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Minority Enrollment in Parkinson's Disease Clinical Trials

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Abstract

Under-representation of minorities in clinical trials limits access to information relevant to all segments of the population. We assessed the enrollment of minority subjects with Parkinson's disease (PD) into clinical trials. We searched PubMed for published studies of PD trials conducted in the US over the past 20 years and found that only 41 reported racial/ethnic participation (17%). In those trials reporting race/ethnicity, 8% of subjects were non-white, compared to 20% of the non-white US population over age 60. Results of this study identified the need for better reporting of racial composition in clinical trials and for the enrollment of more minority participants in research studies.

Keywords

Parkinson's disease; clinical trials; minority enrollment; health disparities

Introduction

Parkinson's disease (PD) is a chronic, degenerative and incurable neurological disorder which causes a progressive loss of independence resulting in significant disability and considerable financial burden to medical care systems [1–4]. PD afflicts one percent of individuals over the age of 60 in industrialized countries [4]. It is estimated that 600,000 to 1 million individuals have PD in the US alone, with an estimated incidence of 70,000 new cases each year [5]. It is certain that with the aging of the population, the number of persons with PD will continue to grow. The motor decline, disability and economic impact associated with PD make it a potentially major public health problem.

PD occurs in all countries and affects diverse racial and ethnic groups worldwide [6]. Approximately one-fifth of all PD in the US is diagnosed in minority populations, defined as persons belonging to racial and ethnic groups other than non-Latino Caucasian [7]. No persuasive evidence exists to suggest that rates of PD in the US population vary according to

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race [8]. In order to provide clinicians with thorough research results that can be applied to both minority and non-minority persons in their practice, clinical trials targeting PD should have minority enrollment proportional to minority representation in the US general population. Inclusion of under-represented groups in clinical trials is important to determine possible differences in disease outcomes, response to interventions, and therapeutic benefits among different groups. NIH instituted guidelines mandating the inclusion of women and minorities to increase their enrollment in clinical research in 1993. However, many years later, minority members are still under-represented in clinical trials and most drugs are approved without minority participation [9]. In this paper, we assess minority participation in PD clinical trials and explore the possible reasons for the under-representation observed. Potential solutions to promote equitable representation in future trials are proposed.

Methods

A systematic search of PubMed which queried for “Parkinsons disease” was completed to assess minority participation in published PD clinical trials. Published trials were examined in order to examine the reporting of race/ethnicity and no attempt was made to obtain information on unpublished trials. The following PubMed “Limits” were utilized: 1) Humans, 2) English language, 3) Randomized Controlled Trial, and 4) a publication date between January 1, 1985 and December 31, 2007. The queried trials were imported into Reference Manager v10 (Stamford, Conn.). Trials were identified as being conducted in the US if the primary author was in the US and the majority of subjects were enrolled in the US, although some studies enrolled subjects from other countries (e.g. Parkinson Study Group has sites in the US and Canada).

The clinical trials published during this time frame included futility trials conducted by the National Institutes of Health (NIH) Exploratory Trials in Parkinson’s Disease (NET-PD), sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) [10,11]. Race/ethnicity data collected on both screened and enrolled individuals were obtained from these NET-PD trials. Enrollment screening logs and reported reasons for those individuals declining participation in the NET-PD trials were analyzed by race/ethnicity. It is important to note that eligibility assessment generally stopped when a potential participant was deemed ineligible. Subsequently, the reported reasons may not represent all of the possible reasons for ineligibility. The NET-PD enrollment data were analyzed using SAS 9.1 (Cary, NC).

Results

A total of 711 references were obtained from the PubMed search and imported into Reference Manager. Three hundred twenty publications were identified as having a US primary author and a majority of US participants enrolled. Of these, 81 publications were case reports, journal reviews, or methodological publications related to randomized controlled trials in PD and were excluded from further review. Of the remaining 239 publications, only 41 publications representing 33 distinct studies reported racial/ethnic participation (17% [41/239]). A summary of these 33 studies and the publications in which they were described is presented in Table 1. These 33 distinct studies enrolled a total of 7,481 participants, of whom approximately 8% were non-white. The Prime study [12] enrolled an entirely minority-based study population. A total of 7,337 participants were enrolled in the 32 remaining studies, of whom 414 (5.6%) were non-white.

Of the 32 studies (excluding Prime), only nine studies reported detailed racial/ethnic composition and not just percentage of “White/Caucasian” enrolled [13–21]. The NET-PD futility trial publications reported both “White/Caucasian” and “Latino/Hispanic” participation but did not report enrollment of other minority groups. These nine studies enrolled a total of

1,009 participants. Based upon the information in the publications, these studies enrolled only 17 African American and 13 Latino participants, 1.7% and 1.3% of the total enrollment respectively.

Table 2 presents the combined screening logs from the NET-PD futility trials [10,11] by race/ethnicity. As can be seen, enrollment of minority participants in trials was significantly lower than for non-Latino Caucasians (χ^2 (14) = 64.4570, $p < 0.0001$). However, this difference is due to a larger percentage of unreported screening outcomes in the Asian and Other race/ethnicity groups than the other groups. When comparing just non-Latino Caucasian, African American and Latino groups, a significant difference in screening outcomes is not seen (χ^2 (6) = 9.1546, $p = 0.165$). African Americans screened in the NET-PD trials had the smallest proportion of ineligibility while also having the largest proportion who declined participation. Overall, 91% of those enrolled in the NET-PD futility studies were non-Latino Caucasian.

The primary reasons given by minority individuals for declining participation did not differ greatly from those given by non-Latino Caucasians (Table 3). One notable difference is that non-Latino Caucasians (especially women) declined participation more frequently due to reasons related to travel and doctor's advice.

Discussion

This review of the clinical trial literature review showed that only 17% of published US studies reported information about the enrollment of under-represented minorities. In those publications that did report race/ethnicity, the proportion of minority participants was much lower than in the general US population. Approximately 6% of study participants (excluding Prime) were non-white in the reported studies while non-whites represent 20% of the general US population age 60 and over [22]. This suggests that there is more than three-fold under-representation of non-whites in PD clinical trials. It is striking that the reviewed trials which reported detailed demographic categories had an African American enrollment of only 1.7%. This constitutes a five-fold under-representation when compared to the proportion of African Americans age 60 and over in the general US population (8.6 %) [22]. It is important to note that two of the nine studies that reported detailed racial/ethnic composition also reported some missing racial data [13,14]. It is unknown whether this missing information would impact this observation of minority under-representation.

Although promoting diversity of study subjects has reportedly been ignored in previous studies [23–26], the Prime study, NET-PD and other current studies are placing more emphasis on minority recruitment. PD clinical trials are generally conducted by investigators who sub-specialize in PD. However, a disproportionately low number of minority patients are seen in movement disorders clinics, an experience that has been documented in most of the NET-PD site investigations [10]. Ineligibility among minority groups did not limit the NET-PD futility studies, as the proportion of ineligible participants was not significantly different in the non-Latino Caucasian, African American, Asian and Latino groups, although this proportion was lower in African Americans than in any of the other groups. It has been suggested that fewer African Americans participate in research studies and clinical trials due to exclusion criteria related to the presence of medical co-morbidities [27,28]. However, in NET-PD, co-morbidities were less likely to be the reason for failing to enroll in the trial (only 7% of study participants were ineligible, including those with co-morbidities). It seems evident that minority groups were under-represented in the screened population and that study coordinators had little to no access to minority populations.

Reasons given by minority individuals for declining participation presented did not differ greatly from those given by non-Latino Caucasians. This is a surprising finding which when

coupled with the similarity seen in screening outcomes may indicate that once included in the screening process, minority and Caucasian participants have a similar enrollment experience. This suggests that disproportionate enrollment of certain racial groups is not due to bias introduced by the inclusion/exclusion criteria or on the part of study sites. We must look to an explanation based on events that occur before screening, which might include minority group awareness or geographic placement of sites.

Under-representation may be in part explained by the fact that African Americans are less likely to have primary care providers and are seen less often by specialist physicians than Caucasians [29,30]. In addition, African Americans may have less knowledge about risk factors, symptoms, detection, and treatments [31–33]. Fear of stigma to the family, of losing services, and of lack of confidentiality on the part of minority group members may also inhibit enrollment [34–36]. Moreover, there is evidence that minority elderly are more likely to consider some health conditions to be part of the normal aging process [37]. PD mimics the aging process with gradual and insidious progression of motor slowing, loss of dexterity, and problems with gait and balance. Although PD prevalence is highest among the elderly, they are generally less likely to participate in clinical trials [38,39].

Successful strategies to increase minority enrollment may be learned from the Prime study, which specifically targeted minority PD participants, and from recruitment studies like the AAMEN (African American Men) project [40], which compared strategies for recruiting older African American men into a cancer screening trial and determined that intensive face-to-face contact through church-based recruitment provided the best enrollment yield. The face-to-face strategy addressed cultural, individual, economic and study design recruitment barriers. Similarly, the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) project has nearly doubled the proportion of black subjects enrolled in trials by increasing community awareness of Alzheimer's disease and enhancing staff sensitivity to minority needs [35]. Community outreach approaches for PD might include focus groups to assess attitudes and beliefs, building working relationships with community gatekeepers, particularly primary care physicians and clergy [34,40] and keeping them informed about available PD studies, and partnering with community agencies. Moving research sites from academic to local community settings or providing funds to sites with better potential for diverse enrollment and reducing economic and transportation barriers may also help [27,41–43]. Given the low prevalence of PD in the community and the scarcity of minority practitioners, grassroots projects by PD patients to increase minority enrollment may ultimately be important [44].

Strengths of the study include its originality and its importance in identifying apparent inattention to the under-enrollment of minority persons into PD clinical trials within the research community. There are some limitations to this study. For consistency, we limited our search to publications in PubMed. We were therefore limited by the availability and accuracy of information in published papers. Perhaps future studies could broaden the scope and include the FDA Summary Base of Approvals or trial summaries in the Neuropharmacology division that include demographic descriptions of study participants. These sources might reveal specific information about trials that could be studied in relation to minority participation, like objectives (drug in early vs late development), length of the trial, study of an approved drug, whether placebo controlled, whether sponsored by industry vs academia, or enrollment of early or late stage subjects. However, findings from this study clearly show a low frequency of reporting racial composition of PD trial populations and an overwhelming Caucasian predominance in nearly all PD sample populations where racial composition was reported. The detailed list of reasons for excluding subjects showed that once included in screening, minority and Caucasian PD trial candidates have similar enrollment experiences.

PD affects all racial and ethnic groups and minority populations bear substantial disease burden. Access and logistical barriers to PD clinical trials still need to be overcome [28]. Despite increasing recognition of barriers to recruitment, participation, and retention of racially and ethnically diverse populations, minority representation in clinical trials is still inadequate. An important lesson can be learned from the NET-PD futility trials, which indicate that the barrier to racially-representative clinical trials may be a function of accessing minority populations and not of ineligibility or failure to enroll. Progress should be measured by achieving minority representation in clinical trials that is proportional to PD prevalence.

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33 U.S. PD Clinical Trials in 41 Published Articles from Jan 1, 1985 – Dec 31, 2007 which reported race/ethnic enrollment

Table 1

Study	N	Non-Hispanic Caucasian	African-American	Hispanic	Asian	Other/Not Reported
FS1 [10]	200	188 (94.0%)	—	6 (3.0%)	—	6 (3.0%)
FS-Too [111]	213	191 (89.7%)	—	8 (3.8%)	—	14 (6.5%)
DATATOP [45–46]	800	781 (97.6%)	—	—	—	19 (2.4%)
Propath [13]	46	41 (89.1%)	2 (4.3%)	1 (2.2%)	—	2 (4.3%)
Lazabemide [47]	201	189 (94.0%)	—	—	—	12 (6.0%)
Lazabemide [48]	137	133 (97.1%)	—	—	—	4 (2.9%)
Pramipexole [49]	264	256 (97.0%)	—	—	—	8 (3.0%)
Entacapone [50]	205	197 (96.1%)	—	—	—	8 (3.9%)
Clozapine [51]	60	58 (96.7%)	—	—	—	2 (3.3%)
HRQOL [14]	141	123 (87.2%)	2 (1.4%)	3 (2.2%)	—	13 (9.2%)
Remacemide [52]	200	192 (96.0%)	—	—	—	8 (4.0%)
CALM [53–57]	301	287 (95.3%)	—	—	—	14 (4.7%)
Remacemide [58]	39	36 (92.3%)	—	—	—	3 (7.7%)
Remacemide [59]	279	267 (95.7%)	—	—	—	12 (4.3%)
Olanzapine [15]	83	72 (86.8%)	3 (3.6%)	4 (4.8%)	—	—
Tempo [60–63]	404	383 (94.8%)	—	—	—	21 (5.2%)
Presto [63]	472	431 (91.3%)	—	—	—	41 (8.7%)
Rotigotine [64]	242	227 (93.8%)	—	—	—	15 (6.2%)
Neuronal Implant [65]	40	34 (85.0%)	—	—	—	6 (15.0%)
Pallidotomy [16]	36	34 (94.4%)	2 (5.6%)	—	—	—
Ellidopa [66]	361	327 (90.6%)	—	—	—	34 (9.4%)
Neuronal Implant QOL [17]	30	27 (90.0%)	1 (3.3%)	1 (3.3%)	—	—
Rasagiline [67]	56	51 (91.1%)	—	—	—	5 (8.9%)
Aripiprazole [68]	14	13 (92.9%)	—	—	—	1 (7.1%)
TCH346 [18]	301	286 (95.0%)	3 (1.0%)	—	3 (1.0%)	9 (3.0%)
Transdermal Rotigotine [69–70]	277	268 (96.8%)	—	—	—	9 (3.2%)
Sumanitrole [71]	609	565 (92.8%)	—	—	—	44 (7.2%)
Apomorphine (APO302) [19]	62	60 (96.8%)	—	1 (1.6%)	1 (1.6%)	—
Apomorphine (APO303) [20]	56	52 (92.8%)	—	3 (5.4%)	—	1 (1.8%)
Zydis Selegiline [21]	254	239 (94.1%)	4 (1.6%)	—	2 (0.8%)	9 (3.5%)

Study	N	Non-Hispanic Caucasian	African-American	Hispanic	Asian	Other/Not Reported
Precept [72]	806	771 (95.7%)	—	—	—	35 (4.3%)
Selegiline (Study 025) [73]	148	142 (95.9%)	—	—	—	6 (4.1%)
Prime [‡] [12]	144	—	48 (33.3%)	54 (37.5%)	42 (29.2%)	—
Total (excluding Prime)	7337	6921 (94.3%)	17 (0.2%)	27 (0.4%)	11 (0.1%)	361 (4.9%)
Total (including Prime)	7481	6921 (92.5%)	65 (0.9%)	81 (1.1%)	53 (0.7%)	361 (4.8%)

[‡] Study did not enroll white individuals.

Table 2
Screening logs from the NET-PD Futility Studies (FS1 and FSToo combined) by race/ethnicity.

Race/Ethnicity	Outcome of Screening *				
	Ineligible	Declined	Not reported	Enrolled **	Total
Non-Latino Caucasian	123(17%)	143(20%)	93(13%)	376(51%)	735
African/American	2 (7%)	11 (37%)	6 (20%)	11 (37%)	30
Asian	5 (15%)	4 (12%)	13(39%)	11 (33%)	33
Latino †	4 (17%)	6 (26%)	2 (9%)	11 (48%)	23
American Indian/Alaskan Native	0	0	0	1 (100%)	1
Native Hawaiian/Other Pacific Islander	1 (100%)	0	0	0	1
Other ‡	17(35%)	6 (12%)	23(47%)	3 (6%)	49
Not reported	6 (21%)	7 (25%)	15(54%)	0	28
Total	158	177	152	413	900

* $P < 0.0001$ (χ^2 (14) = 64.4570). Chi-square test comparing screening categories by race/ethnicity, excluding race/ethnicity = "not reported". Percents may not add to 100% due to round-off error.

** 79 participants were enrolled but were not included in the screening logs. These participants were included in the table as "Enrolled".

† Among those classified as "Latino", 4 were identified as belonging to more than one race and being Latino.

‡ Among those classified as "Other", 3 were African American and Latino.

Table 3
Reasons recorded for declining participation in the NET-PD Futility Studies (FS1 and FSToo combined) by race/ethnicity.

Primary Reason Declined	Minorities*			Non-Latino Caucasian*		
	Women (n=13)	Men (n=20)	Total (n=33)	Women (n=56)	Men (n=84)	Total (n=140)
Protocol related	8%	5%	6%	7%	7%	7%
Placebo	8%	5%	6%	7%	1%	4%
Travel requirements	8%	0%	3%	20%	7%	12%
Doctor's advice	0%	0%	0%	11%	5%	7%
Family advice	8%	10%	9%	2%	7%	5%
Not Interested	15%	10%	12%	14%	19%	17%
Other	46%	55%	51%	30%	35%	32%
Phone contact**	8%	10%	9%	5%	12%	9%
Enrolled other study	0%	5%	3%	5%	6%	6%

* Minority is other than non-Latino Caucasian. Percents do not add to 100% due to round-off error.

** Individual declined during pre-screening with no further reason recorded.