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Greater improvement in quality of life following unilateral deep brain stimulation surgery in the globus pallidus as compared to the subthalamic nucleus

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Abstract

While deep brain stimulation (DBS) surgery is a well-accepted treatment for Parkinson disease (PD) that improves overall quality of life (QoL), its effects across different domains of QoL are unclear. The study reported here directly compared the effects of unilateral DBS in subthalamic nucleus (STN) or globus pallidus (GPi) on QoL in 42 non-demented patients with medication-refractory PD. Patients were enrolled in the COMPARE trial, a randomized clinical trial of cognitive and mood effects of STN versus GPi DBS conducted at the University of Florida Movement Disorders Center. Patients underwent motor, mood, verbal fluency and QoL (Parkinson disease questionnaire: PDQ-39) measures before and 6 months following surgery. Groups experienced motor and mood improvements that did not differ by target. Patients with STN DBS evidenced a slight decrement on letter fluency. On average, all patients endorsed better *overall* QoL after surgery. However, despite similar motor and mood improvements, GPi patients improved more than STN patients (38 vs. 14%, respectively; $P = 0.03$). Patients reported better QoL on subscales of mobility, activities of daily living (ADLs), emotional well-being, stigma, cognition and discomfort, but not on those of social support and communication. Improvements on the mobility, ADLs, stigma and social support subscales were greater amongst GPi patients. In regression analyses, only depression changes independently predicted changes in overall QoL as well as emotional well-being and social support changes. Within the STN group only, declining category fluency scores correlated with poorer QoL on the communication subscale. Unilateral DBS in both STN and GPi improved QoL overall and in disparate domains 6 months after surgery. Patients receiving GPi DBS reported greater improvements that cannot be explained by differential mood or motor effects; however, verbal fluency changes may have partially contributed to lesser QoL improvements amongst STN patients.

Keywords

Cognition; Deep brain stimulation; Depression; Parkinson disease; Quality of life

Introduction

Deep brain stimulation (DBS) surgery is a well-accepted treatment for medication-refractory Parkinson's disease (PD) [18,26]. In addition to improving cardinal motor symptoms of PD, DBS surgery reduces burdensome complications accompanying dopaminergic therapies (e.g. motor fluctuations, dyskinesias) [18]. However, non-motor features of PD also impact quality of life (QoL), even moreso than motor dysfunction for many patients [7]. The effects of DBS on non-motor symptoms (i.e. cognition, psychological functioning) are variable [12,19,28].

Currently, the impact of DBS on QoL is most frequently assessed using the summary index from the PD QoL questionnaire (PDQ-39). This has resulted in some debate regarding both the magnitude of improvement as well as the generalizability across different QoL domains [8,15]. Most studies have focused on the effects of bilateral DBS targeting the subthalamic nucleus (STN) and have reported *overall* improvement ranging from 14 to 62% [4–6,29]. Although there have been fewer studies, bilateral DBS targeting the globus pallidus internus (GPi) appears to improve overall QoL to a comparable extent [22].

While DBS improves *overall* QoL, it is unclear which domains of functioning are most influenced [i.e. mobility, activities of daily living (ADLs), emotional and social well-being, cognition, communication, disability, stigma, bodily discomfort]. Improvements, no differences, and even decrements in particular areas have been reported by different investigators [4,13,15,22]. For example, DBS may exert a positive effect on physical markers of QoL but not on psychosocial or cognitive aspects [6,23].

The present article sought to directly compare, for the first time, the effects of unilateral DBS in the STN or GPi on various domains of QoL. Patients were randomized to receive either STN or GPi DBS, and QoL data were collected before and 6 months after surgery with the PDQ-39.

Methods

Participants

The COMPARE trial (*Co*gnition and *M*ood in *Par*kinson Dis*e*ase in STN versus GPi DBS; see http://clinicaltrials.gov.,registration no. NCT00360009) is a National Institutes of Health-funded, randomized trial of unilateral STN versus GPi DBS conducted at the Movement Disorders Center (MDC) at the University of Florida. All patients were diagnosed with idiopathic PD, as established using extensive neurological screening by fellowship-trained movement disorder specialists using UK Brain Bank criteria [9]. Patients evidencing dementia [i.e. a score on the Dementia Rating Scale-2 (DRS-2; [14]) <130] were excluded. A detailed description of the study protocol is available elsewhere [16]. COMPARE was specifically designed to examine mood and cognition; however, PDQ-39 outcomes were also collected. The study complied with guidelines outlined by the Declaration of Helsinki and was approved by the local institutional review board prior to its initiation. All patients signed informed consent before participating.

Of the 42 patients described in this report, 22 underwent DBS in the GPi, and 20 underwent DBS in the STN. The only inclusion criterion used to compose this subset of the larger COMPARE trial was having completed the PDQ-39 both at baseline and 6 months after surgery. Of the three patients who completed the COMPARE protocol but for whom baseline and/or follow-up PDQ-39 data were unavailable, one had received GPi DBS and two had received STN DBS. Demographic and disease characteristics of the present patient sample are presented in Table 1.

Procedures

Patients completed cognitive and psychosocial measures at two time points: (1) prior to receiving surgery (baseline visit) and (2) during a research visit 6 months after implantation (post-surgical visit). During the baseline visit, patients completed all measures in the on-medication state. During the post-surgical research visit, patients completed psychosocial measures in the on-medication, on-stimulation state. Alternate forms of cognitive measures were administered to patients off medications in four separate stimulation states: optimal, ventral, dorsal, and off stimulation. Only results from cognitive assessments during optimal DBS stimulation (i.e. off medication, on stimulation) were examined in this study. A significance level of $P = 0.05$ was used to determine statistically significant results.

Quality of life assessment

Quality of life was assessed using the PDQ-39, which is a 39-item, patient-report survey of common problems experienced by patients with PD [21]. Respondents report how often in the past month they have encountered each problem using a 5-point Likert-type scale ranging from *Never* to *Always* or *Cannot Do*. Factor analysis has identified eight discrete

domains: mobility, ADLs, emotional well-being, stigma, social support, cognition, communication and bodily discomfort. Scores from each domain are computed into a scale ranging from 0 to 100, with lower scores indicating fewer problems and better QoL. The PDQ-39 has been extensively studied and shown to be appropriately reliable, valid and sensitive to change. Higher order factor analysis of the dimension scores supported a PDQ-39 summary index score (PDQ-SI) as an index of overall QoL and is computed by summing the eight domain scores and standardizing the score on a 0–100 scale [10].

Mood and cognitive measures

Depression severity was assessed using the Beck Depression Inventory, 2nd edition (BDI-II; [3]). Verbal fluency was assessed using alternate forms of both letter and semantic fluency [16]. In each task, patients were given 1 min to generate words beginning with a particular letter (e.g. “F”) or belonging to a particular semantic category (e.g. “animals”).

Results

Group characteristics

Demographics, disease and cognitive characteristics for the STN and GPi groups are displayed in Table 1. A series of independent samples *t* tests revealed no significant differences between groups on these measures.

Surgical outcome

To localize implanted leads, high-resolution computed tomography (CT) scans were acquired 1 month after implantation and then fused to pre-operative, high-resolution magnetic resonance imaging (MRI) scans. Locations were ascertained using the mid-commissural point (MCP)-based (*x*, *y*, *z*) coordinates of the center of the ventral aspect of the deepest contact, as fully described elsewhere [16]. Optimal contacts were chosen based on motor responses obtained in the clinic. Coordinates of the center of the active contact (cathode) are displayed in Table 2.

As shown in Table 3, a two-way analysis of variance (ANOVA) revealed that both groups benefited from surgery, as defined by improvement from pre-surgical Unified Parkinson Disease Rating Scale (UPDRS-III) scores off medication to post-surgical UPDRS-III scores off medication, on stimulation ($P < 0.001$). On average, the STN and GPi groups exhibited 26 and 28% improvement, respectively. The amount of improvement did not differ by target ($P = 0.98$). Post-surgical UPDRS-III scores obtained on medication, on stimulation were similar to the pre-surgical scores obtained on medication ($P = 0.57$). Mean levodopa equivalent dose (LED) did not change significantly following surgery ($P = 0.61$), and mean changes did not vary by target ($P = 0.52$). Scores on the BDI-II improved after surgery ($P < 0.001$), and there was no target-by-time interaction ($P = 0.27$). There was no main effect of time on either verbal fluency measure; however, there was a target-by-time interaction for letter fluency ($P = 0.034$). Follow-up comparisons revealed that, on average, STN patients produced 5.7 fewer words at post-surgical testing than before surgery ($P = 0.01$). It should be noted that this level of significance did not reach pre-defined criteria [16].

Quality of life changes

Table 4 presents the mean PDQ-39 scores before and after surgery for each group. To assess overall QoL change, we performed a two-way analysis of covariance (ANCOVA; target × time) in which the dependent variable was PDQ-SI. The results of this ANCOVA are shown in Table 5. Because the groups differed on the PDQ-39 stigma subscale at baseline, this was included as a covariate after confirming that the assumption of homogeneity of regression slopes had not been broken. A main effect of time indicated that regardless of surgical

target, patients experienced improved overall QoL ($P = 0.016$). There was also a significant target-by-time interaction ($P = 0.032$), as depicted in Fig. 1, which indicated that while the STN and GPi groups did not differ in PDQ-SI scores at baseline, GPi patients had significantly lower PDQ-SI scores than STN patients 6 months after surgery. Furthermore, while STN patients exhibited a 14.6% reduction in PDQ-SI that was not significant ($P = 0.062$), GPi patients exhibited a significant 38.1% average reduction ($P < 0.001$). A main effect of target ($P = 0.003$) was produced by inclusion of the covariate.

To examine the influence of DBS on individual QoL domains, we conducted a two-way multivariate analysis of variance (MANOVA; target × time) comprising the eight PDQ-39 subscales. Multivariate analysis identified a main effect of time [F (33, 8) = 7.76; $P < 0.001$; $\eta_p^2 = 0.65$] such that QoL improved following surgery. A target-by-time interaction did not reach significance [F (33, 8) = 2.14; $P = 0.06$; $\eta_p^2 = 0.34$]. Univariate analyses, shown in Table 6, were examined to clarify effects. Significant main effects of time were identified for six of the eight domains (mobility, ADLs, emotional well-being, stigma, cognition and discomfort), but not for social support and communication. Regardless of surgical target, patients endorsed fewer QoL problems on these six subscales following surgery (see Table 4).

Significant target-by-time interactions were identified for mobility, ADLs, stigma and social support, but not for emotional well-being, cognition, communication, or discomfort. The decomposition of these interactions revealed the following: (1) at baseline, STN and GPi groups did not differ on any subscales except stigma; (2) following surgery, the STN and GPI groups did not differ on any of these subscales except for ADLs, on which the GPi group endorsed fewer problems than the STN group ($P = 0.050$); (3) in terms of pre- to post-surgery DBS changes, the average scores obtained by GPi patients improved significantly on all four subscales: mobility ($P < 0.001$), ADLs ($P = 0.001$), stigma ($P < 0.001$) and social support ($P = 0.007$). In contrast, only scores on the stigma subscale improved following DBS in the STN group ($P = 0.050$).

Variables related to QoL changes

A final set of analyses was conducted to identify the relative contributions of certain variables to QoL changes. A total of nine multiple regression models, one for PDQ-SI and one for each PDQ-39 domain, were performed. Standardized residual change scores on the measure of interest served as the dependent variables, while target (GPI vs. STN), motor change (post- surgery UPDRS-III off medication, on stimulation—pre-surgery UPDRS-III off medication), depression change (post-surgery BDI-II—pre-surgery BDI-II) and combined change in raw scores on both animal and letter fluency [post-surgery (animals + letters off medication, on stimulation)–pre-surgery (animals + letters on medication)] were entered as independent variables. Standardized residual change scores were chosen for dependent variables because they are statistically independent of initial levels and control for test–retest effects and individual variability.

While this model significantly predicted *overall* QoL change ($R^2 = 0.246$; $P = 0.034$), it only reached significance for individual domains of emotional well-being ($R^2 = 0.282$; $P = 0.016$) and social support ($R^2 = 0.293$; $P = 0.012$). In each of these models, only BDI-II change emerged as a significant independent predictor of overall QoL ($\beta = 0.315$; $P = 0.040$), emotional well-being ($\beta = 0.341$; $P = 0.024$) and social support ($\beta = 0.386$; $P = 0.011$), with improved depression associated with improved QoL.

Given the slight differences in cognitive changes following surgery between STN and GPi patients, a series of exploratory Pearson bivariate correlations were conducted to evaluate

whether these changes were associated with changes in QoL. In the STN group, animal fluency decline was moderately and significantly correlated with reduced patient-reported QoL on the communication subscale of the PDQ-39 ($r = -0.60$; $P = 0.005$).

Discussion

Overall improvements in quality of life

Our finding of a 14.6% improvement in the overall QoL in the STN group is in line with the only other identified study reporting changes in PDQ-SI after unilateral STN DBS, which documented an improvement of 15% [24]. The vast majority of studies have examined bilateral surgery and have reported PDQ-SI reductions of between 14 and 62% [5]. Our finding of a 38.1% improvement in overall QoL in the GPi group is comparable to the 30% improvement found in the only other identified study reporting PDQ-SI change after unilateral GPi, in which patients undergoing unilateral and bilateral procedures showed similar QoL improvements [22]. It should be noted that only four patients in that study underwent unilateral DBS.

Differential changes in individual QoL domains

As a group, patients in this study evidenced improvements on the PDQ-39 domains of mobility, ADLs, emotional well-being, stigma, cognition and discomfort, but not on social support or communication. These findings are in line with the vast majority of studies of DBS for PD that have included PDQ-39 subscale data [4,6,11,13,22]. Of these studies, all have reported improved mobility, ADLs, stigma and discomfort, and some also reported improved emotional well-being or cognition. None of these reports noted improvements in social support or communication. Thus, the results of our study support the view that DBS for PD improves not only physical aspects of patient-reported QoL but also certain emotional and cognitive aspects. Indeed, patients reported significantly fewer depressive symptoms following DBS, regardless of target, as measured with the BDI-II. With regard to cognition, verbal fluency scores were slightly lower following surgery in STN, as compared to GPi. However, it should be noted that verbal fluency assessments were conducted with patients on dopaminergic medication at baseline and off medication, on stimulation at the post-surgical follow-up.

The absence of improvement on the social support subscale likely reflects the static nature of patients' social networks over this relatively short period of time (6 months) and/or the surgical candidate selection process, which considers family or social factors that may negatively contribute to outcome [17]. However, some authors have described family and/or marital conflicts following DBS that, when present, may prevent improvement in this domain [20,23]. Scores on the social support subscale improved amongst patients who received surgery in GPi, but not STN. The absence of improvement on communication may relate to verbal fluency declines that are often encountered subsequent to DBS surgery, even when performed unilaterally [30]. Indeed, worse scores on the communication subscale of the PDQ-39 have been reported in DBS patients relative to patients treated with levodopa medication [15].

Differences between QoL changes following STN versus GPi DBS

A key finding in this study is that GPi patients reported more QoL improvement than STN patients despite comparable improvements on measures of both motor (off medication) and depression severity and only slight differences in letter fluency ability. This was observed for overall QoL, as well as for mobility, ADLs, stigma and social support. It has been suggested that STN DBS is associated with more peri-operative complications, such as delirium and confusion [2], as well as more long-lasting behavioral and neuropsychiatric

consequences [27], perhaps due to the greater risk of tissue around the target area being affected due to the smaller size of the STN. Indeed, in the COMPARE trial, more patients in the STN group experienced post-surgical mood and cognitive adverse events (e.g. anxiety, confusion, irritability, aggressiveness, obsessive compulsive or manic symptoms, decreased confidence/motivation) than those in the GPi group, and the number of general post-surgical adverse events was higher in the STN group [16]. In addition, STN patients experienced a slight decline in the number of words generated during a verbal fluency task following surgery, while GPi patients did not. Interestingly, performance declines on a category fluency task were associated with worsened QoL on the communication subscale of the PDQ-39, suggesting that subtle cognitive changes subsequent to DBS surgery may indeed have real-world implications.

Another factor relevant to our finding of lesser QoL improvements following STN DBS may be that all patients underwent unilateral surgery in our study. The majority of previous studies have reported on patients who underwent bilateral surgery [4,6,13,29]. The relative effectiveness of bilateral versus unilateral STN DBS with regard to measures such as motor score and medication reduction is not clear, although it seems that significant medication reduction only occurs after *bilateral* STN DBS, as compared to unilateral [1]. In our study, there was no significant LED reduction following surgery in either site. However, the larger COMPARE study, in which mean LED values were virtually identical, identified a trend for medication reduction amongst STN patients [16]. Studies with unilateral STN DBS have reported more modest QoL effects than are typically observed following bilateral surgery [24]. Of note, preliminary reports suggest comparable effects for unilateral versus bilateral GPi DBS [22]. Finally, this study did not take into account the architecture of STN and GPi or surrounding neuroanatomy and fiber systems, which may also contribute to differences [25].

Summary and future directions

In conclusion, unilateral DBS in both STN and GPi led to significant improvement in overall QoL 6 months after surgery. However, patients who received GPi DBS reported differentially greater improvements *overall* as well as in the individual domains of mobility, ADLs, stigma and social support. These findings cannot be explained by differential mood or motor effects of surgery, as both groups experienced significant improvements in motor functioning and depression that were similar in magnitude. However, STN patients, but not GPi patients, evidenced a slight decrement in letter fluency following surgery. While combined fluency change was not a significant predictor of *whole-group* QoL changes in regression models, animal fluency changes correlated with QoL changes in the communication domain amongst STN patients only. Future studies should examine the relative effects of STN versus GPi stimulation on non-motor measures, identify underlying mechanisms and link findings to real-world functioning.

In addition, systematic investigations of the differential impact of unilateral versus bilateral procedures on non-motor symptoms and QoL should be carried out. Bilateral DBS is more common than unilateral DBS at the present time; however, unilateral DBS may be more appropriate for select patients. This study does not provide conclusive evidence that GPi is a safer or more efficacious target for unilateral DBS, although in cases where medication reduction is not a primary issue, GPi seems to be a reasonable target for DBS in PD. Future studies should also examine differences in QoL outcomes following bilateral surgery in STN versus GPi.

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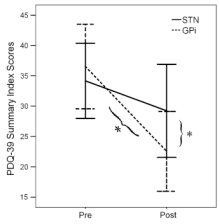

Figure 1.

Parkinson disease questionnaire (*PDQ-39*) summary index scores before and 6 months following deep brain stimulation (DBS) by surgical target. While patients did not differ in self-reported overall quality (QoL) of life prior to surgery (*pre*), those who went on to receive DBS in the globus pallidus (*GPi*) reported significantly improved QoL 6 months after surgery (*post*), while subthalamic nucleus (*STN*) patients' scores did not change significantly. In addition, GPi patients reported significantly better overall QoL than STN patients at the 6-month follow-up

Table 1

Group characteristics at baseline

Demographic and disease characteristics of patient cohort	STN (*n* = 20)	GPi (*n* = 22)	*t* test	*P*
Age	61.3 (9.0)	61.3 (5.5)	0.01	0.99
Sex (M/F)	14/6	16/6		
Disease duration (months)	162.8 (46.6)	148.3 (43.0)	1.05	0.30
Side of surgery (R/L)	7/13	9/13		
UPDRS-III “on”	21.5 (7.3)	22.3 (8.3)	−0.34	0.74
UPDRS-III “off”	43.8 (10.6)	41.8 (10.0)	0.64	0.53
LED	935.9 (374.0)	1,199.8 (576.9)	−1.7	0.09
BDI-II	10.8 (6.5)	11.6 (6.7)	−0.41	0.69
STAI state	36.5 (10.9)	35.8 (11.2)	0.20	0.84
STAI trait	34.8 (10.6)	33.5 (11.6)	0.34	0.73
MMSE	28.5 (1.6)	28.6 (1.3)	−0.41	0.68
DRS-2	136.9 (7.0)	139.2 (4.5)	−1.25	0.22
Letter fluency (raw)	37.9 (9.9)	36.5 (13.5)	0.36	0.72
Animal fluency (raw)	18.5 (4.5)	19.2 (4.9)	−0.50	0.62
PDQ-39 summary index	34.2 (13.3)	36.5 (15.7)	−0.52	0.60
Mobility	49.3 (24.5)	48.6 (19.0)	0.09	0.93
ADLs	41.9 (20.4)	40.5 (18.2)	0.23	0.82
Emotional well-being	31.9 (21.8)	30.1 (22.4)	0.26	0.80
Stigma	23.5 (20.6)	38.7 (19.1)	−2.49	0.02
Social support	13.7 (16.9)	19.7 (19.5)	−1.05	0.30
Cognition	31.6 (19.4)	34.4 (25.4)	−0.40	0.69
Communication	32.1 (21.3)	36.0 (21.0)	−0.60	0.56
Discomfort	49.6 (20.9)	44.3 (23.2)	0.77	0.45

M Male, *F* female, *R* right, *L* left, *STN* subthalamic nucleus, *GPi* globus pallidus internus, *UPDRS-III* Unified Parkinson Disease Rating Scale–motor portion, *LED* levodopa equivalent dosage, *BDI-II*, Beck Depression Inventory, 2nd edition, *STAI* Stait-Trait Anxiety Inventory, *MMSE*, Mini-Mental State Exam, *DRS-2*, Dementia Rating Scale, *ADLs*, activities of daily living, *PDQ-39* Parkinson’s Disease Questionnaire

Values are given as the mean with the standard deviation (SD) in parenthesis

Table 2

Mean coordinates of active electrode contacts by target

Target	*x*	*y*	*z*
STN (*n* = 20)	±11.9 (2.2)	−0.8 (2.1)	−1.2 (3.2)
GPi (*n* = 22)	±22.1 (1.5)	3.5 (1.6)	0.3 (1.5)

x Lateral distance from mid-commissural point, *y* anterior/posterior distance, *z* axial distance from mid-commissural point

± indicates absolute value

Table 3

Motor scores, medication levels and depression severity pre-surgery and post-surgery for the STN and GPi groups

	STN (*n* = 20)		GPi (*n* = 22)	
	Pre-surgery	**Post-surgery**	**Pre-surgery**	**Post-surgery**
UPDRS-III on	21.4 (7.5)	20.9 (9.5)	22.2 (7.5)	21.0 (8.8)
UPDRS-III off*	43.8 (910.6)	32.2 (15.4)	41.8 (10.0)	30.1 (11.8)
LED	935.9 (374.0)	915.0 (447.9)	1199.8 (576.9)	1300.5 (817.0)
BDI-II*	10.8 (6.5)	8.2 (5.6)	11.6 (6.7)	7.0 (5.7)
Letter fluency	37.9 (9.9)	32.5 (10.3)*	36.5 (13.5)	37.9 (15.9)
Animal fluency	18.5 (4.5)	18.9 (5.9)	19.2 (4.9)	19.6 (6.4)

Values are given as the mean with the standard deviation (SD) in parenthesis

*Significant changes between time points ($P < 0.001$)

Table 4

Scores on PDQ-39 subscales pre-surgery and post-surgery for the STN and GPi groups

PDQ-39 subscales	STN (*n* = 20)			GPi (*n* = 22)		
	Pre-surgery	Post-surgery	Difference	Pre-surgery	Post-surgery	Difference
Mobility	49.3 (24.5)	43.8 (26.7)	−5.5	48.6 (19.0)	32.3 (23.2)	−16.3
ADLs	41.9 (20.4)	39.4 (26.4)	−2.5	40.5 (18.2)	25.4 (17.9)	−15.1
Emotion	31.9 (21.8)	26.3 (25.3)	−5.6	30.1 (22.4)	13.6 (14.2)	−16.5
Stigma	23.5 (20.6)	15.6 (19.2)	−7.9	38.7 (19.1)	14.5 (21.0)	−24.2
Social support	13.7 (16.9)	16.3 (18.0)	+2.6	19.7 (19.5)	9.5 (18.8)	−10.2
Cognition	31.6 (19.4)	23.1 (19.1)	−8.5	34.4 (25.4)	22.7 (24.0)	−11.7
Communication	32.1 (21.3)	34.6 (21.3)	+2.5	36.0 (21.0)	31.4 (22.7)	−4.6
Discomfort	49.6 (20.9)	35.0 (22.7)	−14.6	44.3 (23.2)	31.1 (25.9)	−13.2
PDQ-SI	34.2 (13.3)	29.2 (16.4)	−5.0	36.5 (15.7)	22.6 (14.8)	−13.9

PDQ-SI Parkinson's Disease Questionnaire summary index

Values are given as the mean with the standard deviation (SD) in parenthesis

Table 5

Univariate analysis of overall quality of life

	SS	MS	*F*	*P*	Effect size (η_p^2)	Power
Overall QoL (PDQ-SI)						
Target	1,861.83	1,861.83	10.36	0.003	0.21	0.88
Covariate	8,616.83	8,616.83	47.96	0.000	0.55	1.0
Error (between)	7,006.70	179.66				
Time	423.36	423.36	6.29	0.016	0.14	0.69
Target × time	334.11	334.11	4.96	0.032	0.113	0.58
Covariate × time	7.35	7.35	0.11	0.743	0.003	0.06
Error (within)	2,625.19	67.31				

QoL Quality of life, *SS* sums of squares, *MS* mean squares

Table 6

Follow-up univariate analyses of individual quality of life domains

	SS	MS	*F*	*P*	Effect size (η_p^2)	Power
Mobility						
Target	765.76	765.76	0.8	0.38	0.02	0.14
Error (between)	38,194.66	954.87				
Time	2,503.91	2,503.91	17.66	0.000	0.31	0.98
Target × time	618.19	618.19	4.36	0.043	0.098	0.53
Error (within)	5,670.8	141.77				
ADLs						
Target	1,232.02	1,232.02	1.77	0.19	0.04	0.26
Error (between)	27,830.95	695.77				
Time	1,631.79	1,631.79	9.24	0.004	0.19	0.84
Target × time	838.21	838.21	4.74	0.035	0.11	0.57
Error (within)	7,067.51	176.69				
Emotional well-being						
Target	1,083.77	1,083.77	1.65	0.21	0.04	0.24
Error (between)	26,359.77	658.99				
Time	2,556.76	2,556.76	10.67	0.002	0.21	0.89
Target × time	615.87	615.87	2.57	0.12	0.06	0.35
Error (within)	9,587.36	239.68				
Stigma						
Target	1,035.22	1,035.22	1.6	0.21	0.04	0.24
Error (between)	25,850.92	646.27				
Time	5,356.80	5,356.80	35.33	0.000	0.47	1.0
Target × time	1,398.39	1,398.39	9.2	0.004	0.19	0.84
Error (within)	6,065.41	151.64				
Social support						
Target	3.58	3.58	0.007	0.935	0.00	0.05
Error (between)	21,405.8	535.15				
Time	313.47	313.47	2.23	0.143	0.05	0.31

	SS	MS	*F*	*P*	Effect size (η_p^2)	Power
Target × time	850.97	850.97	6.05	0.018	0.13	0.67
Error (within)	5,626.68	140.67				
Cognition						
Target	30.56	30.56	0.03	0.854	0.001	0.05
Error (between)	35,722.208	893.06				
Time	2,115.09	2,115.09	21.33	0.000	0.35	1.0
Target × time	54.13	54.13	0.55	0.464	0.01	0.11
Error (within)	3,967.32	99.18				
Communication						
Target	2.93	2.93	0.004	0.948	0.000	0.05
Error (between)	27,158.12	678.95				
Time	21.72	21.72	0.09	0.772	0.002	0.06
Target × time	259.34	259.34	1.02	0.319	0.03	0.17
Error (within)	10,190.06	254.75				
Discomfort						
Target	443.66	443.66	0.47	0.495	0.01	0.10
Error (between)	37,431.37	935.78				
Time	4,059.74	4,059.74	27.03	0.000	0.40	1.0
Target × time	9.27	9.27	0.06	0.805	0.002	0.06
Error (within)	6,008.34	150.21				