Depression correlates with quality of life in people with epilepsy independent of the measures used

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ABSTRACT

Purpose: A number of studies have suggested that depressed mood is one of the most important predictors of quality of life (QoL) in patients with epilepsy. However, the QoL measure used in previous studies was limited to the Quality of Life in Epilepsy (QOLIE) scales. It could be questioned whether correlation of QOLIE with measures of depression is influenced by the properties of the instruments used rather than being a valid effect. By using visual analogue scales, the current study aimed to clarify whether depression and QoL are truly correlated in patients with epilepsy.
Methods: Data from a sample of 261 outpatients with epilepsy attending the Epilepsy Clinics of the Atkinson Morley Outpatient Department, St George's Hospital in London, were analyzed. Patients were screened using the European Quality-of-Life scale (EQ-5D-3L) which includes an overall visual analogue score (EQ-VAS), the Emotional Thermometer (ET7), the Beck Depression inventory—II (BDI-II), the Hospital Anxiety and Depression scale (HADS), and the Major Depression inventory (MDI).
Results: Depression was found to significantly correlate with EQ-VAS score with r coefficient ranging from 0.42 to 0.51 and r^2 coefficients ranging between 0.18 and 0.26. In addition, we identified patients who were depressed according to DSM-IV criteria (MD) and those with atypical forms of depression (AD). The EQ-5D-3L scores in these subjects compared with those without depression (ND) showed a different impact of AD and MD on QoL.
Conclusions: The relationship between depression and QoL in people with epilepsy has been demonstrated to be a robust and valid effect, not a result of potential bias of the specific measures used. However, the strength of the association is influenced by the individual instrument. Atypical or subsyndromic forms of depression are as relevant as DSM-based depression in terms of impact on QoL.

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1. Introduction

Depression is the most frequently reported psychiatric comorbidity among patients with epilepsy. The lifetime prevalence rates range between 24% in community-based studies [1] and 50% in tertiary referral centers or surgery programs [2]. Reasons for such a close link are both biological and psychosocial [3]. In fact, on the one hand, epilepsy is a chronic disorder which brings about social discriminations, burden, and limitations [4]; on the other hand, neuroimaging and neurobiological studies are emphasizing the biological contribution to this association based on neuroanatomical and neurochemical principles [5]. This is further supported by epidemiological studies suggesting a bidirectional relationship between the two disorders, namely that depression does not always follow the onset of the epilepsy but it may also precede the onset of a seizure disorder [6,7], suggesting an underlying common neurobiological background [8].

A number of studies pointed out that depression is the most important predictor of quality of life (QoL), perhaps even more than seizures themselves [9–12]. In addition, depression has been shown to be associated with poor response of epilepsy to antiepileptic drugs (AEDs) [13], as well as poor outcome after epilepsy surgery [14]. So far, the effect of depression on QoL in patients with epilepsy has been demonstrated using the same QoL scale, namely Quality of Life in Epilepsy (QOLIE, either 89 or 31). Moreover, most of the studies have used the Beck Depression inventory (BDI) as a measure for depression and, only recently, the Hospital Anxiety and Depression scale (HADS). While the evidence to date shows a strong correlation between depression scores and QoL, it remains unclear whether this is a true effect or a function of potential biases associated with the specific scales used, namely QOLIE and Beck

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Depression inventory (BDI) or Hospital Anxiety and Depression scale (HADS).

This study aimed to examine the association between depression and QoL in patients with epilepsy using a different independently validated QoL instrument consisting of a visual analogue scale and four different validated measures of depression including a visual analogue scale-based instrument. The potentially different impact of different forms of depression, satisfying DSM-IV criteria and atypical forms or subsyndromic forms, on QoL was also examined.

2. Methods

This study included data collected as part of a service improvement project at the Outpatient Epilepsy Clinics, Atkinson Morley Neurosciences Centre, St George's Hospital in London. Over a ten-month period, as a routine, all patients with an established diagnosis of epilepsy according to ILAE criteria were given a number of questionnaires including those for mood and QoL. Patients with severe learning disabilities, gross cognitive abnormalities, or poor English language skills were excluded from this study.

Participation was voluntary, and anonymously collected data were subsequently analyzed for the purpose of this study. Local Research Ethic Committee deemed the project as a service development project not requiring formal research ethics approval for anonymized data previously collected.

All subjects completed the Beck Depression inventory (BDI-II) [15], the Hospital Anxiety and Depression scale (HADS) [16], the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) [17], and the Emotional Thermometer (ET7) [18]. A Diagnostic and Statistical Manual—IV (DSM-IV) diagnosis of depression was made using the Major Depression inventory (MDI) [19], which was administered to all patients. Quality of life was measured using the EQ-5D-3L [20] which includes an overall visual analogue scale (EQ-VAS).

Both BDI-II and HADS are well-known screening instruments for depression, and both have been validated in the epilepsy setting [21,22]. The NDDI-E is a well-known clinical instrument, developed for the rapid and objective detection of a major depressive episode in patients with epilepsy. It has been found to be a very practical and user-friendly screening instrument in an outpatient setting. The ET7 is a screening tool made up of seven visual analogue scales also validated in patients with epilepsy with a sensitivity of 85.1% and specificity of 78.8%, PPV of 0.463, and NPV of 0.961. The MDI is a self-administered WHO scale which is able to generate an ICD-10 or DSM-IV diagnosis of clinical depression in addition to an estimate of symptom severity.

The EQ-5D-3L consists of two measures, namely the European Quality-of-Life Visual Analogue scale (EQ-VAS) and the European Quality-of-Life 5 Dimension scale (EQ-5D). The EQ-VAS is a visual analogue scale, similar in appearance to a thermometer, for recording an individual's rating for their current health-related quality-of-life state from 'best imaginable health state' at the top with a rating of 100 to 'worst imaginable health state' at the bottom with a rating of 0. Patients mark the point on the scale corresponding to their overall health state. The EQ-5D consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these dimensions can take one of three responses representing three levels of severity: no problems, some or moderate problems, or extreme problems.

Frequencies of categorical, demographic, and clinical variables were analyzed using the χ^2 analysis or Fisher's exact test. Continuous demographic and clinical variables, BDI, HADS, AEP, and ET scores were compared using the Student's t-test for independent samples. Correlations were tested using a bivariate two-tailed parametric correlation procedure (Pearson's coefficient) and simple linear regression procedures. The alpha error was set at 0.05.

Patients with depression were then categorized in two different groups: those with a DSM-IV diagnosis according to the MDI and those who did not satisfied DSM criteria but presented a positive

Table 1
Clinical and demographic characteristics (Total N = 261).

Mean age, (years range)	39.3 (16–89)
Gender %	
Female	54.0%
Male	46.0%
Ethnicity %	
White	80.1%
Black	8.1%
Asian	6.1%
Mixed race	4.2%
Unknown	1.5%
Epilepsy type %	
Generalized	37.2%
Focal	57.8%
Unknown	5.0%
DSM-IV diagnosis of depression (MDI)	17.6%
BDI mean score (SD)	13 (11)
HADS-D, mean score (SD)	4.9 (4.4)
HADS-A, mean score (SD)	7.2 (4.9)
ET-D, mean score (SD)	3.0 (2.9)
NDDI-E, mean score (SD)	12.3 (4.3)
NDDI-E positive screening for depression	34.5%
EQ-VAS mean score (SD)	66.8 (21.4)

DSM IV, Diagnostic & Statistical Manual IV edition; BDI, Beck Depression Inventory; MDI, Major Depression Inventory; ET-D, Emotional Thermometer-Depression; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; HADS-A, Hospital Anxiety and Depression Scale - Anxiety; HADS-D, Hospital Anxiety and Depression Scale - Depression; EQ-VAS, European Quality-of-Life Visual Analogue scale.

screening at the NDDI-E, representing atypical forms of depression. One-way analysis of variance (ANOVA) with post hoc pairwise Tukey's comparisons was used to compare EQ-5D-3L scores in these patients compared with those in subjects without depression (negative MDI and NDDI-E). In this case, the probability level was set to 0.016 (0.05/3) to reduce the Type-I error associated with multiple comparisons. All statistical analyses were 2-tailed and conducted using the Statistical Package for Social Sciences (Version 21 for Windows, SPSS Inc., Chicago, IL).

3. Results

Our sample included 261 patients. Clinical and demographic characteristics are shown in Table 1. The EQ-VAS scores inversely correlated with all measures of depression with coefficients ranging between $r = -0.509$ ($p < 0.001$) for BDI-II and $r = -0.420$ ($p < 0.001$) for NDDI-E (Table 2). Adjusted linear regression scores and scatter plots are shown in Fig. 1.

Utilizing the MDI, 41 patients received a DSM-IV diagnosis of major depression (MD) while 90 had a positive screening with the NDDI-E. We, therefore, identified 49 patients who scored positively according to the NDDI-E screening but did not fulfill DSM criteria for depression representing a group of patients with either atypical forms of depression (AD) or subsyndromic depressive episode (SSDE). The EQ-5D-3L scores in these subjects when compared with those without depression (ND) showed a different impact of AD and MD on QoL (Table 3). Atypical depression was as relevant as MD in terms of QoL in general, as measured with the EQ-VAS, and limitations in daily activities (e.g.,

Table 2
Correlations of EQ-VAS with depression screening scales.

Pearson correlation	EQ-VAS	BDI-II	HADS-D	ET-D	NDDI-E
EQ-VAS	1	−0.509[**]	−0.505[**]	−0.443[**]	−0.420[**]
BDI-II	−0.509[**]	1	0.771[**]	0.741[**]	0.773[**]
HADS-D	−0.505[**]	0.771[**]	1	0.689[**]	0.661[**]
ET-D	−0.443[**]	0.741[**]	0.689[**]	1	0.695[**]
NDDI-E	−0.420[**]	0.773[**]	0.661[**]	0.695[**]	1

BDI, Beck Depression Inventory; ET-D, Emotional Thermometer-Depression; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; HADS-D, Hospital Anxiety and Depression Scale - Depression; EQ-VAS, European Quality-of-Life Visual Analogue scale.
[**] $p < 0.001$.
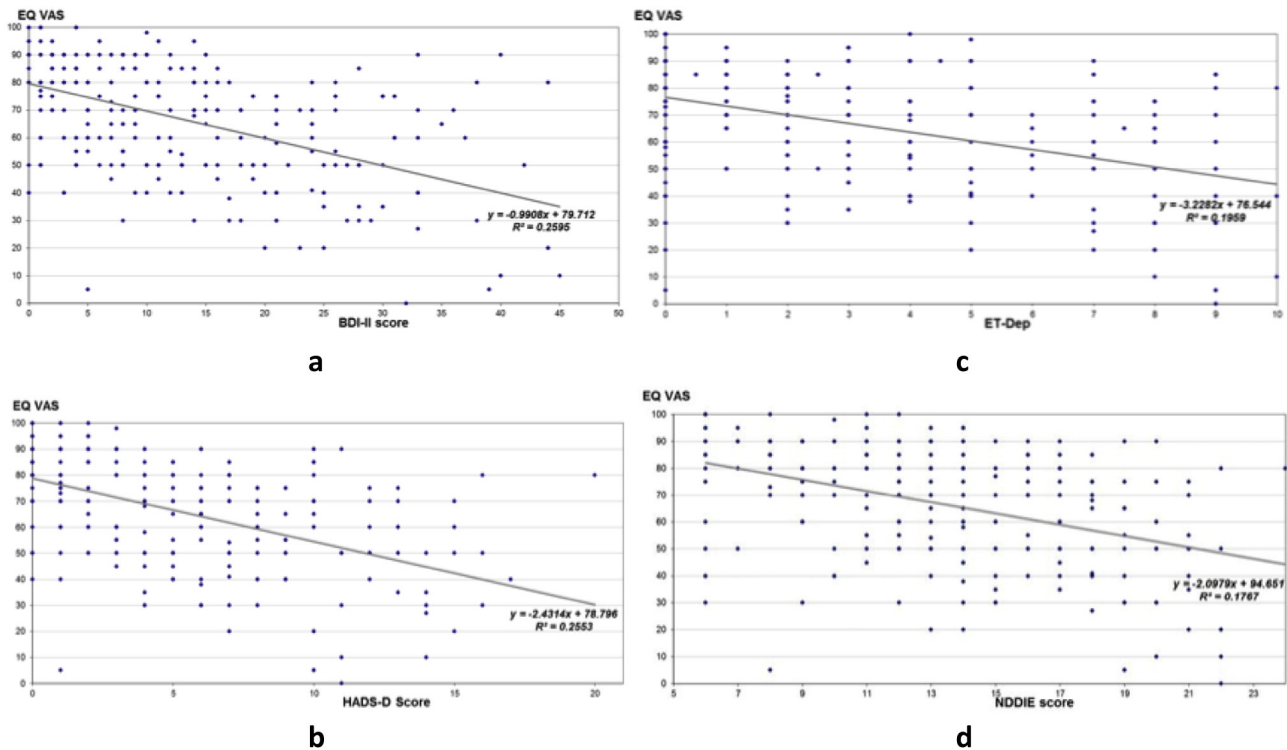
Fig. 1. Scatter plot for EQ-VAS and BDI-II (a), HADS-D (b), ET-Dep (c), and NDDI-E (d). BDI, Beck Depression Inventory; ET-D, Emotional Thermometer-Depression; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; HADS-D, Hospital Anxiety and Depression Scale - Depression; EQ-VAS, European Quality-of-Life Visual Analogue scale.

work, study, housework, family, or leisure activities), as measured with the EQ-5D usual activities subscale.

4. Discussion

Our results confirm that QoL correlates with depression in patients with epilepsy irrespective of the instruments used to measure either QoL or depression including the use of visual analogue measures. This suggests that the correlation of depression with QoL is a valid effect and not a function of potential biases of the individual scales used. In fact, the EQ-VAS is a visual analogue scale and, by definition, neutral in terms of specific items that might have a strong correlation with depression as it happens for the QOLIE. In addition, correlation coefficients are quite similar among the four different clinical instruments for depression used in our study, further confirming the true correlation with QoL.

Our results should be discussed in light of previous studies on QoL in epilepsy. The paper by Boylan [9] using the BDI and QOLIE31 reported a $r^2 = 0.51$, with values ranging from $r^2 = 0.18$ for seizure worry to 0.44 for emotional wellbeing. An earlier paper by Cramer et al. [10], using the Center for Epidemiologic Studies Depression scale (CES-D) and QOLIE89, reported a correlation score r = −0.723. A subsequent paper from the same group using the HADS-D and the QOLIE10 found a correlation coefficient $r^2 = 0.51$ [23]. Our study showed coefficients $r^2 = 0.259$ for the BDI-II and $r^2 = 0.26$ for the HADS-D, suggesting that depression indeed correlates with QoL but the strength of the association could have been influenced by the adopted clinical instrument. In fact, the QOLIE questionnaires have three specific subscales covering emotional wellbeing, energy and fatigue, and cognitive functioning, and all these domains strongly correlate also with depression [10]. In the first paper by Cramer et al. [10], CESD scores showed correlation scores up to −0.776 for the emotional wellbeing compared with those for other domains such as seizure worry (r = −0.386) or physical function (r = −0.320). It is, thus, evident that the way the individual instrument is structured may influence the strength of the association with depression (Fig. 2).

The aim of this study was not to criticize the QOLIE series (QOLIE10, 31, or 89) or their reliability. On the contrary, our aim was to finally demonstrate that depression truly correlates with QoL in patients with epilepsy. Having said that, QoL is a multidimensional construct, and as such, good clinical instruments should include generic domains (i.e., those designed to assess health status among patients with different

Table 3
Quality-of-life scores (EQ-5D-3L) in patients with a DSM-based diagnosis of Major depression (MD), atypical depression (AD), and without depression (ND).

	MD N = 41	AD N = 49	ND N = 166	ANOVA p value	Tukey p value
EQ-VAS (SD)	52.1 (24.8)	60.5 (18.2)	72.7 (19.2)	F = 20.609 p < 0.001	MD > ND p < 0.001 AD > ND p = 0.001
EQ mobility (SD)	1.4 (0.5)	1.2 (0.4)	1.2 (0.4)	F = 5.385 p = 0.005	MD > ND p = 0.004
EQ self-care (SD)	1.2 (0.4)	1.1 (0.3)	1.0 (0.2)	F = 5.177 p = 0.006	MD > ND p = 0.007
EQ activities (SD)	1.7 (0.7)	1.6 (0.6)	1.2 (0.5)	F = 16.853 p < 0.001	MD > ND p < 0.001 AD > ND p = 0.001
EQ pain (SD)	1.8 (0.7)	1.5 (0.5)	1.3 (0.5)	F = 13.825 p < 0.001	MD > AD p = 0.015 MD > ND p < 0.001
EQ Anx/Dep (SD)	2.1 (0.5)	1.7 (0.5)	1.3 (0.5)	F = 43.797 p < 0.001	MD > AD > ND p = 0.001

EQ-VAS, European Quality-of-Life Visual Analogue scale; EQ-5D-3L, European Quality-of-Life 5 Dimension scale.
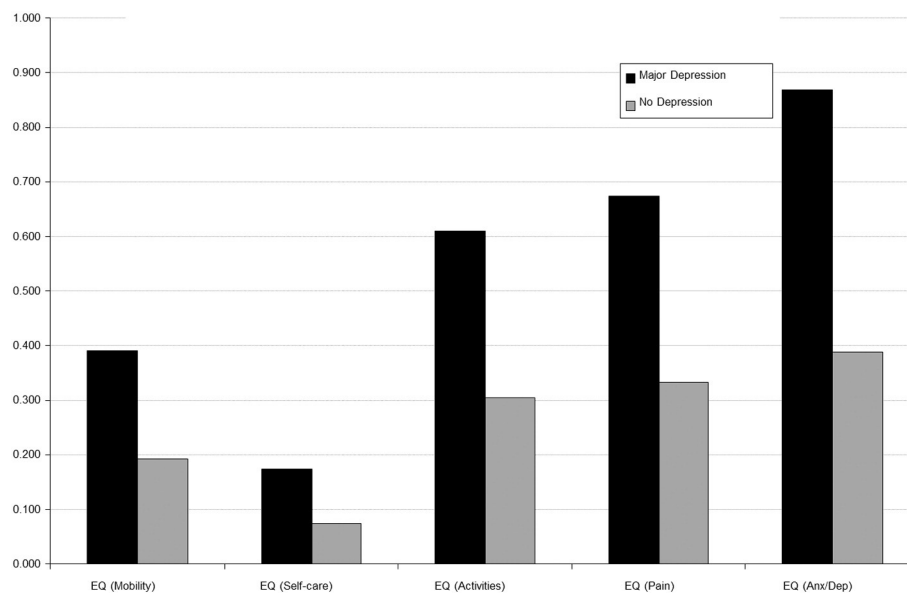
Fig. 2. QoL impairment by EQ-5D domains in patients with and without a DSM-IV diagnosis of depression. EQ-5D, European Quality-of-Life 5 Dimension scale; DSM, Diagnostic & Statistical Manual.

health states, conditions, and diseases) and domains specific to single diseases. It is now established that emotional wellbeing is an important part of QoL in patients with epilepsy, and it is, therefore, evident that questionnaires covering all these aspects, such as the QOLIE series, should be preferred when planning a QoL study in epilepsy.

Obviously, other differences may be responsible for the different correlations observed in our study. In the study by Boylan et al. [9], the prevalence of depression was as high as 54% while, in our study, it was 18%. An interaction between the two factors may therefore be more difficult to tease out or less profound in our study. Most of the studies focused on selected samples of patients with drug-refractory epilepsies while our study investigated an unselected sample of consecutive patients referred to our outpatient clinics.

The different pattern of QoL impairment among people with typical depression fulfilling DSM criteria (MD) and atypical depression (AD) or subsyndromic depressive episode (SSDE) is another interesting finding of our study. Major depression showed to have a significant impact on each of the five domains of EQ-5D. Obviously, it is difficult to say whether all patients who had a positive NDDI-E screening were depressed considering that it has a positive predictive value of 53%. However, our data suggest that, probably, these patients have either an atypical form of depression which does not get diagnosed as major depression as per DSM criteria or subsyndromic depressive episode as they presented with lower scores for QoL compared with patients without depression and in a similar fashion compared with patients with a DSM-based diagnosis of depression. It is now evident that mood disorders in epilepsy present a number of atypical features that are not efficiently captured by standardized clinical instruments shaped on DSM criteria. Reasons for such atypical features are still a matter of debate [5,24]. On the one hand, they may be secondary to the antiepileptic drug (AED) treatment and periictal symptoms. On the other hand, increasing evidence is pointing out that some patients may present with a peculiar mood syndrome largely atypical from those described by international diagnostic systems (i.e., ICD and DSM), namely the interictal dysphoric disorder (IDD) [25]. It is not possible to be certain whether the patients had IDD in our sample.

Finally, our findings should be considered bearing in mind the following limitations. First, seizure frequency was not reported as well as the proportion of seizure-free patients. However, our aim was not to dissect out the relative contribution of depression to QoL compared to depression but verify the correlation between QoL measure and a neutral clinical instrument, namely a visual analogue scale, against different measures of depression. Second, our results may not be representative of the general population of patients with epilepsy as they come from a tertiary referral center where patients with more severe and drug-refractory seizures are present. However, the majority of other studies in this area have been done in selected samples.

In conclusion, our study helps substantiate the finding of correlation of depression with QoL in patients with epilepsy. However, clinical utility of this finding must be explored. All the evidence so far has looked at this correlation in cross-sectional studies. It remains unclear whether identification and treatment of depression in patients with epilepsy would lead to an appreciable, real-world improvement in their QoL. It seems logical to assume; however, there may be as yet unidentified moderators involved in the process, and isolating the depressive effects of AEDs would need to be controlled for. Prospective cohort studies are now required to clarify whether this would indeed be the case.

Disclosures

Alex J Mitchell holds the copyright on the revised Emotional Thermometers tool but has made it freely available (royalty-free) for noncommercial and clinical use. The remaining authors have no conflicts of interest. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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