Relationship Between Health-Related Quality of Life (HRQoL) and Pain Response in Patients with Diabetic Peripheral Neuropathic Pain (DPNP)

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INTRODUCTION

Diabetic peripheral neuropathic pain (DPNP) is a common complication of diabetes melitus that can have negative impacts on both quality of life and functional status (e.g., mobility, productivity, quality of sleep) beyond that associated with the patient's underlying disease (Benbow et al., 1998; Schmader, 2002; Galer et al., 2000; Gore et al., 2004a, 2004b).

Patients with DPNP frequently report symptoms such as tingling, burning, sharp pains, cramps, extreme sensitivity to touch, numbness, and insensitivity to pain or temperature.

Duloxetine, a 5-HT and NE uptake inhibitor, has been shown in acute treatment studies to be superior to placebo in reducing pain severity in patients with DPNP (Goldstein et al. 2005, et al., 2005a, 2005b).

Objective

The objective of this study was to use a large sample of pooled EQ-5D data to evaluate the relationship between HRQoL and neuropathic pain severity and pain response, and the HRQoL improvement with duloxetine compared to placebo over a 12-week trial period.

METHODS

Pain Severity Assessment

HRQoL data were pooled from three pivotal randomised phase III clinical trials assessing the efficacy of duloxetine in patients with clinically diagnosed DPNP (Goldstein et al., 2005; Raskin et al., 2005a, 2005b) (Table 1).

Table 1. Duloxetine Clinical Study Baseline Statistics

	Pooled	HMAVa	HMAVb	HMAW
Number of Patients	1,139	334	348	457
Number on DLX (%)	800 (70.24)	226 (67.66)	232 (66.67)	342 (74.84)
Mean Age (SD)	59.88 (10.59)	60.65 (10.57)	58.82 (10.10)	60.11 (10.93)
Number of Patients Responded to the EQ-5D	1,041	312	312	417
Average Pain Score (SD)	5.84 (1.47)	6.05 (1.54)	5.56 (1.22)	5.90 (1.56)
Average Utility Score (SD)	0.58 (0.26)	0.55 (0.27)	0.55 (0.26)	0.61 (0.24)

Patients were randomised to either duloxetine (60 mg QD or 60 mg BID) or a placebo control arm. One study also included a lower dose duloxetine 20 mg QD study arm (Goldstein et al., 2005).

- Pain severity was assessed weekly and at the start and end visit of a 12-week study period.
- Pain severity was assessed using a standard 11-point Likert scale—the 24-hour average pain assessment scale (APS) where 0 represents "no pain" and 10 represents "pain as bad as you can imagine."
- Patients were required to have a minimum pain severity score of 4 on the APS.

Quality of Life Assessment

HRQoL was assessed using the standard self-reporting generic EQ-5D assessment tool.

- General population weights were used to calculate overall utility weights, representing patients' health state preference at each assessment point on a 0–1 scale (1 represents "perfect health" and 0 represents "death") (Dolan et al.,1997).
- The EQ-5D was applied, alongside pain severity assessments, at start and end visits of each study, which provided us with a set of paired data points for pain severity and self-reported HRQoL.

Pain Response

Pain response was categorised in the analysis using two clinically meaningful thresholds, based on a ≥30% and a ≥50% improvement in baseline pain severity.

Patients were allocated into the three discrete pain response groups:

- No response (<30% improvement)
- Partial response (30–49% improvement)
- Full response (≥50% improvement)

Statistical Analysis

Three specific levels of statistical analyses were conducted:

- The strength of evidence of a correlation between pain severity and HRQoL utility levels (assessed using a standard Spearman's rank correlation test and visual plots)
- The strength of evidence of a relationship between pain response and endpoint HRQoL utility levels (assessed using standard ANOVA and F-tests)
- The significance in the level of observed improvement in HRQoL utility for patients on duloxetine (60 mg QD or 60 mg BID) over the 12-week study period (assessed using standard T-tests), and when compared to the difference in HRQoL seen for placebo (assessed using standard one-way ANOVA and F-tests)

All analyses were conducted using the STATA software system, PC version 8.0.

RESULTS

Analysis 1: Significant Negative Correlation Between HRQoL Utility and Pain Severity Score

- A statistically significant negative correlation was found between the average 24-hour pain severity score and EQ-5D utility score (Spearman's rank = -0.434; p<0.0001) (Figure 1).
- Patients defined as having mild pain (0–3 on the APS scale) had significantly higher EQ-5D utility scores (mean = 0.76; SD = 0.15) than patients in either the moderate pain group (4–6 on the APS scale) (mean utility = 0.63; SD = 0.21) or the severe pain group (7–10 on the APS scale) (mean utility = 0.41; SD = 0.31) (Figure 2).
- The impact of increased pain severity on HRQoL and utility was generally reflected in changes in the Pain, Mobility, and Usual Activity domains of the EQ-5D (Figure 3).

Analysis 2: Significant Difference Between HRQoL Utility When Stratified by Pain Response

- The mean utility scores when stratified by response groups were full 0.78 (SD = 0.16), partial 0.70 (SD = 0.16) and no response 0.61 (SD = 0.24) (Figure 4).
- Full response (≥50% improvement) was found to have a statistically significant higher mean utility at trial endpoint compared to both the no response (<30% improvement) and partial response (30–49% improvement) patient groups (p<0.0001). The mean utility score of the partial response group was also significantly higher than that of the no response group (p<0.0001).

Analysis 3: Significant Improvement in HRQoL After Duloxetine Treatment for DPNP

- Patients treated with duloxetine (60 mg OD or 60 mg BID) had a statistically significant increase in mean HRQoL utility score over the 12-week trial period of 0.140 (95% CI: 0.16–0.12) (p<0.0001) (Figure 5).
- Patients randomised to the placebo-control arm experienced a mean change of 0.082 (95% CI: 0.112–0.053) (p<0.0001).
- The improvement in mean HRQoL utility observed for duloxetine was significantly greater than that observed for placebo (p=0.0018) (Figure 6).

Figure 1. Relationship Between Average Pain Score and Utility Value

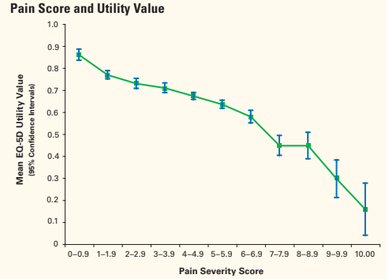


Figure 2. Average Utility Value by Pain Severity Level

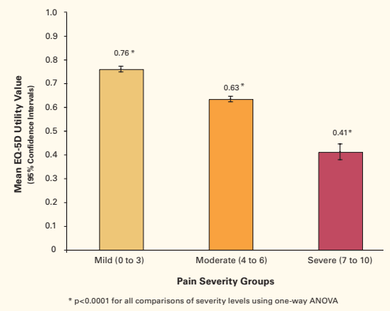


Figure 3. Relationship Between EQ–5D Domain Scores and Pain Severity

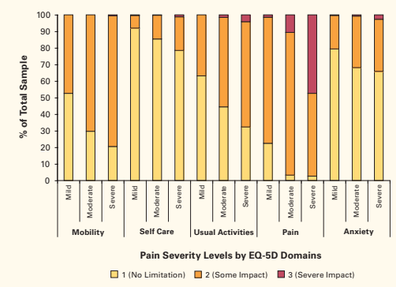


Figure 4. Pooled Utility Scores by Pain Response

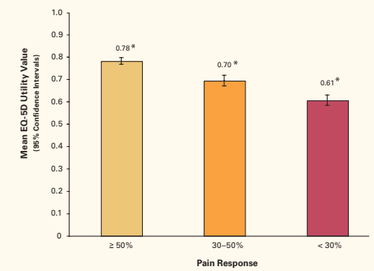


Figure 5. Mean Utility Value at Baseline and Trial Endpoint

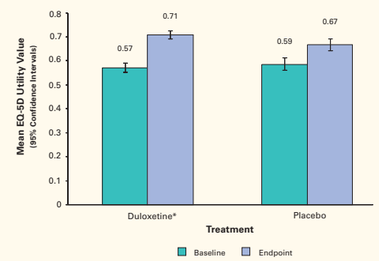
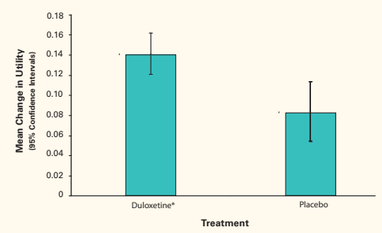


Figure 6. Comparison of Mean Changes in Utility Value from Baseline to Trial Endpoint



DISCUSSION

Our study results suggest:

- Increased levels of pain response in patients with DPNP are associated with statistically significant improvements in HRQoL utility
- A statistically significant negative correlation between stratified pain severity (mild, moderate, and severe pain) and HRQoL utility
- A statistically significant improvement in HRQoL utility over a 12-week treatment period for duloxetine that is significantly greater than placebo (0.14 improvement versus 0.08)

Possible limitations: a generic HRQoL instrument may miss certain disease-specific aspects of quality of life, and the use of 12-week response data limits extrapolation.

However, the results suggest clear HRQoL merits in achieving pain response rates in excess of a 50% improvement from baseline, despite the fact that a 30% improvement is typically considered a "treatment success" (Farrar et al., 2001).

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