Association between levels of functional disability and health-related quality of life with spinal cord stimulation for chronic pain

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ABSTRACT

Objectives: Pain score, functional disability and health-related quality-of-life (HRQoL) are core outcome domains for chronic pain clinical trials. Although greater levels of pain reduction have been shown to be linked to larger gains in HRQoL, little is known of the association between HRQoL and disability in the setting of chronic pain. The aims of this study were to: i) investigate the association between functional disability and HRQoL, and ii) estimate the utility values associated with levels of functional disability in patients treated with Evoked Compound Action Potential (ECAP) spinal cord stimulation (SCS) for chronic pain.

Materials and Methods: Functional disability assessed using the Oswestry Disability Index (ODI) and HRQoL (EQ-5D-5L) were collected from 204 patients with an Evoke ECAP-SCS device and followed-up to 12-months. SF-6D utility scores were also retrieved for 134 of these patients. Multivariable linear regression models adjusted for baseline utility values and patient demographics were used to compare differences in utility values across ODI categories.

Results: Significant improvements in functional disability and HRQoL were observed at 3 and 12-month follow-up after SCS. Patients reporting 'minimum disability', 'moderate disability', 'severe disability', and 'crippled' had mean EQ-5D scores of 0.82, 0.73, 0.59 and 0.45 respectively. The mean change in EQ-5D score was 0.007 per unit change in total ODI score. The R^2 statistic showed moderate level association (49% to 64% of variance in EQ-5D explained by ODI).

Conclusion: ECAP-SCS results in significant improvements in functional disability and HRQoL. This study shows that improvement in function of people with chronic pain before and after ECAP-SCS is associated with improvement in HRQoL.

Keywords: chronic pain; disability; health-related quality of life; spinal cord stimulation

INTRODUCTION

Chronic pain and pain-related conditions are leadings causes of years of life lost to disability and disease burden globally.[1] Population estimates for the prevalence of chronic pain in the United States (US) range between 11% and 40%,[2] with recent estimates suggesting that 20.5% of adults experience chronic pain.[3] A systematic review reported a pooled chronic pain population prevalence rate of 43.5% with the rate of moderate-severely disabling chronic pain, ranging from 10.4% to 14.3% of people in the United Kingdom (UK).[4] Chronic pain is associated with significant cost implications to healthcare providers and wider society. The annual cost of chronic pain has been estimated to total US$100 billion in the US and £11 billion in the UK.[5, 6] Average expenditures for health care among those with disabilities are 5 to 6 times higher than for those without disabilities.[7, 8] Working-age adults with disabilities are nearly 5-6 times more likely to have seen a physician or been admitted to hospital in the previous 12 months.[9]

Spinal cord stimulation (SCS) is an established and recommended intervention for the management of chronic pain.[10] The effectiveness of SCS has been commonly assessed by a reduction in pain intensity using a numeric rating scale (NRS) or a visual analogue scale (VAS).[11-17] From a patient perspective, improvements in physical function, commonly reported as functional disability may be at least equally important compared to reduction in pain.[18, 19] Several randomised controlled trials (RCTs) evaluating pain treatments other than SCS have considered a primary outcome of improvement in function / disability.[20-23] Physical function is a core outcome domain for chronic pain clinical trials recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) and by the Outcome Measures in Rheumatology (OMERACT) initiative.[24, 25]

Chronic pain also has an impact on health-related quality of life (HRQoL), which is a core outcome domain for clinical trials in non-specific low back pain.[25] The relationship between HRQoL and pain intensity has been investigated including estimates of HRQoL utility values associated with different levels of pain relief.[26] Functional disability has also been found to be significantly related with HRQoL.[27, 28] Estimates of HRQoL utility values associated with different levels of functional disability enable cost-utility analysis considering functional disability-based health states. An improved understanding of the association of disability and HRQoL may also enhance the clinical management of chronic pain. HRQoL utilities also enable comparisons across conditions and interventions to assess impact of novel technologies.

A novel ECAP-SCS system has been developed to treat chronic pain utilising real-time measured evoked compound action potentials (ECAPs) to continuously adjust and deliver

precise therapeutic stimulation to the neural target. Prior to the development of this physiological closed-loop control system, SCS systems could not ensure consistent delivery of therapeutic charge to the targeted fibres involved in modulation of pain inhibition pathways within a dynamic environment between the electrodes and the spinal cord.

HRQoL utility scores associated with disability categories have not been previously reported. The aims of this study were to: i) investigate the potential association between levels of functional disability and HRQoL, and ii) estimate the utility values associated with different levels of functional disability in patients implanted with an ECAP-SCS device for the management of chronic pain.

MATERIAL AND METHODS

Study design

This study used data from a total of 204 patients from two previously reported studies (EVOKE [NCT02924129] and AVALON [ACTRN12615000713594]) in patients with chronic back and leg pain who received ECAP-SCS using the Evoke SCS System (Saluda Medical) with follow up at 3 and 12-months post implant. The Evoke SCS System offers both open-loop, fixed-output and ECAP-controlled, closed-loop stimulation modes. In both stimulation modes, the system continually measures and records ECAPs for every stimulus and ECAPs may also be used optimise programming (i.e., ECAP-guided programming). In closed-loop mode, the system also uses ECAPs to automatically adjust the strength of the stimulus to maintain a consistent neural response at a prescribed target on every pulse. In open-loop, the system delivers fixed-output stimulation, similar to other SCS systems. EVOKE was a multicentre, double-blind, parallel-arm randomised controlled trial (RCT) conducted in 13 centres in the USA with 134 patients randomised 1:1 to closed-loop SCS or open-loop SCS.[11] AVALON was a multicentre, prospective single-arm study conducted in 5 centres in Australia with 70 patients screened.[29] Both studies were conducted in compliance with ethical and regulatory guidelines and were approved by local ethics committees prior to subject enrolment.

Demographic and outcome data

For the present study we obtained individual patient data for demographics (age, sex, duration of pain, previous back operation history), pain intensity (overall pain VAS scores at baseline), functional disability (ODI scores at baseline, 3- and 12-month follow-up) and HRQoL (EQ-5D-5L and SF-6D utility scores at baseline, 3- and 12-month follow-up).

The Oswestry Disability Index (ODI) is a core outcome measure to assess functional disability in people with nonspecific low back pain and a commonly used secondary outcome of RCTs of SCS.[30] The ODI was used to assess the level of pain interference with various activities of daily living. The ODI is a valid measure of condition-specific disability.[31] The ODI consists of 10 items/activities with 6 levels (range 0-5). This questionnaire has been recommended as a tool to measure pain related disability when considering areas other than and including low back pain (24). ODI scores between 0-20% were considered as minimal disability; 21-40% moderate disability; 41-60% severe disability; 61-80% crippled; and 81-100% as bed-bound or exaggerating their symptoms.[31]

HRQoL was derived from participants' responses to the EQ-5D-5L instrument. The EQ-5D-5L descriptive system is a questionnaire designed to be completed by the patient and comprising five dimensions (mobility, self-care, usual activities, pain/ discomfort and depression/ anxiety), where each dimension has five response levels: no problems, slight problems, moderate problems, severe problems, unable to/ extreme problems.[32] The respondent is asked to indicate his/her overall health state by selecting the level that corresponds to his/her quality of life for each of the five dimensions. Responses to the EQ-5D-5L were converted into single (utility) indices using a set of weights (tariff) reflecting population preferences for the health state. Utility scores were obtained by using the EQ-5D-5L responses cross walked to the EQ-5D-3L US value set.[33] The Evoke trial participants also completed the SF-12 questionnaire and health utility scores were determined using the SF-6D algorithm (see supplementary material 1).

Statistical analysis

We retrospectively calculated that 170 patients provided 99% power at 5% alpha to detect a clinically important difference in EQ-5D utility of 0.10 assuming a standard deviation of 0.20.[16]

Probabilities of patients achieving the five different ODI disability categories (minimum disability, moderate disability, severe disability, crippled, bed bound) and associated HRQoL utility values (means and 95% confidence intervals [CIs]) were estimated at each ODI category for EQ-5D and SF-6D data at baseline and 3- and 12-month follow-up.

Linear regression models were used to compare the differences in utility values across the ODI categories. Given the observational nature of these analyses, multivariable models were used to adjust for treatment group (open vs closed loop), patient age, sex, duration of pain, previous back operation history, and baseline overall pain VAS. A secondary regression analysis was undertaken using ODI score as a continuous variable. All models were run separately for EQ-5D utilities at baseline, 3- and 12-month follow-up data and also across all

time points using a repeated measures mixed model. We report the coefficient of determination (R^2), from regression models i.e., the proportion of the variation in HRQoL predictable from the variation in ODI.

All data analyses were undertaken using STATA v17.0.

RESULTS

Between August 2015 to September 2016 (AVALON case series, n=70) and January 2017 to January 2018 (EVOKE RCT, n=134) a total of 204 patients were enrolled in the respective studies (Figure 1). The 12-month follow-up assessment was completed by a total of 146 patients across both studies.

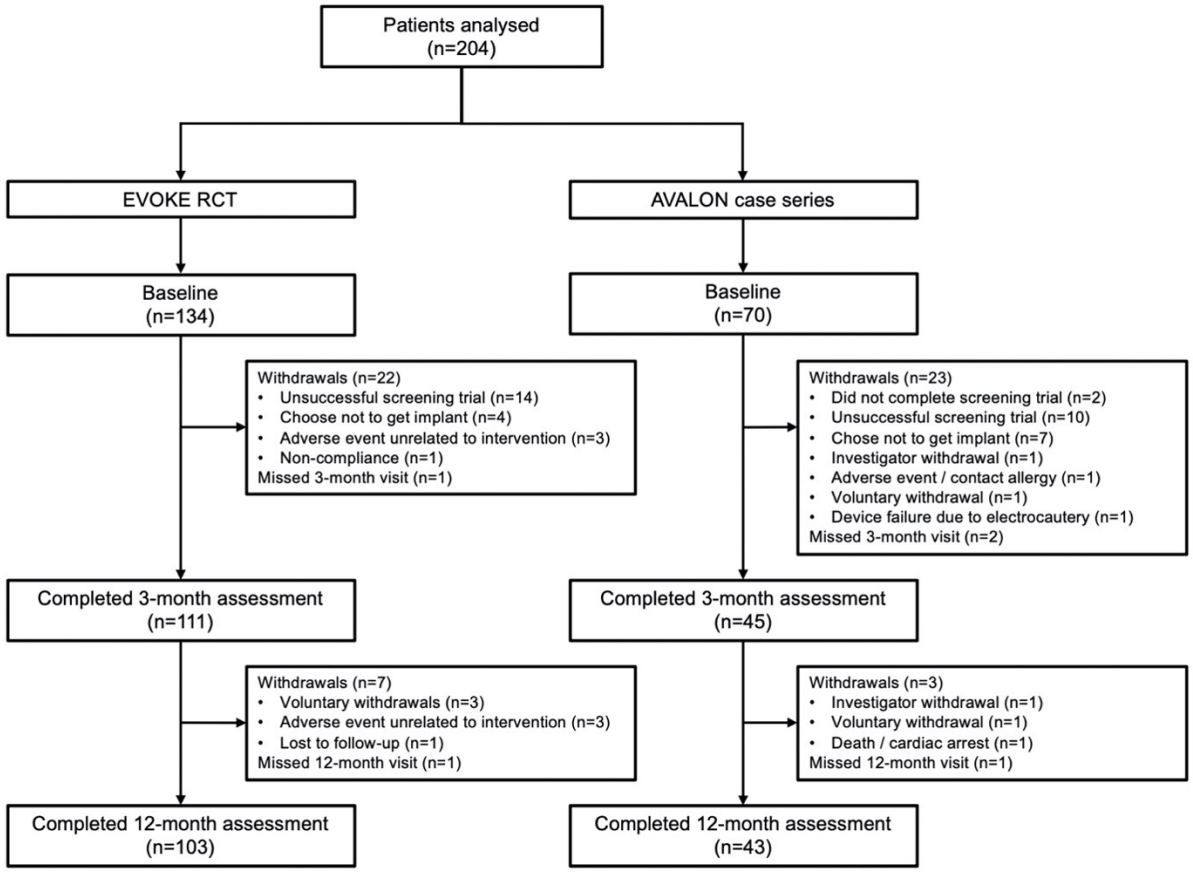

Figure 1. Study flow diagram

Participants in the studies had an average age of 55.6 years and relatively equal representation by sex, with a baseline mean overall VAS pain of 81.8 and primarily a failed back surgery syndrome (FBSS) diagnosis (Table 1).

Table 1. Baseline characteristics

	N=204
Data source EVOKE trial – n (%) AVALON study – n (%)	 134 (66%) 70 (34%)
Age (years) – mean (SD)	55.6 (11.4)
Gender – n (%) Male Female	 104 (51%) 100 (49%)
Duration of pain (years) – mean (SD)	13.0 (10.2)
Previous back surgery – n (%)	128 (63%)
Overall VAS pain 0-100 (mm) – mean (SD)	81.8 (10.3)

SD=standard deviation; VAS=visual analogue scale

Following ECAP-SCS treatment, there was evidence of reduction (improvement) in overall ODI score and increase in the proportion of patients that reported improved disability categories from baseline to 3 and 12-month follow up (Figure 2). The improvements in ODI were significant from baseline to 3 (mean difference [MD] 25.3, 95% CI 22.8 to 27.8, p<0.0001) and 12-month follow up (MD 25.2, 95% CI 22.4 to 28.0, p<0.0001) (Table 2). Similarly, there was a significant increase (improvement) in HRQoL at 3 and 12-months follow up as assessed by EQ-5D (3-months MD -0.23, 95% CI -0.26 to -0.21, p<0.0001; 12-months MD -0.21, 95% CI -0.25 to -0.18, p<0.0001) and SF-6D (3-months MD -0.18, 95% CI -0.20 to -0.15, p<0.0001; 12-months MD -0.15, 95% CI -0.17 to -0.12, p<0.0001) index scores (Table 2).

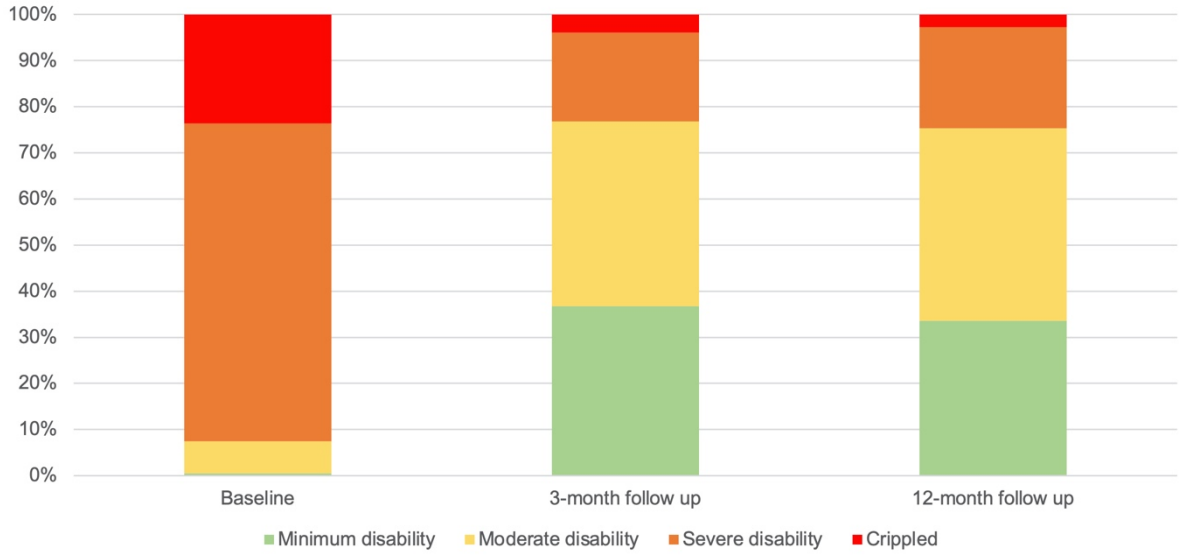

Figure 2. Proportion of patients in the different ODI categories at baseline and 3 and 12-month follow up

Bed bound category not included as only one patient reported this level of disability and only at baseline

Table 2. Level of disability and HRQoL utility at baseline and 3 and 12-month follow up

Mean, (SD), N or n (percent)	**Baseline**	**3-month follow up**	**12-month follow up**
ODI			
Total score - mean, (SD), N	53.9 (10.7), 204	29.0 (16.5), 155	29.1 (16.1), 146
Minimum disability (0-20)	1 (0.5)	57 (36.8)	49 (33.6)
Moderate disability (21-40)	14 (6.9)	62 (40.0)	61 (41.8)
Severe disability (41-60)	140 (68.6)	30 (19.4)	32 (21.9)
Crippled (61-80)	48 (23.5)	6 (3.9)	4 (2.7)
Bed bound (81-100)	1 (0.5)	0	0
EQ-5D index*	0.52 (0.15), 204	0.75 (0.14), 156	0.74 (15.0), 146
SF-6D*	0.53 (0.09), 134	0.70 (0.13), 111	0.67 (0.14), 102

*US values

There was a clear association between HRQoL and disability, with decreasing categories of disability being associated with an increase in EQ-5D index at baseline, 3 and 12-month follow up. In the all-time points analysis, patients reporting 'minimum disability', 'moderate disability', 'severe disability', and 'crippled' had mean EQ-5D scores of 0.82, 0.73, 0.59 and 0.45 respectively (Table 3).

Table 3. Levels of EQ-5D index, by ODI disability states at various timepoints

	Mean EQ-5D^ (95% CI), N	**Comparison of disability states**	
		Contrasts	**P-value***
Baseline			
Minimum disability (MnD)	0.81 (-), 1		
Moderate disability (MoD)	0.71 (0.68 to 0.75), 14	MnD vs MoD	0.52
Severe disability (SD)	0.55 (0.53 to 0.57), 140	MoD vs SD	<0.0001
Crippled (CR)	0.39 (0.35 to 0.43), 48	SD vs CR	<0.001
Bed bound (BB)	0.13 (-), 1	CR vs BB	<0.01
3-month follow up			
Minimum disability (MnD)	0.86 (0.84 to 0.88), 57		
Moderate disability (MoD)	0.74 (0.72 to 0.77), 62	MnD vs MoD	<0.0001
Severe disability (SD)	0.62 (0.58 to 0.66), 30	MoD vs SD	<0.0001
Crippled (CR)	0.46, (0.32 to 0.60), 6	SD vs CR	<0.0001
Bed bound (BB)	-	CR vs BB	-
12-month follow up			
Minimum disability (MnD)	0.86 (0.83 to 0.88), 49		
Moderate disability (MoD)	0.74 (0.72 to 0.76), 61	MnD vs MoD	<0.0001
Severe disability (SD)	0.58 (0.53 to 0.63), 32	MoD vs SD	<0.0001
Crippled (CR)	0.41 (0.23 to 0.58), 4	SD vs CR	<0.0001
Bed bound (BB)	-	CR vs BB	-
All time points			
Minimum disability (MnD)	0.82 (0.73 to 0.90)%		
Moderate disability (MoD)	0.73 (0.70 to 0.76)%	MnD vs MoD	<0.0001
Severe disability (SD)	0.59 (0.57 to 0.61)%	MoD vs SD	<0.0001
Crippled (CR)	0.45 (0.41 to 0.50)%	SD vs CR	<0.0001
Bed bound (BB)	-+	CR vs BB	-

^US values; *adjusted for baseline ODI score, treatment group, age, sex, duration of pain, previous back surgery, baseline overall pain score; + not estimable; %repeated measures regression model margins

The increase in EQ-5D utility score per unit of ODI decrease was statistically significant at baseline, 3- and 12-month follow-up (Table 4). In the all-time point analysis, the mean increase in EQ-5D score was 0.007 per unit decrease in total ODI score. The R^2, which explains the variance in utility score due to disability score showed a moderate level association (i.e., 49 to 64%). Based on these linear regression results, a minimal clinically important difference (MCID) in ODI of 12 to 13 would be associated with a change in EQ-5D of 0.084 to 0.91 which corresponds to a larger improvement than a MCID of 0.074 in EQ-5D index.[34]

A similar level of negative association between ODI score and HRQoL was seen for SF-6D (see supplementary material 1).

Table 4. Levels of EQ-5D index at baseline, 3 and 12-months follow up by ODI score as a continuous variable

	Mean change in EQ-5D utility^ by unit change in ODI disability							
	Univariate analysis				**Multivariate analysis***			
	Mean	**95% CI**	**R^2**	**P-value**	**Mean**	**95% CI**	**R^2**	**P-value**
Baseline	-0.009	-0.010 to -0.007	41%	<0.0001	-0.008	-0.009 to -0.007	49%	<0.0001
3-months	-0.007	-0.008 to -0.006	62%	<0.0001	-0.007	-0.008 to -0.006	63%	<0.0001
12-months	-0.007	-0.009 to -0.006	62%	<0.0001	-0.007	-0.008 to -0.006	64%	<0.0001
All time points	-0.008	-0.009 to -0.008	-[+]	<0.0001	-0.007	-0.008 to -0.006	-[+]	<0.0001

^US values; *adjusted for baseline ODI score, treatment group, age, sex, duration of pain, previous back surgery, baseline overall pain score; [+] not estimable

Finally, ODI showed a negative correlation coefficient with EQ-5D utility values at 3 months (-0.786 [p<0.0001], Figure 3) and 12 months follow-up (-0.787 [p<0.0001], Figure 4) indicating that lower functional disability is associated with higher HRQoL utility levels.

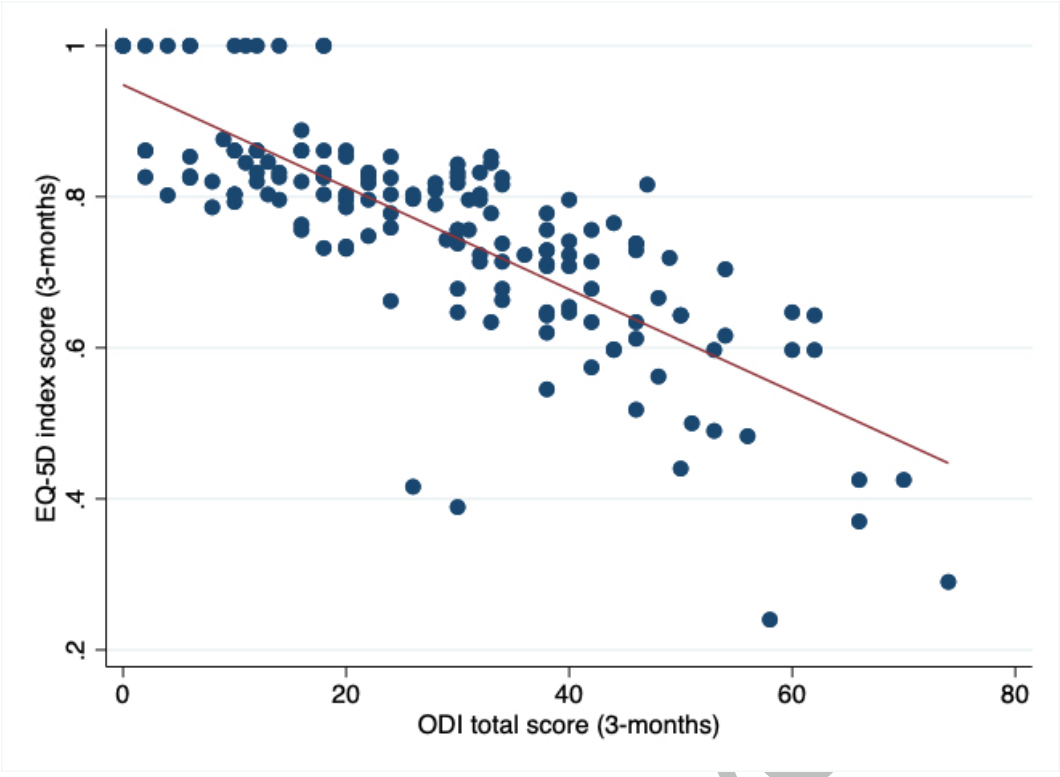

Figure 3. Univariable relationship between EQ-5D utility at 3-months versus ODI total score

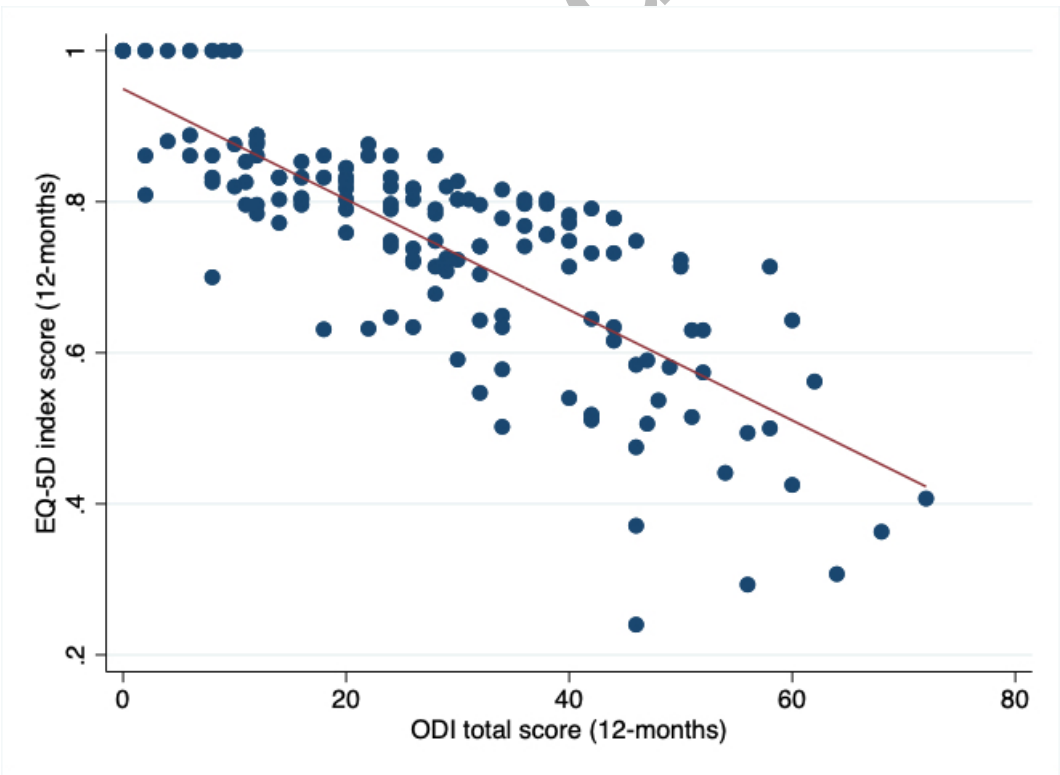

Figure 4. Univariable relationship between EQ-5D utility at 12-months versus ODI total score

DISCUSSION

We carried out an analysis of individual patient data from two studies assessing the effectiveness of ECAP-SCS for patients with chronic back and leg pain.[11, 29] The results of the current study show that ECAP-SCS results in significant improvements in functional disability and HRQoL. In addition, we observed an increase in the proportion of patients that reported less severe functional disability categories from baseline to 3 and 12-month follow up. Improvements in functional disability and HRQoL with ECAP-SCS have been shown to be sustained at the latest reported follow-up of 24-months.[35]

The observed improvements may be attributed to ECAP-guided programming and the delivery of optimum therapeutic dose based on continuous measurement of target neural response that is unique to ECAP-SCS. ECAP-SCS enables understanding of the clinical effects of therapy based on a prescribed physiologic response and may be used to monitor therapy adherence from which the outcomes may be better understood.

A moderate to strong association between functional disability and HRQoL was seen, with greater HRQoL utility scores consistently observed for those with less severe categories of functional disability. This association was observed with both EQ-5D and SF-6D derived utilities. We are aware of only one previous study that has formally quantified the relationship between disability and HRQoL in chronic pain. Carreon et al. prospectively collected both HRQoL (Short-Form 36) and ODI in a cohort of patients undergoing lumbar fusion for degenerative disorders.[36] In line with this study, the authors reported statistically significant association between HRQoL and ODI. However, the mean utility values (derived using the SF-6D UK value set) for each level of functional disability were consistently lower (i.e., minimum disability: 0.73; moderate disability: 0.60; severe disability: 0.52 crippled: 0.43). This discrepancy in utility values may reflect the differing chronic pain populations of the two studies as well the application of different country utility valuation sets (US in the present study versus UK by Carreon et al). It is essential that the instrument and value sets used to derive utility scores are clearly reported since different HRQoL tools can result in large differences in the estimation of utility scores for chronic pain.[37]

The unadjusted R^2 values shows that 41% to 62% of the variance in HRQoL utility is explained by the change in ODI. Adjusting for other factors including baseline ODI score, treatment group, age, sex, duration of pain, previous back surgery and baseline overall pain score held constant, the R^2 ranged from 49% to 64%. A R^2 result explaining the variance in SF-6D utility score due to functional disability score of 67% has been previously observed.[36] In a population of patients with chronic back and leg pain that are candidates for SCS, increases in HRQoL appear to be better explained by a reduction in functional disability than by pain relief.

Interestingly R^2 in an analysis of change in utility scores due to pain relief experienced ranged only from 25% (leg VAS pain at 3-months) to 42% (back VAS pain at 12-months).[26] Historically, RCTs and economic evaluations of SCS have considered a primary outcome of reduction in pain intensity and health states according to pain relief obtained, respectively. The implications of using a primary outcome of functional disability in RCTs of SCS or health states according to levels of functional disability in economic evaluations of SCS needs to be explored in future studies.

MCIDs are patient derived scores that reflect changes in a clinical intervention that are meaningful for the patient and widely used in practice and research to assess treatment success.[38] MCID for the ODI has been suggested to range between 9.5 and 12.8 points,[39-41] and for the EQ-5D, the MCID has been reported to be 0.074.[34] Our regression analysis (i.e. change in EQ-5D utility of 0.007 to 0.008 per unit change in ODI score) indicates concordance between the MCID of these two measures, supporting the validity of our study findings. Consistent with our findings, a previous report observed that a 1-point increase in ODI corresponds to a 0.0069 reduction in EQ-5D utility value.[27]

Strengths and weaknesses

We present an investigation of the longitudinal relationship between generic HRQoL tools and functional disability as measured using the ODI. Our findings were consistent across functional disability categories, instruments used to derive utilities and at the different time points. The analyses conducted considered utility scores derived from both the EQ-5D and SF-6D employing US preference weights. The data used to inform the current study comes from two good quality studies that included patients with chronic back and leg pain with and without prior surgery and different causes of pain.[11, 29] The eligibility criteria used for the studies is pragmatic and reflects clinical practice where clinicians would contemplate the use of SCS for patients with different causes of pain. Patient characteristics and baseline scores are similar to those reported in a recent pragmatic trial to reflect clinical practice in the UK.[14] The EQ-5D and SF-6D utility scores reported in this paper can inform the development of future economic models of chronic pain with health states based on levels of functional disability.

Weaknesses of the current study include the observational comparison of utility values across functional disability levels and therefore, the potential for confounding and selection bias. To minimise such bias, we undertook multivariable analysis adjusting for several patient demographics and baseline scores. Although the number of patients included in the study were sufficient to detect an important difference in HRQoL utility scores, the number of patients with disability scores of 81-100% were insufficient to produce reliable estimates for the bed bound health state.

Implications for practice

The EQ-5D utility scores observed after use of ECAP-SCS are greater than those reported in similar populations after low-frequency SCS (0.47),[42] a combination of patients with low-frequency, high-frequency and burst waveforms (0.55)[14] and conventional medical management (0.25).[42] Similarly, lower levels of disability were observed after use of ECAP-SCS when compared to low frequency SCS (44.9), low-frequency, high-frequency and burst waveforms (38.8) or conventional medical management (56.1). The proportion of patients in ODI categories 12-months after use of ECAP-SCS were greater for minimal disability (33.6 vs 16.9) and lesser for moderate (41.8 vs 46.1) or severe (21.9 vs 34.8) disability when compared to high-frequency SCS.[15]

Since our results suggest that ODI can explain the variance in HRQoL more precisely than pain intensity, ODI may be more appropriate to evaluate the response to SCS treatment than subjective reports of pain intensity. This has implications as well for the evaluation of treatment response during the initial screening trial where a decision is made whether to progress or not to full implantation of the device based on the pain relief observed. A sole focus on pain intensity may result in missing clinically meaningful treatment responses in other domains such as improvements in functional disability.[43] There has been an increased interest in the use of composite outcomes in the field of neurostimulation to evaluate treatment response.[44-47] Disability, pain intensity, and HRQoL are meaningful domains for chronic pain patients and could be included in such a composite outcome as previously demonstrated.[45] This is a subject of future research, and efforts should follow best practice recommendations.[48]

CONCLUSION

Recent development of ECAP-SCS enables the delivery of consistent therapeutic stimulation based on real time measurement of target neural response results in significant improvements in functional disability and HRQoL. This study shows that the HRQoL utility of people with chronic pain before and after treatment with ECAP-SCS is associated with their level of disability. Decreased disability may be a stronger driver of improvements in HRQoL than lower levels of pain.

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