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Antipsychotic Use In a Diverse Population with Dementia: A Retrospective Review of the National Alzheimer's Coordinating Center (NACC) database

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Abstract

A cross-sectional analysis examined medication records to Alzheimer's Disease Centers from 2008 to 2014, in the community dwelling patients with dementia in the National Alzheimer's Coordinating Center Database. Hispanic participants had a 1.62-fold greater use of antipsychotic medications (95% CI 1.32–1.98), largely accounted for by a higher prevalence of neuropsychiatric symptoms and more severe dementia, compared to non-Hispanic Whites. Our results are consistent with reports of later transition to nursing home care among Hispanic participants. Further studies are needed to clarify ethnic differences on how families and physicians address dementia progression and neuropsychiatric symptoms in community dwelling patients with dementia.

Keywords

Alzheimer's dementia; antipsychotics; dementia behaviors; black-box warning; ethnic disparities

Introduction

The increased risk of death from antipsychotic medications among elderly patients with dementia has been extensively studied. The FDA issued a black box warning on atypical antipsychotics in April 2005 and expanded the warning to typical antipsychotics in June 2008.[1–4] Additionally, overreliance on antipsychotic medications in dementia care has been an area of heavy focus by consumer advocacy groups and Center for Medicare and Medicaid (CMS) due to concern about worsening quality-of-life, increased health care costs, in addition to increased mortality.[5] Nevertheless, inappropriate use and overuse of

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antipsychotics for dementia-related neuropsychiatric symptoms (NPS) in the elderly have persisted. In May 2012, CMS launched the "Partnership to Improve Dementia Care Initiative" in an attempt to reduce the overuse of antipsychotics in nursing home residents, calling for a 15% reduction in use of antipsychotics by the end of 2012 in skilled nursing facilities.[6]

Emerging research demonstrated that there are ethnic differences in use of FDA approved dementia medications. In a Medicare database, use of dementia medications was 30% higher among non-Hispanic Whites compared to other racial/ethnic groups.[7] However, there has been little or no examination of racial or ethnic differences in antipsychotic usage in elderly patients with dementia. Identifying ethnic differences in antipsychotic use could potentially lead to effective intervention programs (e.g. educational or pharmacy/psychiatric consultation programs) aimed at reduction of inappropriate antipsychotic use for dementia care. We examined patterns of antipsychotic use in African American, Hispanic, and non-Hispanic White patients with dementia, using existing data from the National Alzheimer's Coordinating Center (NACC) data. Our goals were 1) to characterize the prevalence of antipsychotic use in NACC study participants, overall and by race/ethnicity; 2) to assess whether antipsychotic use was primarily associated with presence, severity, and type of NPS, rather than with dementia severity, and 3) to assess whether differences in antipsychotic use across race/ethnic groups persisted after accounting for NPS, and other demographic and clinical variables.

Methods

Population and Participants

We conducted a retrospective review of prescription medication records for community dwelling NACC participants diagnosed with dementia. The study sample consists of African American, Hispanic, and non-Hispanic White participants diagnosed with dementia who visited an ADC between the years 2008 and 2014 and completed medication forms at visit. For our cross-sectional analyses, an index visit was determined by the participant's first record of prescription information starting in 2008. A total of 8,919 participants fit this description: African American (n = 983), Hispanic (n = 849), and Non-Hispanic White (n = 7087). The NACC database consists of data from 34 federally funded ADCs and is supported by the National Institute of Aging. Details about NACC consortium and its database have been previously described.[8,9] We also considered the subgroup of this population that was diagnosed with either probable or possible Alzheimer's disease (AD) related dementia (n=7,059). The racial breakdown of this subgroup was: African American (n = 872), Hispanic (n = 757), and non-Hispanic White (n = 5430).

Demographic information about participants included age at visit, gender, education level, and race/ethnicity. Clinical information included the diagnosis of dementia and whether it was probable or possible Alzheimer's disease; informant-reported neuropsychiatric symptoms measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q);[10,11] and a clinician assessment of dementia severity using the Clinical Dementia Rating (CDR).[12–14] The NPI-Q rates presence and severity of 12 specific neuropsychiatric symptoms (delusions, hallucinations, agitation or aggression, depression or dysphoria, anxiety, elation or euphoria,

apathy or indifference, disinhibition, irritability or lability, motor disturbance, nighttime behaviors, appetite and eating) for participants with Alzheimer's disease and other forms of dementia; for those with affirmative response each symptoms is further scored by severity (from 1–3), with sum of severity scores used as an overall rating of NPS. The (CDR) uses a five-point scale [0,0.5,1,2,3] for each of 6 cognitive domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care), based on physical examination and informant interview. A CDR score of 0 within a particular domain implies no cognitive impairment, while a score of 3 is indicative of severe impairment. The CDR sum of boxes ranges from a score of 0 to a score of 18.

Study Outcome

The primary outcome was use of antipsychotic drugs at the index visit, including miscellaneous antipsychotics, phenothiazine psychotics, thioxanthenes, and first generation and second generation antipsychotics, based on the informant-reported medication form of the Uniform Dataset 3.0 (revised in 2008). For a full list of medications included in this listing please see the NACC Derived Variables documentation.[15]

Statistical Analysis

Descriptive summaries of the study sample reported continuous variables as mean ± standard deviation (SD), and categorical as numbers and percentages. Initial univariate logistic regression examined the associations of both the primary and secondary predictors with use of antipsychotic drugs. The key hypothesized predictors were then assessed in a series of three multivariate logistic regression models, including potential demographic confounders. The first model assessed whether use of antipsychotic medications differed by race/ethnicity, taking account of key demographic variables: gender, age, and education. The second multivariate model added the NPI-Q sum of severity scores to assess the impact of NPS on use of antipsychotics and determine whether differences across race/ethnic groups might be accounted for by differences in NPS. In the third multivariate model, the CDR sum of boxes was added to the model to assess the impact of dementia severity. Secondary analyses repeated these analyses in the subgroup restricted to dementia associated with AD.

All reported p-values were those of two-sided tests; significance was defined as $p < 0.05$. All analyses were performed using SAS version 9.2 statistical software (SAS Institute Inc., Cary, NC, USA) and/or R version 3.1.1.

Results

Of the 8,919 participants diagnosed with dementia, 930 (10.4%) of them were reported to be taking one or more antipsychotic medications (Table 1a). Participants were predominantly white, with most having at least high school education, and approximately equal in numbers of males and females. Of the 7,059 participants diagnosed with AD related dementia, 625 (8.9%) were on antipsychotic medication.

Univariate Analysis

Table 1a provides unadjusted odd ratios for association with use of antipsychotic drugs for study participants with dementia. Unadjusted for age, education, gender, NPS and CDR, Hispanic participants were 62% more likely (OR=1.62, 95% CI (1.32, 1.98)) to be on antipsychotics when compared to non-Hispanic Whites, in the dementia population. The risk of antipsychotic use increased with increasing NPS severity (OR=1.12 for every one-point increase) and with increasing dementia severity (OR=1.21 for every one-point increase in CDR sum of boxes). Older participants were less likely to be on antipsychotics, with a 1% drop for every year of age (OR=0.99), and fewer years of formal education increased the odds of antipsychotic use, especially for those with less than high school education (OR=1.35).

Among participants with probable or possible AD, Hispanic participants were almost twice as likely to be using antipsychotics compared to non-Hispanic Whites (OR=1.97, 95% CI (1.57,2.46)). Of the participants who were taking antipsychotics, 56% endorsed agitation, 33% disinhibition, 33% delusions, and 25% hallucinations.

Multivariate Analysis

A series of multivariate logistic regression analyses further examined the association of race/ethnicity with antipsychotic use, adjusted for age, education, and gender (Model I) and sequentially adding NPS (Model II) and CDR (Model III), in participants with dementia (Table 2a) and in the subgroup with AD (Table 2b). In both the dementia group and the AD subgroup, Hispanics were significantly more likely to be on antipsychotics, even after adjusting for age, education, and gender, although the odds were reduced from the unadjusted models in Tables 1a and 1b. In Model II with NPS severity score added, the odds for Hispanics of being on antipsychotics, continued to be elevated and remained significant in the probable or possible AD group, but were no longer significantly different in the larger dementia group. After adjusting for overall dementia severity (CDR sum of boxes, Model III), Hispanics were not significantly more likely to be on antipsychotics.

We further examined the effects of NPS severity and the dementia severity on race/ethnic differences in two ways. We looked at the subgroup of participants with higher CDR scores only and saw a significant increase in odds for being on antipsychotics for Hispanics among those with more severe dementia even after adjusting for NPS. We also looked at NPS and found that Hispanic informants generally reported higher levels of NPS across most levels of CDR, both for participants with dementia and among those with probable or possible AD (Figure 1).

Discussion

Use of antipsychotic medicines in NACC participants with dementia was relatively common (10% of subjects overall) with higher use in men, younger participants, and those with more neuropsychiatric symptoms or more severe dementia. Use of antipsychotics was 62% higher in Hispanic participants with dementia than in non-Hispanic Whites and almost two-fold greater among the subset whose dementia associated with probable or possible AD. This

difference was largely accounted for by higher levels of neuropsychiatric symptoms and dementia severity among Hispanic participants. Among just subjects with the highest levels of CDR, however, Hispanics had higher odds of use of antipsychotics even after taking into account the severity of NPS. There was no difference for antipsychotic use between Whites and African Americans.

Hispanic informants also reported greater NPI-Q severity across most levels of dementia severity, especially at the higher levels of dementia severity (Figure 1), and appeared to have greater use in this subgroup of more impaired subjects. This suggests that antipsychotic use is primarily driven by NPS and dementia severity, but that Hispanic participants and informants may be coping with greater severity of NPS that may account for their use of antipsychotics, especially the two-fold increase among participants with AD. These results are consistent with our study of the SALSA participants with cognitive impairment, which found that community dwelling Hispanic participants had higher levels and severity of neuropsychiatric symptoms compared with other studies (of predominantly white non-Hispanics) using similar recruitment and assessment methods.[16] Later work showed that this difference cannot be accounted for by differences in education or source of recruitment.[17] One explanation for our findings is that Hispanic families in the community are more likely to be caring for more impaired demented elders. One previous study of NACC participants showed lower rates of transition to nursing home care for Hispanic participants with dementia.[18] This is also consistent with studies of nationally representative samples showing that Latinos family caregivers report providing more hours of care, on average, to older family members. [19,20]

Predictors of antipsychotic use have received increasing research attention in various settings especially skilled nursing facilities, which are more regulated than assisted-living and community settings. Some studies have reported differences across facilities,[21,22] in that some nursing facilities consistently have higher antipsychotic use (possibly related to referral patterns). Differences in use have also been reported across countries, possibly related to availability of dementia-specific units.[23] Another study found a 23% use of antipsychotics in a community sample of adults with dementia in Canada and found that low income household was associated with higher antipsychotic use.[24] Findings from The Aging, Demographics, and Memory Study (ADAMS) from 2002–2004 found antipsychotic use for nearly 20% of participants and that those who lived with their caregivers were significantly less like to use antipsychotics.[25] Consistent with our finding that higher NPS predicts antipsychotic use, other studies have found that severe behavioral symptoms[26] and hyperactive symptoms (agitation, disinhibition, restlessness, and euphoria) are associated with antipsychotic use.[27–29]

The strength of the NACC database for the present study include the assessment of dementia severity using the CDR and NPS using the NPI-Q in research settings, using validated instruments and trained research clinicians under standardized conditions. However, there are several limitations. The NACC focuses on a population that has sought consultation and clinical care at federally-funded, university-based, Alzheimer's Disease Centers across the U.S.; and the participants and their caregivers are voluntarily participating in research protocols as part of the Alzheimer's Disease Center. The Alzheimer's Disease Centers in

general provide cutting-edge clinical care and research for their catchment areas, and therefore would be expected to have lower antipsychotic use compared to a general community sample. Therefore the participants may not accurately reflect the general community population. Antipsychotic use in dementia population is “off-label” use and generally discouraged in favor of non-pharmacological interventions,[30,31] but similar to other studies, we were unable to assess the degree to which non-pharmacological interventions are being used in the NACC participants, or whether a minority of the antipsychotic use was for approved indications such as for bipolar disorder or schizophrenia. Finally, the findings from this study are cross-sectional in nature and do not address changes in antipsychotic use over time or its relationship to the incidence and progression of dementia and NPS.

In conclusion, we found Hispanics but not African Americans have increased odds of antipsychotic use in the NACC participants with dementia and probable or possible Alzheimer’s disease, compared to non-Hispanic Whites and African Americans. The difference is largely accounted for by higher dementia severity and NPS in Hispanic participants, consistent with other reports that Hispanic dementia patients experience later transitions to nursing homes and that their families provide more hours of care. Our work also suggests higher use among Hispanic participants with the most severe dementia, regardless of NPS severity. Future studies are needed to examine the onset and progression of troubling NPS in community dwelling patients, and the strategies and decision process used by families and physicians, especially in the Hispanic community, when considering non-pharmacologic interventions, antipsychotic medications, and placement in nursing homes as dementia progresses.

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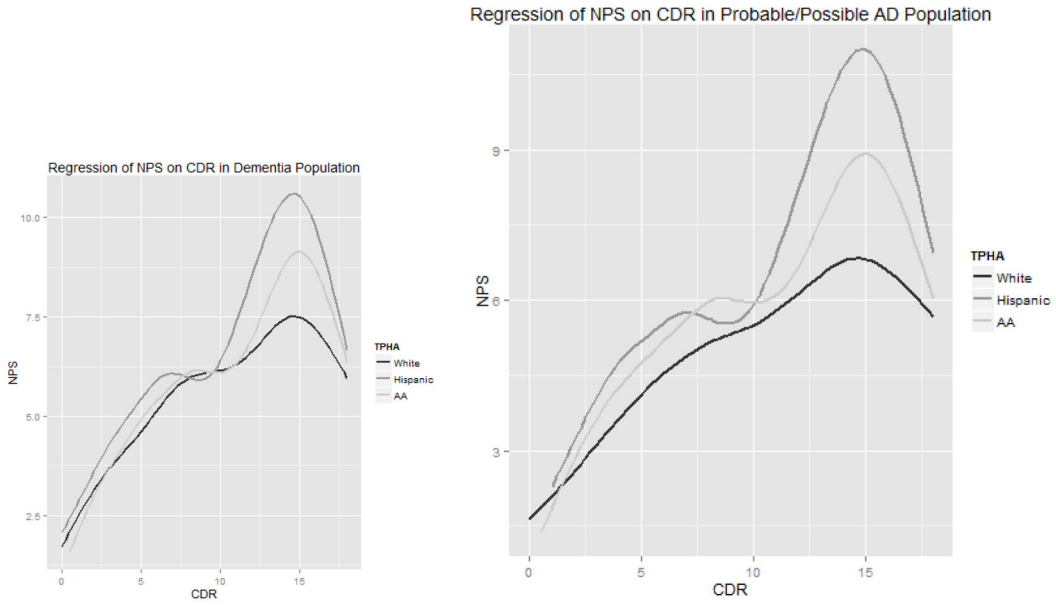

Figure 1.

Figures depict the relationship between Clinical Dementia Rating (CDR) and the caregiver's perception of symptoms. Hispanics report higher NPS scores across almost all levels of dementia ratings; this is more pronounced as the dementia level increases.

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Table 1a

Dementia Population

Descriptive summaries of study sample and univariate comparisons of patients using antipsychotics to those with no antipsychotic drug use

	No Anti-Pyschotic Drug Use	Anti-Pyschotic Drug Use	Percent on Anti-Psychotic Drugs	Univariate Logistic Regression	
Variable	**N = 7989**	**N = 930**	**10.43%**	**OR**	**95% CI**
Primary Predictor of Interest					
Race/Ethnicity					
White	6,377	710	10%	1.00	
Hispanic	719	130	15%	**1.62***	**(1.32,1.98)**
African American	893	90	9%	0.9	(0.71,1.13)
Key Predictors					
Sociodemographic					
Age (M +/− SD)	74+/−10.5	73 +/− 11.1		**0.99**	**(0.98,1)**
<70 years	2570	339	12%	**1.23***	**(1.06,1.43)**
70–75 years	1522	173	10%	1.06	(0.84,1.42)
>75 years	3897	418	10%	1.00	
Gender					
Male	3,846	473	11%	1.00	
Female	4,143	457	10%	0.9	(0.78,1.03)
Education (M =/− SD)	14 +/− 3.8	14 +/− 4.2		**0.96***	**(0.95,0.98)**
<HS	952	152	14%	**1.35***	**(1.11,1.65)**
High School	3292	388	11%	1.00	
College	1857	186	9%	**0.85***	**(0.71,1.02)**
Graduate Education	1888	204	10%	0.92	(0.77,1.09)
NeuroPsych Symptoms Severity					
NPS Sum of Boxes	5+/−4.5	8 +/− 5.9		**1.12***	**(1.1,1.13)**
Clincial Dementia Rating					
CDR Sum of Boxes	7+/−4.3	12 +/− 5.3		**1.21***	**(1.19,1.23)**

*Results in bold are significant at p<0.05.

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Table 1b

Probable or possible AD Population

Descriptive summaries of study sample and univariate comparisons of patients using antipsychotic drugs to those with no antipsychotic drug use

	No Anti-Pyschotic Drug Use	Anti-Pyschotic Drug Use	Percent on Anti-Psychotic Drugs	Univariate Logistic Regression	
Variable	**N = 6434**	**N = 625**	**8.85%**	**OR**	**95% CI**
Primary Predictor of Interest					
Race/Ethnicity					
White	4,991	439	8%	1.00	
Hispanic	645	112	15%	**1.97***	**(1.57,2.46)**
African American	798	74	8%	1.05	(0.81,1.36)
Key Predictors					
Sociodemographic			β		
Age (M +/− SD)	(75+/−10)	(76 +/− 10)		1.00	(0.99,1.01)
<70 years	1690	150	8%	0.87	(0.71,1.06)
70–75 years	1204	114	9%	0.93	(0.74,1.15)
>75 years	3540	361	9%	1.00	
Sex					
Male	2,929	285	9%	1.00	
Female	3,505	340	9%	1.00	(0.85,1.18)
Education (M =/− SD)	(14 +/− 3.8)	(14 +/− 4.4)		**0.96***	**(0.94,0.98)**
<HS	837	121	13%	**1.52***	**(1.21,1.91)**
High School	2642	251	9%	1.00	
College	1475	119	7%	0.85	(0.67,1.06)
Graduate Education	1480	134	8%	0.95	(0.76,1.18)
NeuroPsych Symptoms Severity					
NPS Sum of Boxes	(4+/−4.3)	(7 +/− 6)		**1.12***	**(1.1,1.14)**
Clincial Dementia Rating					
CDR Sum of Boxes	(7+/−4.2)	(12 +/− 5.2)		**1.25***	**(1.23,1.27)**

*Results in bold are significant at p<0.05.

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Table 2a

Dementia Population

Nested logistic regression analysis of Anti-psychotic drug use among socio-demographic factors, level of cognitive impairment as measured by CDR, and severity of neuropsychiatric symptoms.

	Model I		Model II		Model III	
Variable	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Primary Predictor of Interest						
Race/Ethnicity						
Hispanic: White	**1.41***	**(1.11,1.77)**	1.21	(0.95,1.54)	1	(0.77,1.29)
African American: White	0.88	(0.69,1.12)	0.8	(0.61,1.01)	0.79	(0.61,1.01)
Key Predictors						
Sociodemographic						
Age						
Effect of 1 year increase	**0.99***	**(0.98,0.99)**	1.00	(0.98,1)	**0.99***	**(0.98,0.99)**
Sex						
Female compared to Males	**0.86***	**(0.75,0.99)**	0.9	(0.78,1.04)	**0.79***	**(0.68,0.92)**
Education						
<HS compared to HS	**1.26***	**(1,1.58)**	1.17	(0.93,1.48)	1.10	(0.86,1.4)
College compared to HS	**0.83***	**(0.69,1)**	0.87	(0.72,1.05)	0.87	(0.71,1.06)
Graduate Education compared to	0.89	(0.74,1.06)	0.93	(0.77,1.12)	0.95	(0.78,1.16)
NeuroPsych Symptoms Severity						
NPS Sum of Boxes			**1.11***	**(1.1,1.13)**	**1.08***	**(1.06,1.09)**
Clincial Dementia Rating						
CDR Sum of Boxes					**1.2***	**(1.18,1.22)**

* Results in bold are significant at p<0.05

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Table 2b

Probable or possible AD Population

Nested logistic regression analysis of Anti-psychotic drug use among socio-demographic factors, level of cognitive impairment as measured by CDR, and severity of neuropsychiatric symptoms.

	Model I		Model II		Model III	
Variable	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Primary Predictor of Interest						
Race/Ethnicity						
Hispanic: White	**1.74***	**(1.34,2.27)**	**1.46***	**(1.11,1.92)**	1.19	(0.88,1.59)
African American: White	0.99	(0.75,1.28)	0.88	(0.66,1.15)	0.88	(0.66,1.17)
Key Predictors						
Sociodemographic						
Age						
Effect of 1 year increase	1.00	(0.99,1.01)	**1.01***	**(0.99,1.02)**	1.00	(0.99,1)
Sex						
Female compared to Males	0.93	(0.78,1.1)	0.96	(0.81,1.4)	**0.85***	**(0.71,1.03)**
Education						
<HS compared to HS	1.20	(0.92,1.56)	1.11	(0.85,1.46)	1.03	(0.77,1.37)
College compared to HS	0.86	(0.68,1.08)	0.92	(0.72,1.16)	0.91	(0.71,1.17)
Graduate Education compared to	0.97	(0.77,1.2)	1.03	(0.81,1.29)	1.08	(0.85,1.38)
NeuroPsych Symptoms Severity						
NPS Sum of Boxes			**1.12***	**(1.1,1.13)**	**1.07***	**(1.06,1.09)**
Clincial Dementia Rating						
CDR Sum of Boxes					**1.23***	**(1.21,1.26)**

*Results in bold are significant at p<0.01.