**Responsiveness of the QUALID to Improved Neuropsychiatric Symptoms in Patients with Alzheimer’s Disease**

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**ABSTRACT**

**Background**

This study aimed to determine whether the Quality of Life in Late-Stage Dementia (QUALID) scale is responsive to changes in behaviour due to therapeutic intervention.

**Method**

31 long-term care residents with moderate to severe AD and agitation/aggression entered a three-month, open-label trial of memantine 10 mg BID. The relationships between the QUALID and BPSD, global improvement, and cognition at baseline and endpoint, as well as the changes in these scales as a result of treatment, were examined.

**Results**

Despite a significant improvement in agitation and aggression (NPI agitation, F3,90 = 3.721, p = .014; CMAI total, F3,90 = 6.301, p = .001) and overall behaviour (NPI total, F3,90 = 4.035, p = .010), there was no significant change in QUALID score (t30 = -0.278, p = .783). The QUALID was correlated with NPI at baseline (τ = 0.270, p = .037) and endpoint (τ = 0.404, p = .002), but change scores were not correlated (τ = 0.107, p = .412).

**Conclusion**

While the QUALID correlates with behavioural measures at single time points, it does not appear to correlate with changes longitudinally associated with treatment.

**Key words:** QUALID, quality of life, dementia

**INTRODUCTION**

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive cognitive and functional impairment and behavioural and psychological symptoms of dementia (BPSD).(1) These neuropsychiatric symptoms commonly include delusions, hallucinations, agitation, disinhibition, apathy, irritability, anxiety, depression, sleep disturbances, and elation.(2) BPSD are highly common in severe dementia, with 90% of individuals exhibiting at least one behaviour. Up to 50% of patients exhibit at least four behaviours during the course of the illness.(3) It has previously been shown that even modest improvements in these behaviours can result in significant improvement in the quality of life (QoL) for the patient.(4)

Although there is still a lack of agreement about how QoL should be defined and measured, it is generally considered to be a multidimensional construct that includes the individual’s subjective experience of life, as well as objective criteria related to activities valued by society.(5) Engagement in positive activities, presence of positive affect, absence of negative affect, participation in meaningful activity, and a sense of community are assumed to be correlated with QoL in late-stage dementia.(5-7) There is a growing consensus about the need to measure QoL in dementia trials, as such assessments allow researchers to evaluate the benefits and harms of a treatment and elements of health not detected by standard clinical outcomes.(8,9) However, it is very difficult to determine QoL in persons with late-stage dementia(9) as they cannot communicate reliably and are not involved in activities widely accepted by others as rewarding.(10) Due the severity of cognitive impairment of patients with moderate to severe AD, assessment must rely on proxy reports or direct observation.(11) Unfortunately, both of these approaches tend to exclude consideration of the patient’s subjective experiences, which many believe to be an inherent feature of QoL.(8,12)
The Quality of Life in Late-stage Dementia (QUALID) scale was originally developed by Weiner and co-workers in 2000. The QUALID is a late-stage, dementia-specific questionnaire with a one-week window of observation. It provides information about the patient’s quality of life through assessments made by proxy informants. The scale consists of 11 items, comprising both positive and negative dimensions of concrete and observable mood and performance, thought to be indicative of QoL in late-stage dementia. The items are rated by frequency of occurrence on a five-step scale, and scores are summed to range from 11 (best QoL) to 55 (worst QoL). While the QUALID scale has been shown to obtain reliable estimates of QoL and validated in patients with severe dementia residing in long-term care facilities, little is known about the scale’s responsiveness to change due to therapeutic intervention.

The objective of this study was to assess the responsiveness of the QUALID scale to changes in BPSD due to a therapeutic intervention in a population of long-term care residents with moderate to severe AD. As well, this study evaluated the therapeutic intervention at baseline and endpoint. A p value less than .05 was considered statistically significant. The p value was not adjusted for multiple comparisons due to the exploratory nature of the study. Kendall correlation coefficients were obtained between the NPI, CMAI, CGI, and MMSE scales with the QUALID scale. Statistical calculations were performed using IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL).

RESULTS

Thirty-one patients were enrolled in the study, with an average age of 85.8±3.7 years. Twenty-nine (94%) were men. The mean (± SD) MMSE score at baseline was 8.7±6.7, reflecting moderate to severe cognitive impairment. Twenty-four patients (77.4%) completed the study; two died of causes unrelated to the memantine treatment, three discontinued due to increasing agitation, one for significant physical deterioration, and one for significantly increased somnolence.

At baseline, patients had a mean QUALID score of 21.3±6.2, with a range from 13 to 40. Table 1 provides the results of changes in outcome measurements over the course of the trial. There were statistically significant differences in scores for NPI Total (F3,90 = 4.035, p = .001) and its subscale items: Agitation/Aggression (F3,90 = 3.721, p = .014), and Irritability (F3,90 = 3.899, p = .011); and CMAI Total (F3,90 = 6.301, p = .001) and its subscale items: Physical Aggression (F3,90 = 5.928, p = .001) and Verbal Aggression (F3,90 = 3.961, p = .011). No significant improvements were found for QUALID (t = -0.278, p = .783), MMSE (t = 0.819, p = .419), or CGI (F1,84 = 0.760, p = .520).

QUALID scores were compared with scores on the NPI, CMAI, and CGI at baseline and endpoint (Table 2). At both baseline and endpoint, the QUALID scale was correlated with NPI total score (baseline: τ = 0.270, p = .037; endpoint: τ = 0.404, p = .002), NPI Depression (baseline: τ = 0.332, p = .022; endpoint: τ = 0.381, p = .008), NPI Irritability (baseline: τ = 0.288, p = .034; endpoint: τ = 0.346, p = .011), and CMAI Verbal Aggression (baseline: τ = 0.349, p = .009; endpoint: τ = 0.294, p = .028). The QUALID was correlated with NPI Agitation/Aggression only at endpoint (τ = 0.414, p = .002), as was NPI Anxiety (τ = 0.290, p = .049), NPI Hallucinations
### TABLE 1.
Outcome measures at baseline and endpoint

| ITT Population (n=31) | Baseline     | Month 1   | Month 2   | Endpoint   | F or t (p value) |
|-----------------------|--------------|-----------|-----------|------------|-----------------|
| QUALID                | 21.3±6.2     | -         | -         | 21.7±7.5   | t = -0.278 (0.783) |
| MMSE                  | 8.7±6.7      | -         | -         | 8.3±7.3    | t = 0.819 (0.419)  |
| NPI Total             | 31.1±18.9    | 20.5±15.5 | 24.7±20.1 | 23.1±20.2  | $F_{3,90} = 4.035$ (0.010) |
| Delusions             | 1.4±2.8      | 1.0±2.5   | 0.8±2.1   | 1.0±2.8    | $F_{3,87} = 0.396$ (0.756) |
| Hallucinations        | 0.7±1.7      | 0.8±2.1   | 0.7±2.2   | 0.5±1.8    | $F_{3,90} = 0.553$ (0.648) |
| Agitation/Aggression  | 6.6±3.3      | 4.3±3.5   | 5.2±3.7   | 4.9±4.2    | $F_{3,90} = 3.721$ (0.014) |
| Depression            | 2.3±3.2      | 1.0±2.0   | 1.4±2.9   | 1.6±3.0    | $F_{3,90} = 2.057$ (0.112) |
| Anxiety               | 1.6±3.0      | 0.4±1.2   | 0.9±2.4   | 1.0±2.4    | $F_{3,90} = 2.552$ (0.060) |
| Elation/Euphoria      | 0.9±2.1      | 0.5±1.3   | 0.3±1.1   | 0.3±1.2    | $F_{3,90} = 2.528$ (0.062) |
| Apathy                | 3.3±3.3      | 2.7±3.3   | 3.3±4.1   | 3.5±4.3    | $F_{3,90} = 0.496$ (0.686) |
| Disinhibition         | 2.7±3.4      | 2.0±3.4   | 1.7±2.9   | 1.5±2.9    | $F_{3,90} = 1.840$ (0.146) |
| Irritability          | 5.6±3.5      | 3.6±3.4   | 4.1±3.6   | 3.9±3.8    | $F_{3,90} = 3.899$ (0.011) |
| Aberrant Motor Behaviour | 2.4±3.3   | 1.6±3.0   | 2.6±3.8   | 2.2±3.5    | $F_{3,90} = 0.842$ (0.474) |
| Sleep                 | 2.0±3.3      | 1.4±2.7   | 1.9±3.0   | 1.5±2.8    | $F_{3,90} = 0.717$ (0.544) |
| Appetite              | 2.0±3.6      | 1.2±2.4   | 1.7±3.3   | 1.5±2.7    | $F_{3,90} = 0.982$ (0.405) |
| CGI                   | 2.7±1.0      | 2.5±1.0   | 2.7±1.0   | 2.6±1.1    | $F_{3,84} = 0.760$ (0.520) |
| CMAI Total            | 64.1±19.6    | 50.8±15.7 | 54.5±15.0 | 55.5±20.3  | $F_{3,90} = 6.301$ (0.001) |
| Physical Aggression   | 24.3±10.2    | 18.5±8.3  | 20.3±9.5  | 18.5±9.1   | $F_{3,90} = 5.928$ (0.001) |
| Verbal Aggression     | 10.1±5.7     | 8.5±4.9   | 8.6±4.6   | 7.2±4.2    | $F_{3,80} = 3.961$ (0.011) |

### TABLE 2.
Kendall correlations between QUALID and other measures

|                      | Correlation at Baseline | p value | Correlation at Endpoint | p value |
|----------------------|-------------------------|---------|-------------------------|---------|
| CGI-C                | 0.212                   | 0.141   | 0.129                   | 0.377   |
| NPI Total            | 0.270                   | 0.037   | 0.404                   | 0.002   |
|                      | 0.053                   | 0.701   | 0.414                   | 0.002   |
|                      | 0.280                   | 0.052   | 0.290                   | 0.049   |
|                      | 0.072                   | 0.620   | -0.071                  | 0.638   |
|                      | 0.154                   | 0.309   | 0.456                   | 0.002   |
|                      | 0.332                   | 0.022   | 0.381                   | 0.008   |
|                      | -0.069                  | 0.649   | 0.126                   | 0.404   |
|                      | 0.265                   | 0.054   | 0.207                   | 0.410   |
|                      | 0.239                   | 0.092   | 0.322                   | 0.026   |
|                      | 0.288                   | 0.034   | 0.346                   | 0.011   |
|                      | -0.144                  | 0.318   | 0.069                   | 0.626   |
|                      | 0.317                   | 0.030   | 0.206                   | 0.161   |
|                      | 0.276                   | 0.062   | 0.192                   | 0.196   |
| CMAI Total           | 0.193                   | 0.137   | 0.277                   | 0.032   |
|                      | 0.225                   | 0.087   | 0.132                   | 0.319   |
|                      | 0.349                   | 0.009   | 0.294                   | 0.028   |
Correlations were calculated between change scores for the QUALID and NPI total, NPI subscales, CMAI and CGI (Table 3). QUALID change scores were correlated with change scores in NPI Apathy ($\tau = 0.345$, $p = 0.012$). However, there were no significant correlations between QUALID and CMAI, CGI, NPI Total or any subscales that were correlated with QUALID scores at either baseline or endpoint. Concurrent validity was tested by comparing changes scores in patients who improved ($n = 19$) based on the NPI and patients who did not. A decrease in 4 points in baseline score is considered to be clinically meaningful. Mean change in QUALID was similar between groups ($t = 0.873$, $p = .390$).

**Responsiveness**

In time,$^{(10,13,14)}$ however, changes in the QUALID score from baseline to endpoint did not correlate with change scores on the NPI, CMAI or CGI. This lack of relationship suggests that the QUALID scale may not be responsive to changes in BPDS.

Concurrent validity was also tested, by comparing QUALID change scores in patients who improved based on the NPI and patients who did not. As the mean change in QUALID scores was similar between both groups, this once again suggests that the QUALID may not be responsive to changes in BPDS.

A previous study looking at the responsiveness of the QUALID scale to drug treatment found that the QUALID was responsive to the changes in BPDS.$^{(23)}$ The discrepancy in this finding may be due to the difference in study length (i.e., 14 days in the previous study compared to three months in the current). It is possible that any short-term benefits from decreased behavioural problems are washed out by deterioration in overall health status over the long term. Differences in results may also reflect differences in the study population. The population in the previous study included 31 late-stage dementia patients residing in long-term care facilities who were given either olanzapine or risperidone. The patients had a mean baseline QUALID of 30.94 and mean NPI of 53.48, both of which are higher than those of the current study and other papers that have studied the QUALID scale.$^{(10,13,14)}$

This study design reflects a more realistic timeframe for a therapeutic intervention, and is comparable to many other studies using antipsychotics,$^{(23-25)}$ with a drug that has been shown to improve behavioural symptoms in moderate to severe AD.$^{(15)}$ The population is similar to most other studies in terms of mean QUALID and MMSE scores, even though the NPI scores were slightly higher than those previously shown.$^{(10,13,14)}$ Therefore, this analysis presents an appropriate design for a study involving patients with moderate to severe Alzheimer’s disease residing in long-term care facilities and, as a result, should provide more applicable conclusions regarding the responsiveness of the QUALID scale to change when a therapeutic intervention is implemented.

**Limitations**

The major limitation of the study was the open-label design. It is also unclear whether family caregiver assessment of QoL would differ from nurses’ assessments. It is possible that results attained from the QUALID scale are accurate, and that to make an impact in patients’ QoL over the long term, larger changes in behaviour, cognition, and function are necessary. Another possibility is that the effects of memantine were not strong enough to elicit a change in QoL in the long-term, despite significant improvements in behaviour rating scales.

Another limitation is the fact that the majority of the patients in this study were male, and therefore the results may not necessarily be applicable to the general population of institutionalized patients with dementia. However, gender does not appear to have a significant effect on quality of life.
in those with dementia. While one study did find that being female was a significant predictor of lower quality of life as measured by the QUALID, there was no difference between males and females in actual QUALID scores, and the authors did not consider the results robust.

CONCLUSION

QoL assessments provide another format for individuals and their caregivers to express whether an intervention made an important difference in the patient’s life. As important clinical decisions may be drawn from perceived QoL effects, it is vital that the QoL data be reliable, valid, and responsive to change. Although the QUALID scale demonstrated that QoL assessments provide another format for individuals and their caregivers to express whether an intervention made an important difference in the patient’s life, it was unable to reflect change when a therapeutic intervention for BPSD was implemented. These results suggest that methods of assessing QoL in moderate to severe AD that are responsive to change are still needed, especially if they are to play an important role in assessing treatment benefits.

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CONFLICT OF INTEREST DISCLOSURES

H.B., G.E., and A.L. have no potential conflicts of interest to disclose. N.H. and K.L. have received research support and speaker’s honoraria from Lundbeck Canada.

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