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PREDICTORS OF PHYSICIAN REFERRAL FOR PATIENT RECRUITMENT TO ALZHEIMER DISEASE CLINICAL TRIALS

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Abstract

Background—Inadequate recruitment into Alzheimer disease (AD) clinical trials is an important threat to the validity and generalizability of the studies. The majority of dementia patients are first evaluated by community-based physicians; however, physician perceptions of clinical research are largely unknown.

Methods—A survey was distributed to 3,123 physicians in three states; 370 were returned. Survey items assessed attitudes, perceived benefits of and barriers to referral to clinical research and physicians use of the internet for medical information.

Results—The mean age of the respondents was 50.6 ± 10.8y; 70% were male, 78% Caucasian, 61% were primary care providers; 63% used the internet ≥3 times/week. No demographic or medical specialty differences existed between those who were likely (n=193) and unlikely (n=162) to refer patients to clinical trials. Differences were discovered in perceived benefits reported by physicians who were more likely to refer, while differences in perceived barriers existed in primary care compared with specialists. Referral to clinical trials is predicted by close proximity to a research center (OR:4.0,95%CI:1.1–15.6) and availability of internet information regarding diagnostic evaluation (OR:2.3,95%CI:1.1–4.7). Primary barriers included concerns about exposure of patients to uncomfortable procedures (OR:4.7,95%CI:1.2–18.7) and lack of time to discuss research participation (OR:6.8,95%CI:1.4–32.3).

Conclusions—Proximity to a research center and availability of diagnostic clinical tools are strong predictors of clinical trial referral. Concern over risks to patients and lack of time are strong barriers. These results suggest that dementia outreach education targeted to physicians should emphasize the importance of clinical trials with a focus on discussing research participation in a time-efficient manner and increasing awareness of risk reduction and the safety of research protocols. Providing easy access to up-to-date, user-friendly educational materials on dementia diagnosis and research

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via the internet are likely to improve referrals of patients to AD clinical trials from community physicians.

Keywords

Alzheimer's disease; Clinical Trials; Recruitment; Referral; Dementia; Physician

INTRODUCTION

Current treatments for Alzheimer disease (AD) have shown only modest benefits in reducing symptoms. New investigational medications offer hope for disease modification. Clinical trials are indispensable to the drug approval process[1], however, numerous studies across multiple disciplines fail to recruit the planned number of participants in a timely fashion, threatening the validity and success of clinical research.[2–4] Low participation of women, older adults and minorities in clinical trials (particularly Phase III) raises concerns about generalizability of results, and potentially leads to disparities in disease treatment.[5,6] With poor recruitment being such a widespread problem, a number of interventions have been proposed to improve recruitment from community physicians including telephone reminders, monetary incentives, open-label extensions and cultural sensitivity training for research staff with unknown effectiveness.[7,8] Despite the growing public awareness of AD, recruitment problems are particularly common in AD clinical trials.[9,10]

Clinical trial recruitment involves three parties: 1) the researchers who conduct the trials, 2) the patients who participate, and 3) the physicians who make referrals. While several studies have examined patient perception of, willingness to participate in, and self-referral to clinical trials,[5,7,11,12] little research has addressed the role of primary care providers (PCP) in clinical trial referral or factors that may enhance referral rates. The majority of AD patients are first evaluated by their PCPs; a much smaller percentage is seen first by a specialist.[13] Although not a part of routine medical care, clinical trial participation may be of interest to both patients and providers. Attitudinal and structural barriers, however, may preclude clinical trial referral. For example, PCPs often face extreme time pressures related to their practice.[14] Providers not affiliated with a research institution may be less likely to refer to clinical trials,[11] and may lack opportunities to build familiarity and trust in the process.[15,16]

Barriers such as physician concern about patient safety, knowledge about local trials, or beliefs about the importance of clinical research may impact referral patterns. To date, it remains unclear how best to address barriers to clinical trial referral and improve the flow of information to PCPs. One potential mechanism for disseminating accurate information about dementia and the importance of participation in clinical trials is the use of the internet, although little is known about physicians' use of and attitudes towards this resource with respect to dementia care or clinical trial referral.

To address the gap in our understanding of best practices for enhancing recruitment to AD clinical trials, we conducted a survey of physicians to examine: a) perceived benefits of and barriers to referral to clinical research, and b) use of the internet for medical information in general, and for AD-specific treatment and care.

METHODS

Survey Development

A two-page anonymous survey was distributed by mail to 3,123 primary care (PCPs) and specialist physicians practicing geographically located near three National Institute on Aging-funded Alzheimer's Disease Centers in Ann Arbor, MI, St. Louis, MO, and Portland, OR. The

questions were derived de novo based on the published work in this area, the previous research experience of the investigators, priorities of the ADCs that sponsored the study, and numerous planning sessions conducted via telephone conference calls among the three participating sites. No pilot testing of the resulting survey instrument was performed. The sample consisted of physicians identified by statewide medical societies and licensing lists.

Survey items included demographic characteristics (age, race, gender) and questions about medical practice (specialty, percentage of patients over age 65), and use of internet resources in medical practice and participation in on-line CME courses. The items pertaining to accessing medical information via the internet were asked using a 5-point Likert scale with anchor statements (1 = strongly disagree, 5 = strongly agree). Respondents were then asked, “If an authoritative source of on-line information was available, what topics would you be interested in?” Twelve examples of on-line materials (e.g. screening tools, caregiver assessments, community resources, practice guidelines, downloadable patient handouts) were offered; respondents indicated their likelihood of use with a 3-point Likert scale (0 = not at all, 1 = somewhat likely and 2 = very likely).

Two questions assessed physician perceptions of AD research. The first was: "In general, how important do you think research studies involving patients and their families are for understanding Alzheimer disease”. The next item was: "How likely are you to refer a patient to participate in a clinical trial?” Response choices ranged from 1 (not at all important or likely) to 5 (extremely important or likely). Lastly, four perceived benefits of and eight perceived barriers to clinical trial referral were assessed.

Statistical Analysis

All analyses were performed using SPSS, v15.0 (Chicago, IL). Group comparisons were made using two-sided t-test for continuous variables and Pearson chi-square for categorical variables. In addition to descriptive statistics, a primary dichotomous dependent variable, “Likely to refer/ not likely to refer, was created from the question, “How likely are you to refer a patient to participate in a clinical trial?” Responses to this question followed a normal distribution (mean 3.25, SD 1.16, median 3). For the dichotomous outcome variable the 5-point scale was recoded with “low likelihood to refer” (Likert scores 1, 2, and 3) coded as 0 and high likelihood (Likert scores 4 and 5) coded as 1.

Logistic regression models were developed to determine predictors of referral to a clinical trial. Predictor variables included demographic variables, 11 questions on accessing medical information via the internet, 12 items for preferences of internet information, 4 questions ascertaining perceived benefits and 8 questions ascertaining perceived barriers. We used three approaches to test the validity of the models. First, all variables were entered simultaneously to determine which variables independently predicted clinical trial referral. We then used two step-wise approaches (forward and backward) with age, race, gender and medical specialty as covariates and each predictor variable as candidates for step-wise entry. Because similar models were elicited using forward and backward stepwise methods, only results from the fully-adjusted, forward step-wise regressions are reported with odds ratio (OR) and 95% confidence intervals.

RESULTS

Sample Characteristics

Of the 3123 surveys mailed, 370 were returned (12% response rate). The mean age of the respondents was 50.6 ± 10.8y. The sample was 70% male and 78% Caucasian. Sixty-one percent of the respondents reported their medical specialty was primary care (Internal

Medicine, Family Medicine or General Practice). Specialists (39%) included Neurologists, Psychiatrists and Geriatricians. Respondents reported that 40% of their practices were made up of adults over age 65. The respondents frequently used the internet for medical information; two-thirds (63.5%) reported use three or more times per week and 60% participated in on-line CME courses. These results suggest that web-based programming may provide targets for intervention and increasing awareness of AD clinical trials.

Perceived benefits and barriers, reported by likelihood to refer to a clinical trial and by medical specialty, are shown in Table 1. Perceived benefits differed by likelihood to refer; those physicians more likely to refer saw greater benefits to patients, families and their practice. On the other hand, perceived barriers differed by medical specialty; PCPs perceived greater burden to patients, families and their practice.

There were no differences in demographic characteristics, practice parameters or internet use between physicians who were likely to refer to a clinical trial (N=193) and physicians who were unlikely to refer to a clinical trial (N=162) (Table 2). There was a highly significant relationship in the reported likelihood of referring patients for AD research and positive response that to the question about the importance of AD research. There was a significant difference between perceptions of the importance of AD research and the likelihood to refer to a clinical trial. Physicians who were likely to refer to an AD clinical trial were also more likely to place higher importance on patient-oriented AD research (χ^2=12.7, p<.001). Because there were no differences between PCPs and specialists in demographic characteristics, their likelihood to refer to clinical trials (χ^2=1.3, p=.27) or in their perceptions of importance of AD research (χ^2=1.4, p=.26); these groups were combined.

Predictors of Clinical Trial Referral

Logistic regression was performed to determine variables that best predicted high likelihood to refer patients to a clinical trial. When adjusted for demographic variables, the step-wise logistic model suggested that referral to clinical trials by community physicians is strongly predicted by the close proximity (zip code within 20 miles) to a NIH-funded Alzheimer Disease Research Center (OR:4.0, 95%CI:1.1–15.6) and interest in internet information regarding diagnostic evaluation tools (OR:2.3, 95%CI:1.1–4.7). Surprisingly, none of the perceived benefits assessed in the survey were significant predictors of clinical trial referral. Significant barriers to clinical trial referral included physician concerns about exposure of patients to uncomfortable tests and procedures (OR:4.7, 95%CI:1.2–18.7) and lack of time to discuss research participation (OR:6.8, 95%CI:1.4–32.3). Interestingly, a lack of awareness about clinical trials was not a significant barrier suggesting that either community physicians (both PCPs and specialists) were aware of ongoing AD clinical trials or were willing to become aware of local trials.

Because perceptions of the importance of patient-oriented research in AD differed between those who were likely to refer and those less likely to refer, a second regression analysis was performed adjusting for physician perceptions of the importance of patient-oriented research. Again, two significant barriers to clinical trial referral were discovered -- physician concerns about exposure of patients to uncomfortable tests and procedures (OR:3.3, 95%CI:1.1–9.5) and lack of time to discuss research (OR:7.4, 95%CI:2.4–22.7).

DISCUSSION

To increase our understanding of the causes of and effective treatment for dementia, participation in clinical trials is essential. Despite general agreement that physician referral is key to research participation for many families, little is known about how physicians view their role in this process. The current study was conducted to address this gap in our understanding.

Results suggest that referral of patients to AD clinical trials by community-based physicians was predicted by close proximity (less than 20 miles) to a research center and the potential for access to internet clinical tools to assist in the evaluation and diagnosis of AD. The most significant barrier to clinical trial referral was the perceived lack of time to discuss research participation during a clinical visit, followed by concern about potential risks of procedures, testing and investigational medications. These barriers persisted regardless of the physicians' perceptions of the importance of clinical research to increase the understanding about AD.

Other variables that were hypothesized to be important factors for clinical trial referral did not appear to play a role in the decision. For example, we found differences in perceived benefits among those physicians who were more likely to refer, and differences in perceived barriers between PCPs and specialists. However, these differences did not seem to influence the likelihood to refer to clinical trials. Lack of awareness about available clinical trials did not play a role in stated intentions about possible clinical trial referral.

Perceived benefits (i.e., patient/family benefits, interest, enhancing medical care or helpful feedback) appeared to play no role in clinical trial referral. The Health Belief Model[17] proposes that the perceived benefits of a health-related behavior or medical action must outweigh the perceived barriers to doing so. Perceived barriers are most consistently found to influence health behavior,[17] a notion supported by this study, apart from physicians' specialty or perceptions about the importance of clinical research.

Previous research has suggested that maximizing primary care recruitment of patients is promoted by enhancing awareness and delineating benefits of participation. In the past, this approach has focused on mailing letters and personal visits[18,19] Our study suggests that the internet now provides great potential for communicating with PCPs regarding AD since the majority of those surveyed used the internet for medical information and participated in on-line CME courses. Another potential recruitment tool may be to provide incentives to PCPs; however, it is unclear whether the data supports this as an effective strategy. In a meta-analysis of six studies that tested the use of monetary incentives to clinicians, PCPs were concerned that the trial would require extra work and threaten the doctor-patient relationship. In addition, they reported that they were embarrassed to ask the patients to participate.[20] There may also be potential ethical issues (e.g., conflict of interest, disclosure, informed consent) that limited effectiveness of using incentives to promote recruitment.[8]

This study was not without its limitations. The non-random sampling of physicians in the three survey locations, with differential targeting of primary care and specialist physicians was based on local interests. The results from the logistic regression had wide confidence intervals, limiting the accuracy of the point estimates. Although we assessed use of the internet as a potential source of intervention, other factors not asked in this survey that may also contribute to clinical trial referral patterns for physicians. This survey did not assess patient characteristics. Finally, the study was cross-sectional, thus cause-effect relationships between predictor and outcome variables cannot be examined.

The low response rate (12%) limits generalizability of the findings especially because non-response bias is difficult to assess.[21] Reported response rates for mailed surveys to the general population approach 60%, while response rates for physicians varies widely (from 11–90%).[21] In a meta-analysis, Kellerman and colleagues reported that demographic variables (age, gender, income, area, type of practice) are not different between physician responders and non-responders.[22] In addition, physicians were found to be more homogeneous in knowledge, training, attitudes and behaviors than the general population. Interestingly, surveys of individuals (usually mailed to their home addresses) have much higher response rates (60%) than surveys of organizations or businesses (usually mailed to the workplace, 15%) similar to

our study.[23,24] It is difficult to determine whether non-respondents actually ever received the survey as office staff may open and "pre-screen" the mail. An alternative interpretation of the low response rate could be that those who did not respond to the survey had an inherently poor view of research in general or of this particular topic and thus did not respond to the survey.

Based on study results, we have identified two potential targets for outreach efforts designed to improve physician referral to clinical trials. First, considering the impact of proximity to a research center for clinical trial recruitment, the development of satellite clinics may help enrollment. Second, given the frequent use of the internet by the respondents, on-line material may supersede the use of mailed materials. We believe that dementia outreach programs should not simply discuss the importance of AD clinical research but also attempt to provide clinicians with on-line resources to promote benefits and overcome barriers to clinical trial referral. Providing concise and informative educational materials to physicians is needed to promote discussion of research participation with patients and families in a time-efficient manner. Patient information, diagnostic and management tools, caregiver information, community resources and lists of on-going research studies may alleviate some of the time constraints. Attention to the safety concerns of the tests and procedures (e.g., lumbar puncture, PET scan) that may be required for research participation may alleviate physician concerns. We believe that providing easy access to up-to-date and user-friendly educational materials on dementia diagnosis, treatment and care via the internet are likely to improve both diagnosis of AD and referrals of patients to AD clinical trials from the community. Such efforts are likely to improve recruitment and generalizability of results from AD clinical trials.

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Table 1

Perceived Benefits and Barriers by Likelihood to Refer to Clinical Trials and Medical Specialty

	Likelihood to refer to clinical trial			Medical Specialty		
BENEFITS (%)	**Not likely (n=162)**	**Likely (n=193)**	**p-value**	**PCP (n=229)**	**Specialist (n=141)**	**p-value**
Patient and/or Family may benefit from participation	67.4	88.3	<.001	75.5	69.5	ns
Patient and/or Family is interested in research participation	73.6	84.0	.02	78.6	68.1	.03
Participation by the patient may enhance ongoing medical care	62.2	82.1	<.001	70.3	65.2	ns
I may receive helpful feedback to guide my care decisions	43.0	66.0	<.001	55.9	42.6	.01
BARRIERS (%)						
The risks of participation appear to be too great	63.2	72.8	ns	67.7	58.9	ns
Patient may be unable to give informed consent	51.8	51.2	ns	53.7	41.8	.03
Patient may be exposed to uncomfortable procedures or risks	45.6	50.6	ns	50.7	37.6	.02
Family may find participation too overly burdensome	62.2	66.7	ns	61.6	60.3	ns
Not practical based on distance of my patient from the research site	55.4	59.3	ns	66.7	44.7	.004
Patient has expressed no interest in research	46.1	43.2	ns	44.1	40.4	ns
Lack of awareness of research studies	45.1	43.2	ns	41.9	42.6	ns
Lack of time to discuss research participation during clinical visits	43.0	35.8	ns	42.8	29.1	.008

PCP = Primary Care Provider

Ns = not significant

Table 2

Association of demographic and practice characteristics with Likelihood to refer for Alzheimer's research

Variable	Likely to refer (N=193)	Unlikely to refer (N=162)	p-value
Age (y)	50.1 (10.6)	51.4 (11.2)	ns
Gender (%male)	53.6	46.4	ns
Race (%White)	55.7	44.3	ns
Medical Specialty (% primary care)	56.6	43.4	ns
% patients over age 65	37.9	44.0	ns
% participating in on-line CME course	57.2	42.8	ns
% AD research important	89.4	74.6	<.001

Mean (SD)

ns=not significant