ORIGINAL RESEARCH

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, $F_{3,90} = 3.721$, $p = .014$; CMAI total, $F_{3,90} = 6.301$, $p = .001$) and overall behaviour (NPI total, $F_{3,90} = 4.035$, $p = .010$), there was no significant change in QUALID score ($t_{30} = -0.278$, $p = .783$). The QUALID was correlated with NPI at baseline ($\tau = 0.270$, $p = .037$) and endpoint ($\tau = 0.404$, $p = .002$), but change scores were not correlated ($\tau = 0.107$, $p = .412$).

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.[10] 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[10,13] and validated in patients with severe dementia residing in long-term care facilities,[13,14] 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 relationship between the QUALID scale and the severity of BPSD as determined by standard validated research scales.

METHODS

Study Procedure

Patients with moderate to severe AD (Mini-Mental State Examination [MMSE] score ≤ 15) and agitation/aggression (Neuropsychiatric Inventory – Nursing Home Version [NPI] -total score ≥ 10, NPI-Agitation/aggression score ≥ 1) at two long-term care sites were recruited to enter a three-month, open-label trial of 10 mg BID memantine, which has been shown to have a beneficial effect on memory and behaviour in AD patients.[15] Details of the study methodology and major outcomes have been reported previously.[16] This study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board, and was conducted in compliance with all relevant federal guidelines.

Assessments were conducted four times throughout the study: at baseline and months 1, 2, and 3. NPI[17,18] Clinical Global Impression – Caregiver (CGI),[19] and Cohen-Mansfield Agitation Inventory (CMAI)[20] were assessed at each visit by a trained research assistant with the patient's primary nurse. The designated primary nurse working with the patient also completed the QUALID at baseline and endpoint (either month 3 or at time of discontinuation if the patient terminated early). The MMSE[21] was assessed at baseline and endpoint using structured interviews with the patient.

The NPI assesses behavioural disturbances in nursing home patients with dementia and consists of 12 subscales examining specific symptom domains, including agitation/aggression and depression. The CGI is a seven-point, observer-rated scale that measures global improvement or change and therapeutic response. The CMAI is a measurement of agitated behaviour in patients with dementia consisting of 29 behaviours rated on seven-point frequency and disruptiveness scales. The MMSE, used extensively in clinical research on patients with dementia as a measure of cognition, is scored on a scale of 0–30 based on various domains of cognitive functioning.

Study Analysis

The analysis was based on the intent-to-treat (ITT) population using last-observation-carried-forward (LOCF). Repeated measure ANOVA was conducted on assessments that were conducted monthly (NPI, CMAI, CGI). Paired sample *t*-tests were used to compare assessments that were conducted only 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 ($F_{3,90} = 4.035$, $p = .010$) and its subscale items: Agitation/Aggression ($F_{3,90} = 3.721$, $p = .014$), and Irritability ($F_{3,90} = 3.899$, $p = .011$); and CMAI Total ($F_{3,90} = 6.301$, $p = .001$) and its subscale items: Physical Aggression ($F_{3,90} = 5.928$, $p = .001$) and Verbal Aggression ($F_{3,90} = 3.961$, $p = .011$). No significant improvements were found for QUALID (t = -0.278, $p = .783$), MMSE (t = 0.819, $p = .419$), or CGI ($F_{3,84} = 0.760$, $p = .520$).

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: $\tau = 0.270$, $p = .037$; endpoint: $\tau = 0.404$, $p = .002$), NPI Depression (baseline: $\tau = 0.332$, $p = .022$; endpoint: $\tau = 0.381$, $p = .008$), NPI Irritability (baseline: $\tau = 0.288$, $p = .034$; endpoint: $\tau = 0.346$, $p = .011$), and CMAI Verbal Aggression (baseline: $\tau = 0.349$, $p = .009$; endpoint: $\tau = 0.294$, $p = .028$). The QUALID was correlated with NPI Agitation/Aggression only at endpoint ($\tau = 0.414$, $p = .002$), as was NPI Anxiety ($\tau = 0.290$, $p = .049$), 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±21	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	$F_{3,90}$ = 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
Agitation/Aggression	0.053	0.701	0.414	0.002
Anxiety	0.280	0.052	0.290	0.049
Delusions	-0.072	0.620	-0.071	0.638
Hallucinations	0.154	0.309	0.456	0.002
Depression	0.332	0.022	0.381	0.008
Euphoria	-0.069	0.649	0.126	0.404
Apathy	0.265	0.054	0.207	0.410
Disinhibition	0.239	0.092	0.322	0.026
Irritability	0.288	0.034	0.346	0.011
Aberrant Motor Behaviour	-0.144	0.318	0.069	0.626
Sleep Disturbance	0.317	0.030	0.206	0.161
Appetite Disturbance	0.276	0.062	0.192	0.196
CMAI Total	0.193	0.137	0.277	0.032
Physical Aggression	0.225	0.087	0.132	0.319
Verbal Aggression	0.349	0.009	0.294	0.028

($\tau = 0.456$, $p = .002$), NPI Disinhibition ($\tau = 0.322$, $p = .026$) and CMAI Total ($\tau = 0.277$, $p = .032$).

Responsiveness

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 ($\tau = 0.345$, $p = .012$). 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 ($t = 0.873$, $p = .390$).

DISCUSSION

It has been suggested that treatments designed to alleviate BPSD may have beneficial effects for patients' QoL, as a strong relationship between BPSD and QoL has been previously observed.[22] The significant relationship between the NPI and CMAI with the QUALID scores at baseline and final assessment suggest that QoL is associated with behavioural symptoms in moderate to severe AD. This result supports conclusions drawn by previous studies examining the relationship between the QUALID scale and BPSD at a single point 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 BPSD.

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 BPSD.

A previous study looking at the responsiveness of the QUALID scale to drug treatment found that the QUALID was responsive to the changes in BPSD.[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.

TABLE 3.
Correlations between change scores of QUALID and other measures between baseline and endpoint

	Kendall Tau	*p value*
NPI Total	0.107	0.412
Delusions	-0.215	0.144
Hallucinations	0.272	0.072
Agitation/Aggression	0.191	0.149
Depression	0.065	0.653
Anxiety	0.159	0.265
Elation	-0.294	0.052
Apathy	0.345	0.012
Disinhibition	0.117	0.409
Irritability	0.245	0.068
Aberrant Motor Behaviour	0.003	0.985
Sleep	-0.041	0.779
Appetite	0.132	0.363
CMAI Total	0.096	0.462
Physical Aggression	0.223	0.092
Verbal Aggression	0.063	0.632
CGI	0.139	0.333

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.[26-28] 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.[29]

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.[30] 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 is associated with BPSD in moderate to severe AD, 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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