of patients on FGA (25.2%) requiring use of benztropine for EPS would offset some of the cost savings of using older FGA or generic SGA antipsychotics. Cost-effectiveness studies, many originally favoring use of SGA over FGA, were also brought into question during this time period of 2005–2010.[67,68] Indeed, previous studies indicated that the gap between Black and White patients in use of SGA decreased steadily from the period of 1992–2000 as costs for SGA decreased, and studies indicated increased cost effectiveness of SGA.[69] However, gaps compared with White patients persisted for Black patients with psychotic disorders.[4] Another potential source of disparities is diagnostic bias leading to differences in prescribing SGA versus FGA, particularly differential diagnosis of bipolar disorder versus schizophrenia by race.[70,71]

Although significant disparities in use of FGA persist by race, the proportion of the total US patient population using an FGA was estimated at less than 10% for the study period. Although not a focus of this study, use of SGA over FGA was found among patients with central nervous system disorders and neurodegenerative disorders. The use of SGA for neurodegenerative disorders among elderly patients may lead to worse outcomes and premature death, with evidence of continued use despite a black box warning by the FDA.[72–74] Future research using the NAMCS/NHAMCS should monitor prescriptions of SGA among neurodegenerative disorders and other off-label uses as well as the persistence of racial differences in use of antipsychotics and adjunctive psychopharmacologic treatments to reduce EPS including sufficient samples to address potential treatment disparities among other racial/ethnic population groups. Longitudinal studies may also be useful in assessing possible differences in dosing and duration of treatment with specific agents among patients by race, including the timing of switching classes of antipsychotic drugs.[75] The differential diagnosis of schizophrenia and bipolar disorder by race and income level also requires additional research, both for understanding racial disparities in use of antipsychotics and overall therapeutic outcomes.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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KEY POINTS

- Non-Hispanic Black patients are prescribed with first-generation antipsychotics over second-generation antipsychotics nearly twice as often as non-Hispanic White patients.
- Regardless of psychiatric diagnosis, non-Hispanic Black patients are significantly more likely than non-Hispanic White patients to receive higher-potency first-generation antipsychotics.
- Prescribing differences by race were not accounted for by differences in income, payer source, provider setting, psychiatric diagnosis, metabolic factors, severity, or other measured factors.

ETHICS STATEMENT

The NHAMCS is approved annually by the Ethics Review Board of NCHS, with waivers to obtain informed consent and patient authorization for release of patient medical record data by healthcare providers. The current study used de-identified public use files and was exempted from full review by the Institutional Review Board of Mercyhurst University.

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