Rapid detection of major depression in epilepsy: a multicentre study

Frank G Gilliam, John J Barry, Bruce P Hermann, Kimford J Meador, Victoria Vahle, Andres M Kanner

Summary

Background Depression is a common comorbid disorder in epilepsy but is not routinely assessed in neurology clinics. We aimed to create a rapid yet accurate screening instrument for major depression in people with epilepsy.

Methods We developed a set of 46 items to identify symptoms of depression that do not overlap with common comorbid cognitive deficits or adverse effects of antiepileptic drugs. This preliminary instrument and several reliable and valid instruments for diagnosis of depression on the basis of criteria from the Diagnostic and Statistical Manual IV, depression symptom severity, health status, and toxic effects of medication were applied to 205 adult outpatients with epilepsy. We used discriminant function analysis to identify the most efficient set of items for classification of major depression, which we termed the neurological disorders depression inventory for epilepsy (NDDI-E). Baseline data for 229 demographically similar patients enrolled in two other clinical studies were used for verification of the original observations.

Findings The discriminant function model for the NDDI-E included six items. Internal consistency reliability of the NDDI-E was 0·85 and test-retest reliability was 0·78. An NDDI-E score of more than 15 had a specificity of 90%, sensitivity of 81%, and positive predictive value of 0·62 for a diagnosis of major depression. Logistic regression showed that the model of association of major depression and the NDDI-E was not affected by adverse effects of antiepileptic medication, whereas models for depression and generic screening instruments were. The severity of depression symptoms and toxic effects of drugs independently correlated with subjective health status, explaining 72% of variance. Results from a separate verification sample also showed optimum sensitivity, specificity, and predictive power at a cut score of more than 15.

Interpretation Major depression in people with epilepsy can be identified by a brief set of symptoms that can be differentiated from common adverse effects of antiepileptic drugs. The NDDI-E could enable rapid detection and improve management of depression in epilepsy in accordance with internationally recognised guidelines.

Lancet Neurol 2006; 5: 399–405

Published Online
April 3, 2006
DOI: 10.1016/S1474-4422(06)70415-X

Department of Neurology, The Neurological Institute, Columbia University, New York, USA (F G Gilliam MD); **Department of Psychiatry, Stanford University, CA, USA** (J J Barry MD); **Department of Neurology, University of Wisconsin, WI, USA** (B P Hermann PhD); **Department of Neurology, University of Florida, FL, USA** (K J Meador MD); **Department of Neurology, Washington University, USA** (V Vahle MPH); **and Department of Neurology, Rush University Medical Center, IL, USA** (A M Kanner MD)

Correspondence to:
Frank Gilliam, The Neurological Institute, Columbia University, New York, NY 10032, USA
fgilliam@neuro.columbia.edu

Introduction

The diagnosis of major depression in non-psychiatric clinical settings has received much attention in recent years.[1,2] WHO and other national and international health advocacy agencies have explicit guidelines for diagnosis and treatment of major depression in primary care.[3–5] In view of the available evidence, which indicates that major depression is not routinely assessed in neurology clinics,[6] and the fact that most affected patients are subsequently not treated,[7] substantial opportunity exists to improve the quality of care for many people with epilepsy.

Depression is a common comorbid disorder in epilepsy. The prevalence of depressive disorders is reported to be more than 30% in community-based epilepsy samples[8] and 20–55% in specialist epilepsy clinics.[9–11] These rates seem to be higher than in other chronic non-neurological illnesses,[12] and could be associated with specific underlying brain dysfunction.[6,13–16] Depression is a strong predictor of self-perceived health status, independent of seizure rate,[7,17–20] and is associated with increased health-care costs of epilepsy.[21] Furthermore, suicidal ideation and suicide are significantly increased in patients with epilepsy compared with the general population.[22] The relatively high prevalence and subsequent increased disability and mortality make the identification and treatment of major depression important for the optimum management of individuals with epilepsy.[23,24]

Various factors associated with epilepsy could adversely affect the accuracy of a screening technique for depression. For example, side-effects of antiepileptic drugs, such as decreased concentration, fatigue, and sleep disturbance, could overlap with somatic symptoms of depression, as could memory problems, which commonly occur in temporal lobe epilepsy. Also, patterns of symptoms can be atypical in some mood disorders common to epilepsy.[25–27] These confounders could alter the sensitivity and specificity of a screening tool.

The lack of a brief and uncomplicated screening technique specifically designed for use in the outpatient neurology clinic setting could contribute to existing limitations in management. We therefore undertook a multicentre study to assess major depression in epilepsy to develop a brief yet accurate screening technique.

Methods

Participants

Individuals were recruited from outpatient epilepsy clinics of five participating academic medical centres (Stanford University, University of Wisconsin-Madison, Rush University, Georgetown University, and Washington

	Non-depressed (n=170)	Major depression (n=35)
Mean age, years (SD)	38·8 (11·9)	41·5 (11·7)
Sex		
Male	60 (35%)	10 (29%)
Female	110 (65%)	25 (71%)
Ethnic group		
White	130 (76%)	28 (80%)
Black	28 (16%)	3 (9%)
Asian	3 (2%)	0
American Hispanic	7 (4%)	3 (9%)
Other	2 (1%)	1 (3%)
Marital status*		
Married	72 (42%)	12 (34%)
Divorced	21 (12%)	9 (26%)
Widowed	5 (3%)	3 (9%)
Single	72 (42%)	9 (26%)
Employment status		
Retired	4 (2%)	2 (6%)
Employed full-time	66 (39%)	10 (29%)
Employed part-time	16 (9%)	3 (9%)
Full-time student	12 (7%)	2 (6%)
Unemployed	43 (25%)	12 (34%)
Homemaker	13 (8%)	3 (9%)
Other	16 (9%)	3 (9%)
Mean WRAT score (SD)	96·4 (13·5)	96·9 (13·7)
Seizure type		
Simple partial	49 (29%)	14 (40%)
Complex partial	98 (58%)	20 (57%)
Partial evolving to secondary general	59 (35%)	13 (37%)
Absence	16 (9%)	4 (11%)
Myoclonic	8 (5%)	1 (3%)
Clonic	2 (1%)	0
Tonic	2 (1%)	1 (3%)
Tonic-clonic	57 (34%)	9 (26%)
Atonic	2 (1%)	0
Mean time since onset of non-febrile seizures, years (SD)	18·3 (12·9)	18·6 (13·1)
Currently taking medication for depression†	30 (18%)	17 (49%)

Data are number (%) unless otherwise stated. WRAT=wide range achievement test-3. *Two people in the depressed group did not disclose their marital status. †χ^2=18·4, p<0·001; no other significant between group differences.

Table 1: **Demographic and clinical characteristics of the study sample**

	Always or often	Sometimes	Rarely	Never
Everything is a struggle	4	3	2	1
Nothing I do is right	4	3	2	1
Feel guilty	4	3	2	1
I'd be better off dead	4	3	2	1
Frustrated	4	3	2	1
Difficulty finding pleasure	4	3	2	1

For the statements in the table, patients are asked to circle the number that best describes them over the past 2 weeks including the day of the assessment.

Table 2: **Items determined by the discriminant function analysis as the optimum model for identification of major depression (presented as the NDDI-E)**

University). The study protocol and informed consent documents were approved by the human subjects protection committees at each institution. Patients provided written informed consent before study enrolment. Inclusion criteria were: age 18 years or older; current diagnosis of epilepsy requiring treatment with one or more antiepileptic drugs; stable dose of the antiepileptic drug regimen for at least the past 30 days; a score of more than 69 on the wide range achievement test-3 (WRAT-3) to ensure adequate reading ability to complete self-report forms; and ability to provide informed consent and comply with the study protocol. Exclusion criteria were: current treatment with vagal nerve stimulation; presence of clinically significant medical or psychiatric comorbidity (eg, psychosis or delirium) that could, in the opinion of the investigator, prevent accurate completion of the study questionnaires; and inability to speak or read English adequately to follow the study protocol. A separate cohort of patients from two clinical studies (one with similar inclusion and exclusion criteria) was used for validation of the observations from the original sample. One of these studies included two sites (Columbia University and Washington University) that contributed 70 participants and the other was a 15-site study that enrolled 159 patients.

Procedures

The multidisciplinary research team composed of two neurologists (KJM, FGG), a psychiatrist (JJB), a neuropsychologist (BPH), and a physician who was board certified in both neurology and psychiatry (AMK). All had substantial experience of clinical research in epilepsy and associated neuropsychological problems. Each of the investigators was asked to provide items or phrases that would identify symptoms of depression that would not be similar to common adverse effects of antiepileptic drugs—eg, decreased concentration or appetite change—or cognitive problems commonly reported in people with epilepsy—eg, memory dysfunction. The initial instrument consisted of a total of 46 unique items, with each item scored on a Likert-like scale. A stepwise method for the discriminant analysis (SPSS version 11.0.1) was used to ascertain the most efficient set of items that correctly classified patients as having major depression or not based on the mini international neuropsychiatric interview (MINI).[28] The MINI is a previously validated interviewer-administered, structured, diagnostic, psychiatric interview that renders a dichotomous classification of major psychiatric disorders. To assess consistency and validity of the discriminant analysis we compared the Wilk's lambda and unexplained variance methods as well as F value (entry 3·84; removal 2·71) and probability of F (entry 0·05; removal 0·1) criteria.

Statistical analysis

For the items selected for the neurological disorders depression inventory for epilepsy (NDDI-E) by the

discriminant analysis, item-to-item correlation with Spearman correlation coefficient was used to determine redundancy. An item that correlated at an $r \geq 0{\cdot}7$ possibly duplicated the content of the other item, and could be considered for removal.

Internal consistency reliability was ascertained by Cronbach's alpha coefficient.[29] This estimate expresses the degree of consistency of the scores across individuals, and models the random error from item selection. An alpha coefficient of $>0{\cdot}70$ is deemed to be adequately unidimensional and supports summing items into a total scale score.

Test-retest reliability was assessed by comparison of the NDDI-E scores at baseline and then 14 days later. Participants were given the NDDI-E with a self-addressed and stamped envelope to improve compliance in returning the questionnaire. Spearman correlation was used to ascertain the test-retest reliability.

For sensitivity and specificity testing of the NDDI-E, the diagnosis of major depression was defined by a different technique from the MINI; the structured clinical interview for the Diagnostic and Statistical Manual IV (SCID)[30] was assessed by the receiver operating characteristic (ROC) curve analysis (SPSS version 11.0.1). The ROC analyses for the Beck depression inventory (BDI) and the Center for Epidemiological Studies depression (CES-D) scale in a portion of this sample were published previously;[31] the analysis of the complete sample is included in this article for comparison with the NDDI-E. The potential confounding influence of adverse effects of antiepileptic drugs on the assessment of depression was examined by including the adverse events profile[32] as an independent variable and the SCID diagnosis of major depression as the dependent variable in logistic regression analysis. The adverse events profile is a reliable and valid assessment of the 19 most common negative side-effects of antiepileptic drugs,[32] and is recommended by the International League Against Epilepsy Commission on Outcome Assessment.[33] To provide additional data for the NDDI-E's extent of partition from self-reported toxic effects of medication, the independent associations of the NDDI-E and the adverse events profile with subjective health status were assessed through linear regression with the quality of life in epilepsy inventory-89 (QOLIE-89).[34]

As supplemental support for the construct validity of the NDDI-E, we ascertained the correlation with other previously validated screening instruments for depression, including the BDI[35] and the CES-D.[36]

Role of the funding source

The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

***Panel*: Items excluded by discriminant analysis from the model of symptoms that most accurately classifies major depression in epilepsy**

Nothing is good enough
Feel like crying
Afraid to go out
Fearful
Disappointed
Shaky inside
Gloomy
Lonely
Get impatient easily
No hope
Act reckless
Feel like something bad will happen
Agitated
Racing thoughts
Can't make decisions
Moody
People stare at me
Annoyed at everything
Worried
Tired when I wake up
Other people are unfriendly
Restless
Prefer to be alone
Tense or nervous
Hurt all over
Make others uncomfortable
Sad or blue
Feel like killing myself
Need less sleep than usual
Difficulty making friends
I'm blamed for things
Avoid other people
People are out to get me
Too much energy at times
Edgy
Angry
Get upset easily
Have arguments
Irritable or cranky
Don't like myself

Results

205 participants were enrolled in the study. The five participating centres recruited at least 40 patients each. 35 (17%) participants met MINI criteria for the diagnosis of major depression, nine (4%) met criteria for dysthymia, and 30 (15%) reported recent suicidal thoughts. The demographic and clinical characteristics of the sample are presented in table 1. There was no difference between centres for age, sex, duration of epilepsy, marital status, or employment, but the proportion of patients with depression did differ between sites. However, inclusion

Cut score	NPV	PPV	Specificity	Sensitivity	Positives	Negatives	AUC	SE	95% CI	p
>12	0·98	0·40	0·71	0·94						
>15	0·96	0·62	0·90	0·81	32	158	0·940	0·019	0·90–0·98	0·0001
>18	0·92	0·90	0·98	0·56						

AUC=area under curve; SE=standard error; PPV=positive predictive value; NPV=negative predictive value.

Table 3: **ROC and diagnostic efficiency statistics of the NDDI-E for the diagnosis of current major depression, based on the SCID**

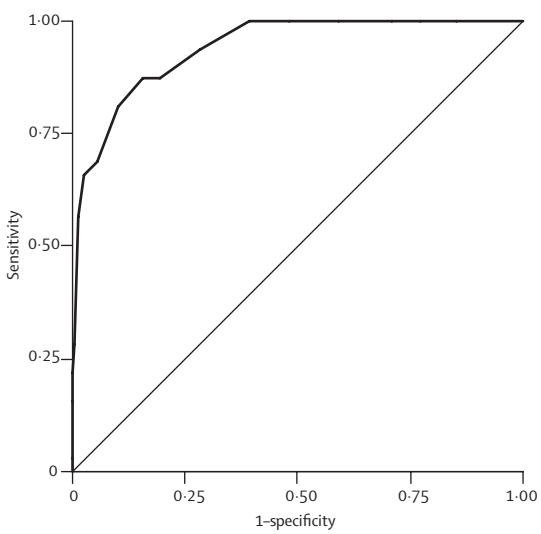

Figure 1: **ROC curve of the NDDI-E, with SCID-defined current major depression**

of site in the logistic regression analysis, as reported below, did not alter the effect of the adverse events profile scores.

Discriminant analysis identified a model of six items that offered the optimum classification of participants as having major depression or not. The model was identical using each method and different *F* criteria in the stepwise analysis. The items and format of the NDDI-E are shown in table 2, and items excluded from the model by the discriminant analysis are presented in the panel. No item-to-item correlation was ≥0·7. Cronbach's alpha for the six items of the NDDI-E was 0·85, indicating acceptable internal consistency reliability. Test-retest reliability was supported by a Spearman correlation of 0·78 for the two NDDI-E assessments done 2 weeks apart.

The results of the ROC analysis of the NDDI-E are presented in table 3 and figure 1. Logistic regression with the SCID diagnosis of current major depression as the dependent variable showed that the NDDI-E had a higher odds ratio than did the BDI or the CES-D, although the 95% CIs overlapped (table 4). Inclusion of the adverse events profile did not significantly change the model of the association of the NDDI-E with major depression, but did affect the models for both the BDI and the CES-D (Wald statistic p=0·03 for both).

Although similar ROC analyses of the BDI and CES-D were previously reported in a portion of the sample,[31] we present the final results for more direct comparison with the NDDI-E. At a cut score of more than 11, the BDI had a sensitivity of 0·93, a specificity of 0·76, a positive predictive value of 0·42, and a negative predictive value of 0·98. At a cut score of more than 14, the CES-D had a sensitivity of 0·90, a specificity of 0·77, a positive predictive value of 0·45, and a negative predictive value of 0·98.

NDDI-E total score, independent of adverse effects of medication, predicted subjective health status, based on the QOLIE-89 total score. However, the adverse events profile was also associated with health status (partial correlation r=–0·60; p<0·0001). More than 70% of the variance of QOLIE-89 summary scores was explained by the NDDI-E and adverse events profile summary scores (adjusted R^2=0·72; p<0·0001). The variance of the QOLIE-89 score explained in a univariate model for the NDDI-E was 0·57, and for the adverse events profile was 0·68. The scatter plot for the comparison of QOLIE-89 to NDDI-E (possible summary score range 6–24) and adverse events profile (possible summary score range 19–76) scores is shown in figure 2.

These results suggested a unique role for the NDDI-E in the assessment of depression in the setting of epilepsy, but additional construct validity was lent support by correlations with previously validated instruments. The Spearman correlation coefficient was 0·78 for the NDDI-E and the BDI, and 0·77 for the NDDI-E and the CES-D (p<0·0001).

The verification sample consisted of 229 epilepsy patients who had been enrolled in two subsequent studies of depression symptoms in epilepsy. The demographic

	OR* (95% CI)	OR† (95% CI)	Change in OR‡
NDDI-E (>15)	41·2 (14·3–119·2)	33·9 (9·1–127·1)	–18%
BDI (>11)	33·5 (10·6–105·6)	15·9 (4·6–57·4)	–53%
CES-D (>14)	35·2 (9·9–124·5)	23·8 (5·9–96·2)	–33%
Adverse events profile (>40)	11·5 (3·8–35·5)	..	..

Dependent variable is a current major depressive episode based on the SCID. *Univariate odds ratio from a logistic regression adjusting for age, sex, and study site. †Model contains the independent variable and the adverse events profile score dichotomised at the cut scores within the parentheses, adjusting for age, sex, and study site. ‡The adverse events profile significantly contributed to the logistic regression models that included the BDI or the CES-D (Wald statistic p=0·03 for both), but not the NDDI-E.

Table 4: **Influence of adverse medication effects on the association of screening instruments with major depression**

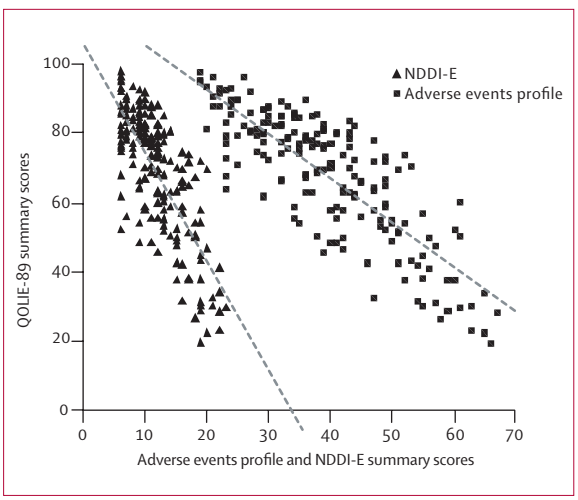

***Figure 2*: Scatter plot of the correlation of QOLIE-89 summary scores with the NDDI-E (partial *r*=–0·39, p<0·0001) and the adverse events profile (partial *r*=–0·60, p<0·0001)**
Adjusted R^2 was 0·72 (p<0·0001) for regression model with QOLIE-89 as the dependent variable.

and clinical epilepsy characteristics of this sample were similar to the validation sample. Specifically, the mean age was 39 years (SD 12·6) and 63% were women. Ethnic group distribution included 13% black, 2% Asian, and 85% white. 71 met MINI criteria for major depression. ROC analysis of the NDDI-E showed an area under the curve of 0·77 (95% CI 0·70–0·83). Sensitivity and specificity for an NDDI-E cut score of more than 15 were 73% and 72%. The positive predictive value for this cut score was 0·53 and the negative predictive value was 0·86. The sensitivity, specificity, and positive predictive values were 0·96, 0·33, and 0·39 for a BDI cut score of more than 11; 0·85, 0·50, and 0·43 for a BDI cut score of more than 15; and 0·74, 0·59, and 0·33 for a CES-D cut score of more than 14. Because of the design of the primary studies, this sample included only patients with significant symptoms of depression based on a CES-D cut score of more than 11; this constriction of the range of mood symptoms could explain the differences in sensitivity and specificity compared with the original validation sample.

Discussion

Internal consistency reliability of the NDDI-E was 0·85 and test-retest reliability was 0·78. An NDDI-E score of more than 15 had a specificity of 90%, sensitivity of 81%, and positive predictive value of 0·62 for a diagnosis of major depression. The model of association of major depression and the NDDI-E were not affected by adverse effects of antiepileptic medication.

Major depression is recognised as a common disorder in medical clinic settings, and multiple national[4,5] and international[3] initiatives have subsequently recommended use of non-psychiatrists to enable early identification and treatment of the disorder. These programmes recognise the potential limitations of non-psychiatrists in the diagnosis of psychiatric disorders, but also emphasise that many patients with depression would never be treated if they were not screened by the physician managing their primary medical condition.[37] Considering the increased prevalence of depression in community epilepsy samples,[8] and the relatively low rates of screening[6] and treatment,[7] major depression could represent an opportunity for improvement in epilepsy care provided by neurologists and epileptologists.

Although screening instruments are not intended to replace clinical judgment in the diagnosis of major depression, they are recommended by many professional and governmental health organisations as aids for identification.[1,38] Systematic screening with appropriate methods could double the sensitivity for diagnosing major depression without compromising specificity in the medical clinic setting.[39] Use of instruments with adequate specificity at a cut score that yields a high sensitivity can keep to a minimum false negative and false positive diagnoses. However, even instruments with high sensitivity and specificity vary in positive predictive value. The positive predictive value of the BDI and CES-D were 0·42 and 0·45 in our epilepsy sample.[31] The patient health questionnaire-2 has been presented as a simple two-item tool, but at the suggested cut score of more than 2, at which the sensitivity is 83% and the specificity is 92% in general medical clinics, the positive predictive value is 0·38.[40] The positive predictive value of 0·62 of the NDDI-E at a cut score of more than 15, with a sensitivity of 81% and specificity of 90%, suggests that the NDDI-E might be more accurate than other available instruments in people with epilepsy. Furthermore, the results of the ROC analysis of the BDI from the verification sample emphasise that depression screening instruments that include common side-effects of antiepileptic drugs as symptoms of depression will increase sensitivity at the expense of worsened specificity; although this trade-off could be viewed as acceptable in certain clinical situations, the high rate of these specific symptoms in people taking common antiepileptic drugs make interpretation of BDI results very difficult in the busy epilepsy clinic setting.

The absence of sadness or irritability items in the NDDI-E, as defined by the discriminant function analysis, is of potential clinical and neurobiological importance. Other studies of depression in epilepsy have also reported increased rates of frustration, anhedonia, and hopelessness compared with sadness or depressed mood.[41] The biological plausibility of this finding is lent support by recent functional neuroimaging studies that show anterior temporal lobe activation during sadness, and frontal activation during volitional suppression of sadness;[42] cortical dysfunction in temporal lobe epilepsy with intact frontal function could result in reduced episodes of sadness during the depressed state. If this notion is correct, symptoms of sadness or depressed mood might

be less useful in screening for depression in some common syndromes such as temporal lobe epilepsy.

The results of this study lend support to and augment previous observations of the association of depression and health status.[7,17–20,43] Most studies have not measured severity of adverse effects of antiepileptic drugs, which could confound the diagnosis of depression through similarity with the somatic symptoms. As recommended by the International League Against Epilepsy Commission on Outcome Measurement, we included the adverse events profile and the QOLIE-89 as supplemental functional measures.[33] Although the adverse events profile correlated with the NDDI-E, both instruments independently correlated with overall health status as estimated by the QOLIE-89. The finding that the combination of NDDI-E and the adverse events profile explained more than 70% of the variance in the QOLIE-89 total score could be useful to physicians who wish to quickly assess specific treatable comorbid disorders in the busy neurology clinic setting.

The current study has several potential limitations that should be considered. The patient sample was ascertained through epilepsy clinics at tertiary care academic centres, and might not reflect community samples of less complicated epilepsy. Additionally, the construct of depression in epilepsy might be more complex and atypical than is subsumed by major depression and needs further study, as suggested by Blumer and colleagues in the description of the interictal dysphoric disorder.[26,44] However, identification and treatment of major depression is a recognised standard of care for the medical community that should also apply to people with epilepsy.[4,5,38,45]

Contributors

FGG and AMK were joint lead investigators, selected the overall study design and variables, and interacted with statisticians for the statistical procedures; FGG wrote the initial version of the manuscript and made subsequent revisions after consultation with the listed authors; BPH, AMK, KJM, and JJB participated in the study design, subject enrolment, data collection, and revision of the manuscript. BPH also participated in the data analysis. VV served as the study coordinator and data manager.

Conflicts of interest

BPH, FGG, and VV have no conflicts of interest. KJM has received grants from GlaxoSmithKline, NeuroPace, SAM Technology, and UCB, is a consultant for Abbott, Cyberonics, Eisai, GlaxoSmithKline, NeuroPace, Novartis, OrthoMcNeil, and UCB, has received honoraria from GlaxoSmithKline, OrthoMcNeil, and UCB, and is Associate Editor of the Journal of International Neuropsychological Society. AMK and JJB have received consultants fees and honoraria from GlaxoSmithKline.

Acknowledgments

This research was supported by National Institutes of Health grants NS40808 and NS047551 (research and salary support for FG), and a research grant from GlaxoSmithKline for partial salary support for a research coordinator at each site.

References

1 Rollman BL. Reflections on the 10th anniversary of the AHCPR's guideline for the treatment of depression in primary care. *J Gen Intern Med* 2003; **18:** 492–93.

2 Olfson M, Marcus SC, Druss B, Elinson L, Tanielian T, Pincus HA. National trends in the outpatient treatment of depression. *JAMA* 2002; **287:** 203–09.

3 WHO. The constitution of the World Health Organization. *WHO Chron* 1947; **1:** 29.

4 AHCPR. Depression in primary care: detection and diagnosis. AHCPR Publication No 93-0550. Clinical Guideline Number 5 (National Library of Medicine DOCLINE Information: CAT/9411422); 1993.

5 Pincus HA, Pechura CM, Elinson L, Pettit AR. Depression in primary care: linking clinical and systems strategies. *Gen Hosp Psychiatry* 2001; **23:** 311–18.

6 Gilliam FG, Santos J, Vahle V, Carter J, Brown K, Hecimovic H. Depression in epilepsy: ignoring clinical expression of neuronal network dysfunction? *Epilepsia* 2004; **45:** 28–33.

7 Boylan LS, Flint LA, Labovitz DL, Jackson SC, Starner K, Devinsky O. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology* 2004; **62:** 258–61.

8 Ettinger A, Reed M, Cramer J. Depression and comorbidity in community-based patients with epilepsy or asthma. *Neurology* 2004; **63:** 1008–14.

9 Lambert MV, Robertson MM. Depression in epilepsy: etiology, phenomenology, and treatment. *Epilepsia* 1999; **40** (suppl 10)**:** S21–47.

10 Gilliam F, Hecimovic H, Sheline Y. Psychiatric comorbidity, health, and function in epilepsy. *Epilepsy Behav* 2003; **4** (suppl 4)**:** S26–30.

11 Hermann BP, Seidenberg M, Bell B. Psychiatric comorbidity in chronic epilepsy: identification, consequences, and treatment of major depression. *Epilepsia* 2000; **41** (suppl 2)**:** S31–41.

12 Beghi E, Spagnoli P, Airoldi L, et al. Emotional and affective disturbances in patients with epilepsy. *Epilepsy Behav* 2002; **3:** 255–61.

13 Bromfield EB, Altshuler L, Leiderman DB, et al. Cerebral metabolism and depression in patients with complex partial seizures. *Arch Neurol* 1992; **49:** 617–23.

14 Quiske A, Helmstaedter C, Lux S, Elger CE. Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis. *Epilepsy Res* 2000; **39:** 121–25.

15 Savic I, Lindstrom P, Gulyas B, Halldin C, Andree B, Farde L. Limbic reductions of 5-HT1A receptor binding in human temporal lobe epilepsy. *Neurology* 2004; **62:** 1343–51.

16 Giovacchini G, Toczek MT, Bonwetsch R, et al. 5-HT1A receptors are reduced in temporal lobe epilepsy after partial-volume correction. *J Nucl Med* 2005; **46:** 1128–35.

17 Gilliam F. Optimising health outcomes in active epilepsy. *Neurology* 2002; **58** (suppl 5)**:** S9–19.

18 Cramer JA, Blum D, Reed M, Fanning K. The influence of comorbid depression on quality of life for people with epilepsy. *Epilepsy Behav* 2003; **4:** 515–21.

19 Perrine K, Hermann BP, Meador KJ, et al. The relationship of neuropsychological functioning to quality of life in epilepsy. *Arch Neurol* 1995; **52:** 997–1003.

20 Johnson EK, Jones JE, Seidenberg M, Hermann BP. The relative impact of anxiety, depression, and clinical seizure features on health-related quality of life in epilepsy. *Epilepsia* 2004; **45:** 544–50.

21 Cramer JA, Blum D, Fanning K, Reed M. The impact of comorbid depression on health resource utilization in a community sample of people with epilepsy. *Epilepsy Behav* 2004; **5:** 337–42.

22 Jones JE, Hermann BP, Barry JJ, Gilliam FG, Kanner AM, Meador KJ. Rates and risk factors for suicide, suicidal ideation, and suicide attempts in chronic epilepsy. *Epilepsy Behav* 2003; **4** (suppl 3)**:** 31–38.

23 Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biol Psychiatry* 2003; **54:** 388–98.

24 Barry JJ, Huynh N, Lembke A. Depression in individuals with epilepsy. *Curr Treat Options Neurol* 2000; **2:** 571–85.

25 Robertson MM, Trimble MR, Townsend HR. Phenomenology of depression in epilepsy. *Epilepsia* 1987; **28:** 364–72.

26 Blumer D, Montouris G, Hermann B. Psychiatric morbidity in seizure patients on a neurodiagnostic monitoring unit. *J Neuropsychiatry Clin Neurosci* 1995; **7:** 445–56.

27 Getz K, Hermann B, Seidenberg M, et al. Negative symptoms in temporal lobe epilepsy. *Am J Psychiatry* 2002; **159:** 644–51.

28 Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; **59** (suppl 20)**:** 22–33.

29 Cronbach LJ. Coefficient alpha and the internal structure of tests. *Psychometrika* 1951; **16:** 297–334.

30 Spitzer RL, Williams JB, Gibbon M, First MB. The structured clinical interview for DSM-III-R (SCID) I: history, rationale, and description. *Arch Gen Psychiatry* 1992; **49:** 624–29.

31 Jones JE, Hermann BP, Woodard JL, et al. Screening for major depression in epilepsy with common self-report depression inventories. *Epilepsia* 2005; **46:** 731–35.

32 Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. *Epilepsia* 1997; **38:** 353–62.

33 Baker GA, Camfield C, Camfield P, et al. Commission on outcome measurement in epilepsy, 1994–1997: final report. *Epilepsia* 1998; **39:** 213–31.

34 Devinsky O, Vickrey BG, Cramer J, et al. Development of the quality of life in epilepsy inventory. *Epilepsia* 1995; **36:** 1089–104.

35 Lustman PJ, Clouse RE, Griffith LS, Carney RM, Freedland KE. Screening for depression in diabetes using the Beck depression inventory. *Psychosom Med* 1997; **59:** 24–31.

36 Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Measure* 1977; **1:** 385–401.

37 Rost K, Nutting P, Smith J, Werner J, Duan N. Improving depression outcomes in community primary care practice: a randomized trial of the QuEST intervention. *J Gen Intern Med* 2001; **16:** 143–49.

38 Pignone MP, Gaynes BN, Rushton JL, et al. Screening for depression in adults: a summary of the evidence for the US Preventive Services Task Force. *Ann Intern Med* 2002; **136:** 765–76.

39 Lowe B, Spitzer RL, Grafe K, et al. Comparative validity of three screening questionnaires for DSM-IV depressive disorders and physicians' diagnoses. *J Affect Disord* 2004; **78:** 131–40.

40 Kroenke K, Spitzer RL, Williams JB. The patient health questionnaire-2: validity of a two-item depression screener. *Med Care* 2003; **41:** 1284–92.

41 Kanner AM, Soto A, Gross-Kanner H. Prevalence and clinical characteristics of postictal psychiatric symptoms in partial epilepsy. *Neurology* 2004; **62:** 708–13.

42 Levesque J, Eugene F, Joanette Y, et al. Neural circuitry underlying voluntary suppression of sadness. *Biol Psychiatry* 2003; **53:** 502–10.

43 Beghi E, Roncolato M, Visona G. Depression and altered quality of life in women with epilepsy of childbearing age. *Epilepsia* 2004; **45:** 64–70.

44 Blumer D, Montouris G, Davies K. The interictal dysphoric disorder: recognition, pathogenesis, and treatment of the major psychiatric disorder of epilepsy. *Epilepsy Behav* 2004; **5:** 826–40.

45 Rollman BL, Reynolds CF 3rd. Minor and subsyndromal depression: functional disability worth treating. *J Am Geriatr Soc* 1999; **47:** 757–58.