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TESTING OBJECTIVE MEASURES OF MOTOR IMPAIRMENT IN EARLY PARKINSON'S DISEASE: FEASIBILITY STUDY OF AN AT-HOME TESTING DEVICE

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Abstract

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The authors have complied with the journal's policy on ghost writing.

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We tested the feasibility of a computer based at-home testing device (AHTD) in early-stage, unmedicated Parkinson's disease (PD) patients over 6 months. We measured compliance, technical reliability, and patient satisfaction to weekly assessments of tremor, small and large muscle bradykinesia, speech, reaction/movement times, and complex motor control. relative to the UPDRS motor score. The AHTD is a 6.5 x 10 computerized assessment battery. Data are stored on a USB memory stick and sent by internet to a central data repository as encrypted data packets. Although not designed or powered to measure change, the study collected data to observe patterns relative to UPDRS motor scores. Fifty-two PD patients enrolled, and 50 completed the six month trial, 48 remaining without medication. Patients complied with 90.6% of weekly 30-minute assessments, and 98.5% of data packets were successfully transmitted and decrypted. On a 100-point scale, patient satisfaction with the program at study end was 87.2 (range 80–100). UPDRS motor scores significantly worsened over 6 months, and trends for worsening over time occurred for alternating finger taps (p=.08), tremor (p=.06) and speech (p=.11). Change in tremor was a significant predictor of change in UPDRS (p=0.047) and was detected in the first month of the study. This new computer-based technology offers a feasible format for assessing PD-related impairment from home. The high patient compliance and satisfaction suggest the feasibility of its incorporation into larger clinical trials, especially when travel is difficult and early changes or frequent data collection are considered important to document.

Introduction

Because many treatment trials in Parkinson's disease (PD) are primarily aimed at intervening in the early phases of disease[1], appropriate measurement tools that can be applied frequently at short intervals and be performed outside the physician's office would allow detection of effects without clinic visits. The gold standard of rating scales for Parkinson's disease is the Unified Parkinson's Disease Rating Scale (UPDRS), but it covers the gamut of disability levels and does not specifically focus on early impairments.[2,3] Further, most long-term clinical trials assess UPDRS scores at baseline and at three-month intervals, precluding detection of change on a weekly or monthly basis.[1] We developed a series of motor tasks that can be performed weekly with a home-based computer module, termed the At-Home Testing Device (AHTD). As a feasibility study, we determined whether recruited patients would comply with the unsupervised testing over six months and whether data could be electronically stored and then transmitted to a central computer bank. We hypothesized that patients would find this assessment technology easy to use and would be committed to the program throughout its duration. Further, we hypothesized that data could be successfully transmitted electronically. The long-term goal of the program is to develop measures that will detect change in function at home and at an earlier time than three month office visits in typical study protocols. To this end, although the current feasibility study was not envisioned nor designed with a sufficient sample size to test the efficacy of the technology to detect small changes, we monitored the test results as a mean monthly change to compare them with changes in office-based UPDRS scores at 3 and 6 months. If a home-based motor testing program is feasible and if the data correlate with UPDRS changes, the AHTD-based outcomes could be utilized in clinical trials, expanding recruitment possibilities to include patients who otherwise might not be able to participate because of work obligations and travel limitations.

Methods

Program organization

An organization meeting, sponsored by the Kinetics Foundation (Los Altos, CA, USA) assembled movement disorder specialists. Tests were prioritized if they were safe and amenable for self-administration by patients, if they could be quickly and frequently performed, if the physical testing apparatus could be incorporated into a box no larger than a portable computer, and if they generated data that could be stored and transmitted electronically and securely to a central data bank. Tests related to tremor, bradykinesia, rigidity, gait and balance, cognition and speech were considered. After discussion and review, rigidity and gait were considered outside the currently available technological and safety limitations of the program and therefore rejected. Selected domains and tasks were: tremor, assessed by a wrist accelerometer worn two full days weekly;[4] bradykinesia, assessed by alternating finger tapping (digitography) and hand tapping;[5] complex motor function, assessed by pegboard plugging; movement time and reaction time;[7] and speech, assessed by vocal intensity decay and several other voice measures.[8] Based on these recommendations, Intel Corporation developed the computer-based AHTD which was tested in healthy subjects and then PD subjects with focus group patient feedback. The planned assessment was designed so that patients with early PD performed all tests weekly in an automatically cued order. The program was designed to take a total of no more than 30 minutes for testing: pegboard 4 min, hand tapping 3 min, reaction/movement times 3 min, finger tapping 4 min, speech 4 minutes, tremor accelerometer downloading 7 min, and data storage/transmission 5 minutes.

Protocol

The study entry criteria were patients with early PD, defined by diagnosis within 5 years, and having at least two of following: rest tremor, bradykinesia and rigidity without evidence of other forms of parkinsonism. All patients were Hoehn and Yahr Stages I or II. Additionally, the patients could not be on symptomatic therapies for PD and by best estimates could remain untreated during the study period of six months. Plans allowed for full training on the AHTD through in-office practice sessions, and only patients who successfully completed training were enrolled. Prior computer experience and special electronic equipment at home were not part of the inclusion criteria.

After signing informed consent, patients were screened for eligibility, and those meeting criteria were trained to use the AHTD. The time needed for confident AHTD operation, test taking, data storage and data transfer was recorded. A UPDRS motor score was obtained at the baseline visit. Patients selected a day and time of the week to perform their testing, and this time was programmed into each AHTD with a reminder alarm. An ongoing check of data arrival allowed patients who were near to missing their two day window each week to be contacted by the study staff. If any problems or questions developed, patients had access to the study staff with backup support from Intel. Patients returned to their physician at 3 months and 6 months when in-office AHTD and UPDRS motor testing was again performed. Satisfaction questionnaires, based on a visual analog scale of 0 to 100, with 0

representing complete dissatisfaction and 100 representing complete satisfaction, were given at the end of training, after three months, and at trial end.

AHTD

The AHTD is a self-contained testing apparatus that measures 10 inches x 6 inches by 2 inches and weighs 10.2 pounds (Figure 1). The device opens with the testing panel on a base that contains a two-key keyboard for finger tapping, two buttons placed 173mm apart for reaction time/movement time and repetitive hand tapping assessments, an eight-peg pegboard, control buttons, and a docking station for the actiwatch device (Cambridge Neurotechnology LTD, Cambridge, UK) measuring tremor. The upper panel contains a LCD screen for displaying instructions and examples of testing requirements as well as a speaker for audio. The device also has a microphone port for voice recording and a data storage USB port. Patients had no access to their prior scores when performing their test battery.

Outcome measures

The clinical trial on feasibility tested the following indices: duration of time for training patients to use the AHTD confidently, compliance in terms of the number of completed testing sessions and their timeliness within a two-day weekly window, ease of use, program satisfaction, success of data transfer and success of data decryption.

Although the study was not envisioned or powered to assess the efficacy of the selected tests, we explored change patterns using several measures. Because the limited sample size in comparison to the number of testing sessions decreased our statistical power, we calculated the monthly average score for each test and conducted a repeated measures analysis of variance on the average scores to determine if the change over time was significantly different from zero. Tremor score was based on a randomly selected 48 hours from the weekly sample and was computed from tremor amplitude (counts) and tremor duration (sec) using the formula: Average Duration % x Average Intensity $^{1/4}$ = Average Score; for digitography (finger tapping), we examined key stroke velocity (mm/s) for the right and left hands, predominantly affected side (as determined by laterality items on the UPDRS Part III), under conditions of normal auditory feedback of key stroke and auditory feedback masked by white noise; for hand tapping movements, we examined the cycle time between successive button presses on right, left, and predominantly affected sides; for pegboard plugging, we measured average time required to complete each peg movement; reaction and movement times were averaged from single movements that followed an auditory cue on right, left, and predominantly affected side; for speech, we measured decay of normal intensity phonation for maximally sustained “Ah” phonation, decay of loud intensity phonation for maximally sustained “Ah”, and intensity decays for descriptions of standardized pictures with and without finger tapping motor distraction.

Data analysis

Subject demographic data were examined by descriptive summary. Feasibility was assessed by summarizing patient compliance measures, measures of patient satisfaction and success of data transfer/decryption. Examination of change in the outcome measures was assessed

using a repeated measures ANOVA design. Huynh-Feldt adjustments to the degrees of freedom were used when assumptions of heterogeneity of variance were not met. Relative contribution of each outcome measure to change in UPDRS motor examination score was assessed using a linear regression model. Relative contribution of individual tests to the regression model was assessed by examination of the standardized regression coefficients for each test. Significance for all assessments was set at $p < 0.05$.

Results

Patient group

52 PD patients fit screening criteria, entered and successfully completed training, and were enrolled in the program. The 20 women and 32 men had a mean age of 63.8 yrs (SD 8.9) with a mean PD duration of 75.4 weeks (SD 68.1). The mean UPDRS motor score at baseline enrollment was 19.5 (SD 7.7). The mean MMSE was 29.5 (SD 0.87). The training period lasted a median duration of one visit (range 1 – 5 visits).

During the six month trial, two patients terminated prematurely within the first six weeks, one because of a motor vehicle accident with a fracture that precluded participation and the other without specific explanation. These two cases were not considered in the analysis. Two of the remaining 50 started dopaminergic medication during the study because of clinical decline, but remained enrolled in the feasibility study. For the efficacy exploratory analysis, their last data point on no medication was considered a final visit and that value was brought forward for statistical analysis for the rest of the study.

Feasibility analysis

The training was well-received by patients with a mean overall satisfaction score (based on 100=full satisfaction) 96.5 (range 91–100) (Table 1). Patients were most satisfied with training for use of the device, and least satisfied with ease of data transmission. There were no serious adverse events during the study, although 5 mild and 9 moderate adverse events occurred, one related to the study from a wrist rash related to the tremor recorder band. At the end of the study, patient satisfaction remained high with a mean overall satisfaction score of 87.2 (range 80–100).

Patient compliance met the pre-specified criterion of acceptability (<10%) with 9.4% of tests missed. The other compliance criterion, fewer than 10% out-of-window testing sessions, was also met (4.9% of tests were performed late). Transmission and decryption failures met the pre-specified criterion of acceptability (5%) with only 1.5% of sessions having problems. Total problem rates (subject non-compliance + storage difficulties + electronic transfer problems + decryption errors) varied by task with pegboard being the most successful with only 9.3% failures. The highest total problem rates occurred with hand tapping (21%), tremor (20%), and finger tapping (15.4%). The latter two tasks were revamped in the mid-phase of the study to correct identified technical difficulties and afterwards, their task specific total problem rates were 8.7% (tremor) and 10.5% (finger tapping).

UPDRS changes

Patients declined in overall motor function over six months (p=0.009), with an increased mean UPDRS motor change score of 2.45 (SD 5.34) from baseline to 3 months which was maintained but not further increased (mean change from three to six months -0.12 (SD 6.60).

AHTD changes

Mean monthly scores on the different primary outcomes showed worsening tremor (p=0.06), finger tapping (p=0.08) and speech (p=0.11). Change in tremor was a significant predictor of change in UPDRS (p=0.047) and was detected in the first month of the study (p =0.018). Most measures remained stable over the trial, although there was a significant improvement in reaction time (p=0.001) (Table 2).

Discussion

Research and education efforts have focused on understanding and overcoming barriers to patient participation in clinical trials across many diseases.[9,10] Clearly identified factors that negatively impact on patient interest are frequent office visits and distant travel.[11] Among 100 patients who appeared to qualify for various study protocols in one of our participating centers, 50 declined specifically because of these two reasons, and 38 of these were patients with early PD who were still employed (personal communication, CG Goetz). Developing methods to allow patients to participate in research and provide data without taking time off from work for travel and appointments offers the possibility of participation for patients who are currently unable to do so. For this reason, we developed the AHTD and focused on feasibility of this new methodology both in terms of patient perceptions and machine technology.

We found the AHTD highly feasible in terms of patient compliance, satisfaction and ease of use. Patients maintained their involvement with the program over six months, and several requested a continuation of the program at study end. We were initially concerned that patients would find the testing process tedious for weekly participation, but the satisfaction ratings did not support this concern. The computer-based technology guided the test-taking smoothly, and data storage/transmission errors were below predicted rates. We encountered more problems with the finger tapping and tremor devices in comparison with the other tasks, but in mid-study, technical correction was achieved. Because the training period was short and the testing was self-administered without direct investigator involvement, we consider that this type of machinery can be incorporated into patient studies with efficiency.

Whereas our primary aim was to test feasibility, we nonetheless used the experience to document changes over time in patient performance in the seven tasks with multiple exploratory outcome analyses. Most tests did not detect change, suggesting that not all the tools utilized may be ideally suited for documenting clinical decline over six months in early PD. In fact, motor functions required for the selected tests may not deteriorate in early PD. In the context that the UPDRS motor exam worsened, especially in the first three months, most of these tests did not appear to be better proxies of progressive parkinsonism. Tremor change by our actigraph measure, however, was significantly correlated with change in

UPDRS, and change with the AHTD detected differences even within the first month of testing. Detection of subtle and early changes that predate but correlate with worsening UPDRS scores is our long-term goal. Because of the exploratory nature of the analysis, we examined multiple indices for some tests, examining right vs. left function and predominant parkinsonian side as well as testing tasks with and without distraction. No test detected a statistically significant decline, although finger taps, tremor, and the speech task involving picture description without distraction showed decline over time. For further development of the AHTD, we plan to retain at least these three items.

An unexpected finding was a progressive improvement in reaction time. The improvement suggests at least the possibility that learning or practice effects occurred with the testing program, raising the question of whether frequent testing of this type may be a form of exercise and cognitive therapy. The overall stability of the testing scores in spite of declines on the UPDRS could represent evidence of a therapeutic intervention. We did not have a group that did not participate in weekly testing to examine their scores on the same tests performed only at 3 months and 6 months. If patients in such a group declined, this evidence would support the learning or practice effect induced by the AHTD when used weekly. In line with the concept of the AHTD as a therapeutic tool, we did not allow patients to see their prior scores at the time they took each weekly test. Depending on the goals of a given study, a potential modification could include providing feedback to patients to encourage maximal effort and the maintenance or improvement in function over prior scores.

Other strategies are being tested for at-home acquisition of data in PD.[12] Some of the current authors (CGG and GTS) have experience with the use of a modified UPDRS that can be performed by a patient and caregiver at home and self-videotaped. This technique allowed for monitoring of parkinsonism, dyskinesia, and fluctuation status (ON/OFF).[13] The AHTD gathers information on overall behavior, and we have not tested the impact of motor fluctuations or dyskinesias on outcome measures. At this point, one technique cannot be favored over the other and, in our view, both deserve further study. In both cases, however, patient interest and compliance were high, demonstrating the feasibility of data collections systems in the home environment.

For our statistical approach, we used all weekly data, but calculated the mean of four weeks so as to reduce the degrees of freedom in the analysis. Given this necessity and the concern over practice effects, we suggest that monthly data collections may be more valuable. The weekly routine, however, was clearly feasible, and a reduced frequency of tests poses the risk that patients may forget to take the test or forget how to use the device. The presence of an automatic alarm facilitates reminding, and patients reported that this type of amendment would be easy to effect.

The cost of such machines and the infrastructural support to maintain them is difficult to estimate from a pilot study. However, the NIH has indicated strong support for the concept of “large simple studies” that allow patients to be enrolled from wide geographical areas and to travel minimally.[14] This pilot study is a “proof of concept” and establishes patient and technical feasibility. If future work detects a panel of tests that registers declining function and correlates or even pre-dates changes in UPDRS scores recorded at more interspersed

office visits, direct incorporation into clinical trials can be actively considered. Having established feasibility of the AHTD, we plan further studies to determine the sensitivity of tests to detect changes in motor function with an interest in developing tests for other domains such as cognitive and gait impairments.

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Figure 1.
Photograph of the AHTD (see text for details).

Table 1

Feasibility Outcomes

Satisfaction with Training (out of 100)	
Overall Satisfaction	96.5 (range 91 – 100)
Satisfaction with Instructions	98 (range 90 – 100)
Satisfaction with Practice	95 (range 92 – 100)
Satisfaction with Practice time	94.3 (range 89 – 100)
Satisfaction with Data Transmission	84.4 (range 81 – 100)
Satisfaction at End of Study	87.2 (range 80 – 100)
Data Transmission/Decryption	
Failed Transmissions/decryptions	1.5%
Patient Compliance	
Failed to take test at all	9.4%
Out of window for exam date	4.9%
Cumulative missing data by test	
Digitography (finger tapping)	15.4%
Reaction Time/Movement Time	7.8%
Pegboard Plugging	9.3%
Tapping	21.2%
Tremor	20.0%
Voice (sustained phonation)	13.5%
Voice (picture description)	9.6%

Table 2

Summary of Efficacy Outcomes

Test	All Subjects (n=50)
Keys no distraction left	Trend (p = .08)[1]
Keys no distraction right	NS
Keys predominant side no distraction	NS
Keys with distraction left	NS
Keys with distraction right	NS
Keys predominant side with distraction	NS
Movement time left	NS
Movement time right	NS
Movement time predominant side	NS
Pegboard	NS
RT left	Significant (p < .001)[2]
RT right	Significant (p < .001)[2]
RT predominant side	Significant (p < .001)[2]
Tapping left	NS
Tapping right	NS
Tapping predominant Side	NS
Tremor	Trend (p = .06)[1]
Regular speech loudness “Ah”	NS
Increased speech loudness “Ah”	NS
Speech picture description no distraction	Trend (p = .11)[1]
Speech picture description with distraction	NS

[1] Change over time represents increased impairment (worsening)

[2] Change over time represents decreased impairment (improvement)