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Long Term Understanding of Study Information in Research Participants with Parkinson's disease

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Abstract

Context—Little is known about research participants' understanding of consent information over the course of a clinical study and the relationship of this information with participant behavior.

Methods—We conducted a cross sectional patient completed questionnaire of comprehension and satisfaction administered at the end of a Parkinson's disease clinical trial.

Main outcome—Scores on 9 comprehension items in a 30 item questionnaire covering the key elements of informed consent.

Results—78% of eligible trial participants completed this sub-study. Greater than 90% of respondents showed good comprehension of the study purpose, method of treatment assignment, experimental nature of drugs, voluntary participation, and expected effect of the trial on their PD. However, 42.3% of subjects incorrectly endorsed that participating in the study was part of the “usual treatment” for their PD. We found no relationship between comprehension, compliance, and satisfaction with whether or not one's own neurologist was also the study doctor. Years of education and cognitive function at baseline were correlated with comprehension of study information.

Conclusions—Overall comprehension of key study information presented in the consent was high after 12 months of trial participation, although there were inconsistencies in responses that need further study.

Keywords

Parkinson's disease; comprehension; understanding; informed consent; clinical trial

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Introduction

Research participants' comprehension of study information has been widely studied near the time of initial informed consent [1]. However, little is known about retention of this information over the course of a study and the effect of this information on participant behavior. If participants fail to appreciate key elements of informed consent, continuing validity of their consent could be compromised.[2,3] This is of particular concern in progressive neurodegenerative disorders affecting cognitive function such as Parkinson's disease (PD), Huntington's disease (HD), and Alzheimer's disease (AD). [2]

In the clinical setting comprehension of treatment information is thought to enhance compliance and satisfaction, although recall of treatment information may deteriorate rapidly over time.[4-6] Participant retention of study information may affect clinical trials by affecting satisfaction, compliance with study procedures, and willingness to participate in future studies. We set out to determine if participants in a 12 month PD clinical trial appreciated key study information at the end of the study, how comprehension was related to cognitive function, and if comprehension was related to compliance and satisfaction with study procedures.

Methods

Participants

Eligible participants were 192 subjects enrolled in an NIH sponsored, Phase II PD clinical trial at 45 of 51 clinical trial sites in the U.S. and Canada.[7] The trial was a 12 month, randomized, double blinded study, testing coenzyme Q10 and GPI-1485. Participants were randomized to one of three arms: active CoQ10 and placebo GPI-1485, active GPI-1485 and placebo CoQ10, or placebo for both agents. The clinical trial and this substudy were approved by the University of Rochester Research Subjects Review Board and the Institutional Review Boards of each participating site. Subjects provided written informed consent to participate in this sub-study on comprehension.

Outcomes

The primary outcome measure was a 30 item multiple-choice, patient completed questionnaire given at the final clinical trial visit. Here we report items assessing satisfaction with the study experience and comprehension of key study elements. The questionnaire was modeled on similar instruments found in the literature and on an instrument developed to assess the quality of informed consent in an oncology clinical trial (Personal communication, E. Emanuel). Pilot testing and face validity assessment were conducted using five individuals with PD not enrolled in the study. The instrument was approved by the clinical investigators conducting the clinical trial, the trial Data Safety Monitoring Board, and each site's Institutional Review Board (IRB). Six sites did not participate due to inability to get timely IRB approval. Compliance was the percentage of study drug taken at each study visit. Cognitive function, at baseline, was measured with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[8] and PD severity by the Unified Parkinson's Disease Rating Scale (UPDRS).[9]

Statistical Considerations

The total sample size was fixed by the number of patients in the clinical trial and number of sites willing to participate in the substudy. With 80% subject participation in this substudy, we would be able to construct 95% confidence intervals of approximately 8% width or smaller for a range of observed proportions (0-100%) of participants giving a response to an individual question. The comprehension score was calculated by summing the total number of correctly answered comprehension items and could range from 0 to 9. Relationships between continuous

variables were assessed with Spearman correlation coefficients. The chi-square test was used for dichotomous variables and the Kruskal Wallis-Test for ordinal variables.

Results

Of 192 eligible participants, 149 (78%) completed the questionnaire. Responders were similar to non-responders on all demographic and baseline disease measures other than race (Table 1). The study investigator was the regular provider of PD care for 58% of respondents.

Comprehension

Table 2 summarizes the response distributions and frequency of correct responses for each of the 9 comprehension questions. The median comprehension score was 7 out of a possible 9 correct. On 6 of 9 questions, the correct answer was given by 90% or more of the respondents, on topics that included the purpose of study, random allocation of treatment, experimental nature of drugs, voluntary participation, and expected effect on their PD. On the placebo question (Q8), 67% correctly stated that they had had a 1/3 chance of having received a placebo, but another 28% stated a higher chance of having received a placebo. On question 1, 42.3% reported that participating in the clinical trial was part of the “usual treatment” for their PD and 47.6% (Q4) of subjects reported being informed that there were “...no risks to this study greater than my usual medical care”.

Comprehension was not correlated with age, gender, PD severity, or satisfaction, but did correlate with years of education ($r=0.30$; $p<0.01$) and cognitive function on the RBANS ($r=0.18$; $p=0.03$). The response to Q1 on “usual treatment” was not associated with whether the study investigator was the subject's regular provider.

Compliance and Satisfaction

Mean compliance as assessed by tablet count was 93.7%. There was no correlation between comprehension and compliance ($r=-0.06$). Ninety-seven percent of subjects were moderately or very satisfied with their overall experience. Ninety-five percent of subjects reported that they received all the information they wanted and were most likely to ask the study coordinator or investigator if they had questions rather than outside sources. Less than 5% of participants reported feeling pressure from any source to join or stay in the clinical trial.

Discussion

Overall, the majority of these early Parkinson's participants understood the key aspects of the study, including random allocation and the chance of receiving placebo. Compliance with study drug and satisfaction with the study experience were very high. This may have contributed to the lack of an observed relationship between comprehension and compliance with satisfaction. Years of education and cognitive function were correlated with comprehension, consistent with studies conducted near the time of consent to participate.[2]

The high level of appreciation of randomization and the chance of receiving placebo is unusual in informed consent studies[1] and may reflect the level of education of participants. While high education levels are common among subjects in PD studies, this finding also suggests that subjects may have learned more about the study during participation.

The most striking finding was the discrepancy between the excellent performance on 7 of 9 comprehension items versus performance on the remaining 2 items that asked about the differences between research and routine care and the understanding of risks (Q1 and Q4, Table 2). One explanation is that the poor performance on the two questions shows that the respondents were exhibiting therapeutic misconception (TM), conflating research and

treatment, or grossly underestimating risks of harm.[10,11] This interpretation raises the interesting question of why the rate of apparent TM is so low in the other 7 questions, some of which were also probes for TM. For example, the phrasing of the placebo question (Q8) specifically allowed testing of the respondents' ability to appreciate how the design of the study might have affected them, not merely to factually understand, the chance of having received a placebo. But only 5% denied the possibility of having received a placebo and 95% of subjects responded that they had a 1/3 or greater chance of receiving placebo.

Another interpretation of poorer performance on Q1 and Q4 is that it reflects the difficulty of operationalizing probes for TM. The phrase “usual treatment” may have been interpreted as describing common medical practices involved in PD treatment, such as taking oral medications. Subjects' perceptions of risk may have been shaped by actual experience in a trial that involved generally safe, well-tolerated agents, and by the respondents' reading of the response option “no risks to this study greater than my usual medical care.” This interpretation is supported by the fact that the responses to questions 1 and 4 were not correlated with whether or not the study investigator was the subjects' usual treating neurologist. This factor should have strongly correlated with subjects' responses if the problem were TM, since one of the main triggers for TM is thought to be one's own doctor acting as a researcher, [12] which is often the case in many PD clinical trials.

The overall findings of this study are encouraging, showing generally good understanding of study information after 12 months of participation among early PD subjects. This may suggest that rather than deterioration of comprehension over time as has been observed in some clinical settings, research participants may retain or even improve comprehension through participation. However, less educated and mildly cognitively impaired PD participants may be at risk for poorer comprehension of study information. This is of particular concern in PD since cognitive function declines over time. The cross sectional designs of the study limits our ability to assess whether comprehension changed over time or was shaped by experience in the study. Future studies in PD should follow subjects longitudinally to assess changes in comprehension and further explore the effects of progression and cognitive decline. This will help to inform procedures for maintaining informed consent in long-term observational studies and clinical trials in PD.

The apparent incongruity in the responses may in fact also be an important finding, raising key questions for future research on informed consent in PD. Although the explanation could be that TM occurred, there are countervailing reasons to doubt this as the definitive interpretation. An alternative interpretation is that what the respondents mean and what researchers mean by phrases such as “usual treatment” and “usual medical care” may be a source of unexpected ambiguity for less educated or mildly impaired laypersons. The closed-end format of the questions limits our ability to assess how the respondents understood the questions, especially given the somewhat inconsistent nature of the responses. In future research on informed consent in PD, it will be important to keep this possibility in mind, by adding a qualitative interview component to probe the answers of the respondents.

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Table 1

Baseline Characteristics and Compliance of Responders and Non Responders

Variable	Non-responders N=43 (22.4%)	Responders N=149 (77.6%)
Male, No (%)	29 (67.4%)	98 (65.8%)
Caucasian, No (%)	34 (79.1%)	143 (96.0%)*
Age, y (sd)	60.6 (11.4)	61.4 (10.0)
Education, y (sd)	15.1 (3.1)	15.3 (3.3)
Total UPDRS (sd)	21.8 (8.2)	22.2 (9.4)
Hoehn & Yahr (sd)	1.42 (0.54)	1.47 (0.53)
GDS (sd)	1.98 (2.6)	1.83 (2.2)
RBANS (sd)	96.9 (14.7)	99.3 (15.6)
Percentage of Study Drug Taken assessed by Pill Count (sd)	88.8% (20.9)	93.7% (10.8)

*
p<0.01

GDS: Geriatric Depression Scale

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status

UPDRS: Unified Parkinson's Disease Rating Scale

Table 2

Understanding of Study Information

Question	Proportion Correct (95% C.I.)	Response Options (correct in <i>italics</i>)
1. Did you view participating in this study as part of the usual treatment for your Parkinson's disease?	0.574 (0.494, 0.659)	a) Yes b) <i>No</i>
2. As a participant in the study you were asked to ...	0.993 (0.963, 1.00) *	a) <i>Come to all planned visits</i> b) Come to visits only if problems existed c) Come to some of the visits
3. What was the main purpose of the study that you participated in?	0.926 (0.871, 0.962) *	a) To understand the causes of Parkinson's disease b) To provide better treatment than you could get outside the study c) <i>To find out if the study drugs might help Parkinson's disease</i>
4. What did the study team tell you were the most likely source of risk or harm?	0.463 (0.377, 0.543)	a) There were no risks to this study greater than my usual medical care b) The study tests, like having blood drawn and examinations c) <i>The Coenzyme Q10 and GPI 1485</i> d) The placebo (sugar pill)
5. When you started in this study what did the study team tell you was going to happen to your Parkinson's disease?	0.933 (0.880, 0.967) *	a) Get better b) Get worse c) Stay the same d) <i>Any of the above could happen</i>
6. Given that the study results are not known yet, how would you describe Coenzyme Q10 and GPI 1485?	0.899 (0.839, 0.943) *	a) The best drugs for Parkinson's disease b) <i>Experimental drugs for Parkinson's disease</i> c) Routine drugs for Parkinson's disease
7. Based on the information the study team told you, how do you think the study team decided who was going to get the different study drugs (Coenzyme Q10, GPI 1485, or placebo)?	0.906 (0.847, 0.948) *	a) What they think is best for each patient b) What each patient wants c) <i>A method like pulling numbers out of a hat</i> d) It depends on who the study team likes best

Question	Proportion Correct (95% C.I.)	Response Options (correct in italics)
8. The study team told you that you could take either placebo, Coenzyme Q10, or GPI-1485. Based on this information, how likely do you think it is that you took placebo (sugar pill) in this study?	0.671 (0.590, 0.746) *	a) Certain that I took placebo b) 2 in 3 chance that I took placebo c) <i>1 in 3 chance that I took placebo</i> d) No chance that I took placebo
9. Were you free to refuse to participate in this study?	0.987 (0.952, 0.998) *	a) <i>Yes</i> b) No

*
p<0.0001 for test of equal proportions