FULL-LENGTH ORIGINAL RESEARCH

Quality-of-life outcomes of initiating treatment with standard and newer antiepileptic drugs in adults with new-onset epilepsy: Findings from the SANAD trial

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Summary

Objective: To compare quality-of-life (QoL) outcomes over 2 years following initiation of treatment with a standard or newer antiepileptic drug (AED) in adults with new-onset epilepsy. To examine the impact of seizure remission and failure of initial treatment on QoL outcomes measured over 2 years.

Methods: We conducted a pragmatic, randomized, unblinded, multicenter, parallel-group clinical trial (the Standard and New Antiepileptic Drugs [SANAD] trial) comparing clinical and cost effectiveness of initiating treatment with carbamazepine versus lamotrigine, gabapentin, oxcarbazepine and topiramate, and valproate versus lamotrigine and topiramate. QoL data were collected by mail at baseline, 3 months, and at 1 and 2 years using validated measures. These data were analyzed using longitudinal data models. Continuous QoL measures, time to 12-month remission and time to treatment withdrawal were explored using joint models.

Results: Baseline questionnaires were returned by 1,575 adults; 1,439 returned the 3-month questionnaire, 1,274 returned the 1-year questionnaire, and 1,121 returned the 2-year questionnaire. There were few statistically significant differences between drugs over 2 years in QoL outcomes. Significant association was identified between QoL scores over the 2-year time frame and the risk of experiencing a 12-month remission or treatment withdrawal over that period.

Significance: The choice of initial treatment had no significant effect on QoL by 2-year follow-up. However, overall QoL was reduced with continued seizures, adverse events, and failure of the initial treatment.

KEY WORDS: Outcomes research, Joint models, Antiepileptic drugs, Seizure remission, Treatment failure.

Previous studies comparing different drugs or treatment policies for the management of epilepsy have not systematically addressed quality of life (QoL) outcomes.[1,2] Many have either focused on clinical outcomes only or included only limited QoL assessments. For example, a recent Cochrane review evaluating the effectiveness of levetiracetam add-on therapy for drug-resistant focal epilepsy found that only 4 of 11 trials provided data on QoL outcomes, making firm conclusions difficult.[3] Individual trials comparing different antiepileptic drugs (AEDs) include those by Saetre et al.[4] and Kowalik et al.,[5] but in both, outcome assessment was limited to only a few QoL domains.

Furthermore, the majority of trials have largely involved patients with refractory partial seizures. Few have involved those patients with new-onset epilepsy. The SANAD (Standard and New Antiepileptic Drugs) Trial is one of the only ones to make head-to-head comparisons of initiating treat-

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ment with different AEDs, and to assess clinical and cost effectiveness and QoL in a new-onset population; and, due to its pragmatic nature, is reflective of current clinical practice.

In this article, we compare the effects of the policies of initiating treatment with either carbamazepine versus lamotrigine, gabapentin, oxcarbazepine, and topiramate, or valproate versus lamotrigine and topiramate on QoL outcomes over a 2-year time frame. Our broad hypotheses were the following: that the newer drugs will show fewer effects on neuropsychological/psychological and, hence, on broader social function than the older ones; and that they will therefore be associated with reduced QOL burden.

An analysis involving an incomplete responder sample and including only a subset of the QoL outcomes collected at the 2-year time point has been reported previously.[6–8] Herein we provide a full account of *all* QoL outcomes for *all responding* patients at *all* data collection time points up to 2 years. Furthermore, we provide an in-depth examination of the association between QoL over 2 years and the experience of a 12-month seizure remission or treatment failure due to unacceptable adverse events or poor seizure control.

Methods

The study methods have been described in detail elsewhere.[6–8] Briefly, SANAD was a pragmatic, randomized, unblinded, parallel-group clinical trial comparing clinical and cost-effectiveness of the policies of initiating treatment of new-onset epilepsy with either a standard or one of the newer AEDs. SANAD recruited 2,437 patients, ages 5 years and older with a history of two or more clinically definite unprovoked seizures in the previous year, from hospital-based outpatient clinics in the United Kingdom. Patients were entered into one of two randomization arms. Patients with focal epilepsies, for whom clinicians considered carbamazepine to be the standard treatment choice, were allocated either to carbamazepine or to gabapentin, lamotrigine, oxcarbazepine, or topiramate (Arm A). Patients with generalized or unclassified epilepsies, for whom clinicians considered valproate to be the first choice, were allocated either to valproate or to lamotrigine or topiramate (Arm B). Patients were randomized between January 1999 and August 31, 2004. Primary outcomes were time to treatment failure and time to 12-month remission.

It is important to highlight here that the primary purpose of SANAD was to assess the longer term consequences of the policies of initiating treatment with one of a number of possible AEDs. Patients were therefore followed according to the principle of intention-to-treat, being retained for follow-up even where they were withdrawn from the AED to which they were originally randomized. Indeed, during the course of SANAD, clinicians attempted to maximize positive outcomes by making dose and treatment changes as clinically indicated, according to patients' reported experience of seizures or adverse effects. Treatment policies were therefore iterative and representative of routine clinical practice.

QoL was investigated, as a secondary outcome, in those ages 5 years and older, and without any substantial learning disability (as judged by the randomizing clinician from the history and examination). Patients in the QoL substudy were followed for 4 years (up to August 31, 2008) to permit analysis of longer term QoL outcomes. In this article, we focus on the QoL outcomes in adults (defined in this context as aged 16 years or older at time of randomization) measured over the first 2 years following randomization. QoL profiles of the children were assessed using a child-specific battery and have been described elsewhere.[9]

Eligible adults were asked to self-complete QoL questionnaires as early as possible following randomization and commencement of taking an AED, and then at 3 months and annually thereafter. The adult QoL assessment involved use of a battery of previously validated generic and epilepsy-specific measures taken from the NEWQOL (Newly Diagnosed Epilepsy Quality of Life) battery, which examines physical, psychological, social, and cognitive functioning in persons with new-onset seizures.[10] In addition, a revised 12-item version of the "impact of epilepsy scale,"[11] a single item measure of global QoL,[12] and single items relating to education, employment, driving, and marital status were included in the adult assessment. In the 3-month questionnaire, the only QoL outcomes assessed were anxiety, depression, and adverse events; however, all QoL outcomes were assessed in all of the other questionnaires.

Questionnaires were mailed within 1 week of the date of randomization, with a single mailed reminder being sent to nonresponders 3 weeks after the initial mailing and telephone contact made after an additional 3-week period to those failing to respond to the mailed reminder. All questionnaires were accompanied by a cover letter explaining the purpose of the QoL study and a paid reply envelope.

Patients declining to return either a baseline or 3-month questionnaire were sent no further follow-up questionnaires, the assumption being that those who declined to complete questionnaires at this early stage in the life of the trial were "active" refusers who would be unlikely to return later questionnaires. In contrast, all patients completing either the baseline or 3-month assessment were cued to receive all subsequent questionnaires, regardless of whether they returned them at each individual time point, thus maximizing the amount of data collected.

Standard protocol approvals, registrations, and patient consents

The SANAD study (ISRCTN38354748) was commissioned by the Health Technology Assessment (HTA) Programme of UK NHS Research and Development. It received appropriate multicenter and local ethics and

research committee approvals. All patients provided written informed consent for inclusion and for long-term follow-up.

Statistics

All statistical analyses were conducted using R version 3.0.3[13] Sample size for the QoL study was determined by the number of participants enrolled in the clinical trial and defined as eligible for the QoL assessment (see above). Throughout, a p-value < 0.01 denotes statistical significance.

Clinical and demographic characteristics were compared between full responders (those who returned all of the baseline, 3-month, and 1- and 2-year questionnaires), partial responders (returned some but not all of these questionnaires), and nonresponders (did not return any questionnaire) using chi-square, analysis of variance (ANOVA) and Kruskal-Wallis tests, as appropriate. In addition, an exploratory analysis into time taken to respond to a questionnaire was conducted using a Cox proportional hazard model, with age, gender, and their interaction included as covariates.

Continuous NEWQOL measures included anxiety and depression,[14] sense of mastery,[15] Liverpool Adverse Events Profile (AEP),[16] Aldenkamp-Baker Neuropsychological Assessment Schedule (ABNAS),[17] and the Epilepsy Stigma Scale.[18] For the purposes of this analysis, the following categorical NEWQOL items were transformed to a binary response: seizure worry about past seizures (very/fairly/a little vs. not at all), seizure worry about future seizures (very/fairly/a little vs. not at all), social restrictions (severely/fairly/a little vs. not at all), global QoL (poor vs. good), general health perception (excellent, very good, good vs. fair/poor), and health transition (better/same vs. worse than 1 year ago).

Longitudinal models

To make the most efficient use of the QoL data collected, we included all patients who had returned at least one of the questionnaires over the first 2 years of follow-up in a longitudinal model, with QoL as the response variable.

Although questionnaires were intended to be completed at 3 months, 1 year, and annually thereafter from the date of randomization, there was, inevitably, some slight variation in the dates at which patients actually completed questionnaires. To make the most efficient use of these data, all patients were included in the longitudinal models regardless of the exact timing of completion of questionnaire, which was accounted for in the model by inclusion of a variable, "time from randomisation to completion of questionnaire," in addition to variables representing randomized treatment. Random intercept and slope models were initially fitted (to allow estimated baseline QoL outcomes and their predicted rate of change over time to vary between patients); however, where there were model convergence issues, random intercept only models were fitted.

Joint models

To explore the relationship between patient-recorded QoL outcomes over 2 years and clinically recorded outcomes of time to 12-month remission and time to treatment failure, joint longitudinal and time-to-event models were used. These models allowed us to establish whether QoL scores were associated significantly with time to achieve a particular clinical end point—for example, whether shorter time to treatment failure of randomized drug or longer time to achieve 12-month remission was associated with worsening depression scores over 2 years.

The relationship with time to treatment failure was analyzed first by considering failure due to Any Reason (AR) and second by taking into account the Competing Reasons (CRs) for failure (unacceptable adverse event or inadequate seizure control). These two outcomes will be referred to as treatment failure (AR) and treatment failure (CR), respectively. The joint models involving time to 12-month remission and time to treatment failure (AR) were fitted using the JOINER package.[19,20] As the facility to fit models involving competing failure reasons does not currently exist in the JOINER package, models involving treatment failure (CR) were fitted using the JM package.[21,22] The longitudinal component of all joint models contained the same variables as the longitudinal models fitted earlier in the study.

Because of the late inclusion of oxcarbazepine (OXC), all analyses and comparisons including OXC (Arm A only) were based on data for patients randomized after the introduction of OXC (June 1, 2001). Comparisons between the remaining drugs in Arm A were based on all randomized patients during the entire trial period.

Given the number of comparisons undertaken, the type I error rate may have increased. To address this issue, we therefore opted to apply the Bonferroni correction. Examination of the Bonferroni correction to the confidence intervals (CIs) gave intervals close to the 99% level, and therefore for ease of interpretation, 99% CIs are presented throughout.

Values for continuous measures are coefficients from fitted models representing the difference between groups identified by the independent variables with 99% CIs. Values for categorical measures are exponentiated coefficients, to provide odds ratios from fitted models with 99% CIs. Values from the time-to-event components of the joint models are reported as both coefficients and hazard ratios (HRs), both with 99% CIs. The estimate of the association between the longitudinal continuous QoL outcomes and the time-to-event data is given as a coefficient with 99% CIs or as a coefficient and HR both with 99% CIs dependent on the model-fitting methods.

Missing data

In QoL studies, missing data can arise because a participant fails to return a questionnaire, a participant

returns a questionnaire but fails to answer any questions on a particular dimension, or a participant returns a questionnaire and has partially answered questions in a dimension. For the latter, we imputed the mean observed value for that individual within that dimension. No attempt was made to impute values for any dimension with a <50% response to its constituent items. The effect of nonresponse on QoL outcome was investigated by performing a sensitivity analysis for the longitudinal models fitted, using a best case and worst case data set (Tables S2, S3, S4, and S5) generated by identifying the best and worst QoL values recorded in each questionnaire for each arm (across all treatments within that arm). These questionnaire and arm-specific best and worse values were then used to impute values for individuals failing to return that particular questionnaire.

Results

Response rate

Of the 1,983 adults randomized into SANAD, 1,868 (94%) were eligible for QoL assessment; 1,443 in Arm A and 425 in Arm B. A total of 1,575 adults (84% of those eligible) returned a baseline questionnaire, 1,439 adults (77%) returned a 3-month questionnaire, 1,274 (68%) returned a 1-year questionnaire, and 1,121 returned a 2-year questionnaire (73% of those sent a 2-year questionnaire; 60% of those originally eligible). Reasons for nonresponse are shown in the relevant box in Figure 1. The number (and percentage) of patients returning questionnaires at each timepoint for each treatment group within each arm is shown in Table S1. Of note is that the percentage of responders is not markedly dissimilar across treatment groups.

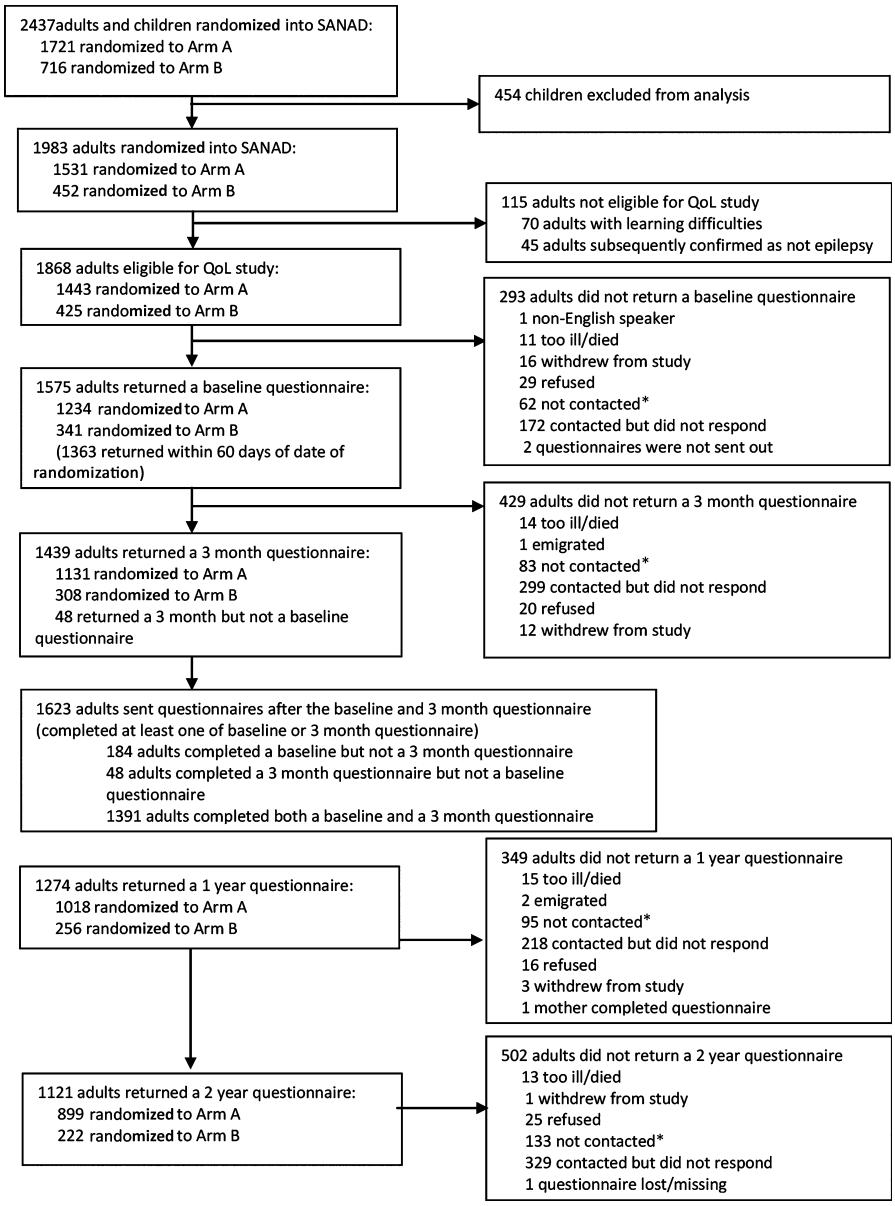

Figure 1.
Flow diagram for participants in QoL analyses. QoL, quality of life.
*Patients were defined as "non-contacts," where we were unable to establish (despite checking with general practitioner (GP)/hospital notes, calling any recorded telephone number(s), and sending a noncontact letter sent to the occupier) whether they were at the address we had on file and were therefore unable to definitively classify them as nonresponders.

Baseline demographic and clinical characteristics

Clinical and demographic details of the patients eligible for the QoL analyses are shown in Table 1. Comparisons of baseline clinical and demographic characteristics between full responders, partial responders, and nonresponders (Table 2) showed that women were more likely to respond than men, the age of full responders was higher than that of partial or nonresponders, and a larger proportion of partial responders than full or nonresponders had a first-degree relative with epilepsy or an idiopathic generalized syndrome, whereas a larger proportion of full responders had a symptomatic/cryptogenic partial syndrome.

Time to respond to questionnaire

For many questionnaires, men and older patients were more likely to return questionnaires faster. However, the interaction between age and gender was often significant, indicating that younger men and older women tended to return questionnaires faster. The Cox proportional hazards assumption appeared reasonable overall.

Impact of initial AED treatment policy

Longitudinal analysis

For Arm A (Table 3) there were few statistically significant differences in QoL outcomes over 2 years between randomized treatment groups. There was an indication that those assigned to topiramate were at higher risk of depression than those assigned to oxcarbazepine (coefficient −1.27 [99% CI 0.13–2.41]). There was also evidence that those randomized to carbamazepine were less likely to worry about past seizures (odds ratio [OR] 0.35 [99% CI 0.13–0.94]) than those initially treated with lamotrigine. In addition, those assigned to gabapentin were more likely than those assigned to oxcarbazepine to experience fair/poor general health perception rather than good/excellent (OR 3.44 [99% CI 1.17–0.09]).

For Arm B (Table 4), there were no statistically significant differences in QoL outcomes by randomized group.

Effect of questionnaire nonresponse

Sensitivity analyses using a best case and worst case dataset (Tables S2, S3, S4, and S5) indicated that no significant results from the original dataset remained significant for both the best and worst case datasets. Patients randomized to gabapentin were more likely than those randomized to oxcarbazepine to experience fair/poor general heath perception rather than good/excellent in both the best and original dataset, but this relationship was not identified in the worst case dataset.

Whether the best or worst case data were used had an impact on statistical significance: notably, with the best case dataset, patients randomized to gabapentin had significantly worse AEP scores than those randomized to oxcarbazepine. This sensitivity analysis indicates that results discussed here may be affected by the reasons for nonreturn of questionnaires.

Joint modelling of longitudinal QoL and time-to-event outcomes

The coefficients for the treatment comparisons for the longitudinal and time-to-event components of all joint models fitted are shown in supplemental Table S6. There was little change in values for the effect of different treatments between the longitudinal analyses and the longitudinal components of the joint models. In the time-to-event components for treatment failure (CR), there was a large proportion of cases for which treatments increased the risk of failure due to inadequate seizure control while reducing risk due to unacceptable adverse events, or vice versa. This effect sometimes resulted in the treatment comparison term remaining insignificant for the overall treatment failure (AR) model, but displaying opposite significant effects for the failure reasons in the competing risks analysis.

A significant association at the 0.01 level was found between time to 12-month remission and the QoL measures of anxiety, depression, AEP, ABNAS, stigma, and sense of mastery for all but one of the treatment comparisons (topiramate [TPM] vs. lamotrigine [LTG] in Arm B for mastery), which achieved significance at the 0.05 level (see Table S7). These results suggest that as the chance of 12-month remission increases, QoL measures show a corresponding improvement (Table S7).

The joint models also showed a significant association between treatment failure (AR) and measures of anxiety, AEP, depression, ABNAS, stigma, and sense of mastery for many treatment comparisons, indicating that an increased risk of treatment failure was generally associated with a worsening score for these QoL outcomes.

For the joint model involving treatment failure (CR), there were model fitting issues for the majority of the models involving sense of mastery in the longitudinal component, and for some of the Arm B treatment comparisons for the models involving ABNAS and stigma (see Table S7). This may be because these three QoL outcomes were not assessed at the 3-month questionnaire, and so contributed fewer data points than the QoL outcomes assessed in all questionnaires.

Nevertheless, there was statistically significant association at the 0.01 level between risk of treatment failure (CR) and anxiety, depression, AEP, and ABNAS scores for many of treatment comparisons, with more achieving statistical significance at the 0.05 level. More of the associations for sense of mastery and stigma were not close to being significant, but significant associations were still observed between stigma scores and risk of treatment failure (CR) for some treatment comparisons. Throughout the significant results, worsening QoL scores were associated with increased risk of treatment failure due to inadequate seizure control or unacceptable adverse events. For all QoL out-

Table 1. Baseline demographic and clinical characteristics by treatment group (adults that completed at least one of baseline or 3-month questionnaire)

	Arm A						Arm B			
	CBZ (n = 281)	GBP (n = 288)	LTG (n = 272)	OXC (n = 154)	TPM (n = 272)	Total (n = 1,267)	LTG (n = 118)	TPM (n = 113)	VPS (n = 125)	Total (n = 356)
Sex, n (%)										
Male	148 (52.7)	158 (54.9)	142 (52.2)	79 (51.3)	144 (52.9)	671 (53)	76 (64.4)	74 (65.5)	81 (64.8)	231 (64.9)
Female	133 (47.3)	130 (45.1)	130 (47.8)	75 (48.7)	128 (47.1)	596 (47)	42 (35.6)	39 (34.5)	44 (35.2)	125 (35.1)
Treatment history, n (%)										
Untreated	228 (81.1)	230 (79.9)	227 (83.5)	135 (87.7)	219 (80.5)	1,039 (82)	97 (82.2)	89 (78.8)	102 (81.6)	288 (80.9)
Monotherapy	47 (16.7)	48 (16.7)	41 (15.1)	18 (11.7)	46 (16.9)	200 (15.8)	15 (12.7)	16 (14.2)	16 (12.8)	47 (13.2)
Recent seizures after remission	6 (2.1)	10 (3.5)	4 (1.5)	1 (0.6)	7 (2.6)	28 (2.2)	6 (5.1)	8 (7.1)	7 (5.6)	21 (5.9)
History, n (%)										
Neurologic deficit (yes)	22 (7.8)	22 (7.6)	19 (7.0)	11 (7.1)	21 (7.7)	95 (7.5)	1 (0.8)	2 (1.8)	5 (4.0)	8 (2.2)
Neurologic disorder, n (%)										
Stroke/cerebrovascular	25 (8.9)	22 (7.6)	17 (6.2)	10 (6.5)	14 (5.1)	88 (6.9)	0 (0)	0 (0)	0 (0)	0 (0)
Intracranial surgery	11 (3.9)	15 (5.2)	12 (4.4)	2 (1.3)	20 (7.4)	60 (4.7)	1 (0.8)	0 (0)	0 (0)	1 (0.3)
Head injury	10 (3.6)	14 (4.9)	10 (3.7)	6 (3.9)	19 (7.0)	59 (4.7)	2 (1.7)	2 (1.8)	3 (2.4)	7 (2)
Meningitis/encephalitis	4 (1.4)	6 (2.1)	11 (4.0)	2 (1.3)	8 (2.9)	31 (2.4)	2 (1.7)	1 (0.9)	1 (0.8)	4 (1.1)
Other	18 (6.4)	19 (6.6)	13 (4.8)	8 (5.2)	25 (9.2)	83 (6.6)	4 (3.4)	2 (1.8)	4 (3.2)	10 (2.8)
History of seizures, n (%)										
Febrile convulsions	22 (7.8)	8 (2.8)	13 (4.8)	7 (4.5)	10 (3.7)	60 (4.7)	2 (1.7)	7 (6.2)	9 (7.2)	18 (5.1)
Any other acute symptomatic seizures	3 (1.1)	10 (3.5)	13 (4.8)	5 (3.2)	8 (2.9)	39 (3.1)	2 (1.7)	0 (0)	1 (0.8)	3 (0.8)
Epilepsy in relatives, first-degree	30 (10.7)	31 (10.8)	24 (8.8)	18 (11.7)	24 (8.8)	127 (10)	26 (22)	15 (13.3)	18 (14.4)	59 (16.6)
Epilepsy syndrome[a], n (%)[b]										
Idiopathic partial	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.5)	0 (0)	0 (0)	1 (0.3)
Symptomatic/cryptogenic partial	255 (99.2)	257 (99.2)	243 (99.6)	136 (97.8)	239 (98.4)	1,130 (89.2)	10 (14.9)	6 (8.8)	12 (14.5)	28 (7.9)
Idiopathic generalized	2 (0.8)	2 (0.8)	1 (0.4)	3 (2.2)	4 (1.6)	12 (0.9)	56 (83.6)	62 (91.2)	71 (85.5)	189 (53.1)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unclassified	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Median (IQ range) interval between first and most recent seizures, days	567 (1,758)	465.5 (2,610)	556 (1,747.8)	484 (1,182.8)	630.5 (1,971.5)	546 (1,861)	767.5 (2,346)	835 (2,774)	750 (2,388)	777.5 (2,541)
Median (IQ range) interval between most recent seizure prior to randomization and randomization, days	13 (37)	14 (36.3)	16 (36.5)	15 (32.8)	11.5 (28.3)	14 (34)	23 (54.8)	14 (44)	16 (49)	16 (52)
Median (IQ range) number of seizures	14 (79)	14.5 (75.3)	12.5 (80.3)	10 (39.8)	13 (96)	13 (76)	5 (97)	6 (97)	7 (47)	5 (97)
Mean age (SD) in years	43.9 (16)	41.6 (16.3)	42.3 (16.2)	44.2 (16)	42.7 (16.6)	42.8 (16.2)	30.0 (13.9)	29.9 (12.7)	29.6 (14.2)	29.8 (13.6)

CBZ, carbamazepine; GBP, gabapentin; LTG, lamotrigine; TPM, topiramate, OXC, oxcarbazepine; VPS, valproate; IQ, interquartile.
[a]Syndrome descriptions are those employed in SANAD and therefore do not match directly to the terminology and concepts recently proposed by Berg et al., 2010.
[b]Missing data for epilepsy syndrome Arm A: CBZ (24), GBP (29), LTG (28), OXC (15), TPM (29); Arm B: LTG (51), TPM (45), VPS (42).

Table 2. Comparison of baseline demographic and clinical characteristics by response to QoL questionnaires

	Full responders (n = 997)	Partial responders (n = 626)	Nonresponders (n = 245)	Total (n = 1,868)	p-Value
Sex, n (%)					
Male	529 (53.1)	373 (59.6)	162 (66.1)	1,064 (57)	<0.001
Female	468 (46.9)	253 (40.4)	83 (33.9)	804 (43)	
Treatment history, n (%)					
Untreated	819 (82.1)	508 (81.2)	191 (78)	1,518 (81.3)	0.097
Monotherapy	156 (15.6)	91 (14.5)	45 (18.4)	292 (15.6)	
Recent seizures after remission	22 (2.2)	27 (4.3)	9 (3.7)	58 (3.1)	
History, n (%)					
Neurologic deficit	65 (6.5)	38 (6.1)	16 (6.5)	119 (6.4)	0.931
Neurologic disorder, n (%)					
Stroke/cerebrovascular	58 (5.8)	30 (4.8)	16 (6.5)	104 (5.6)	0.531
Intracranial surgery	39 (3.9)	22 (3.5)	5 (2)	66 (3.5)	0.364
Head injury	41 (4.1)	25 (4.0)	16 (6.5)	82 (4.4)	0.213
Meningitis/encephalitis	21 (2.1)	14 (2.2)	3 (1.2)	38 (2)	0.629
Other	59 (5.9)	34 (5.4)	13 (5.3)	106 (5.7)	0.886
History of seizures, n (%)					
Febrile convulsions	44 (4.4)	34 (5.4)	9 (3.7)	87 (4.7)	0.470
Any other acute symptomatic seizures	24 (2.4)	18 (2.9)	5 (2.0)	47 (2.5)	0.740
Epilepsy in relatives, first-degree	97 (9.7)	89 (14.2)	24 (9.8)	210 (11.2)	0.015
Epilepsy syndrome, n (%)					
Idiopathic partial	1 (0.1)	0 (0)	0 (0)	1 (0.1)	<0.001
Symptomatic/cryptogenic partial	747 (74.9)	411 (65.7)	160 (65.3)	1,318 (70.6)	
Idiopathic generalized	108 (10.8)	93 (14.9)	28 (11.4)	229 (12.3)	
Unclassified	0 (0)	0 (0)	0 (0)	0 (0)	
Missing	141 (14.1)	122 (19.5)	57 (23.3)	320 (17.1)	
Median (IQ range) interval between first and most recent seizures, days	577 (2,064)	558 (1,870)	606 (1898.5)	577 (1994.5)	0.584
Median (IQ range) interval between most recent seizure prior to randomization and randomization, days[a]	16 (39)	13 (35.75)	15.5 (40.5)	14 (38)	0.454
Median (IQ range) number of seizures[a]	11 (78)	12 (62.25)	8 (46.5)	10 (72)	0.395
Mean age (SD) in years	43.2 (16.7)	34.8 (15.1)	36.2 (16.1)	39.5 (16.6)	<0.001

Full responders are individuals who returned all of the first four questionnaires (baseline, 3 month, and 1- and 2-year questionnaires); partial responders are individuals who returned some but not all the first four questionnaires; nonresponders are individuals who returned none of first four questionnaires; IQ, interquartile.

[a]One nonresponder with missing data.

comes across all treatment comparisons, a larger number of the associations between the longitudinal QoL and time-to-event components were significant for failure due to inadequate seizure control rather than due to unexpected adverse events.

Discussion

As part of the analysis of secondary outcomes in the SANAD trial, we compared QoL outcomes over 2 years associated with initiating treatment with alternative AEDs in individuals followed prospectively. Our findings suggest that there are no consistent differences in QoL outcomes between pairs of AEDs for either study arm. In addition, our findings suggest that significant associations exist between QoL outcomes measured over 2 years and time-to-event outcomes such that as the risk of remission increases QoL improves and as the risk of treatment failure due to either poor seizure control or adverse drug effects increases, QoL worsens.

These findings are clinically plausible and support conclusions of previous research. The impact of continuing seizures for QoL is well documented in the literature[23–27] and the current findings are consistent with findings from our earlier trials of drug withdrawal following seizure remission[28] and treatment for single seizures and early epilepsy.[29] Similarly, other studies have shown that adverse effects of AEDs are one of the strongest predictors of impaired health-related quality of life.[30]

It is important to emphasize here that SANAD was a pragmatic clinical trial that examined competing treatment policies, and the time points for follow-up and analyses performed of the QoL data were chosen to reflect this aim. These policies consisted of starting treatment with the randomized drug, followed by dosage adjustments, and then, if necessary, drug changes in an attempt to maximize benefit

Table 3. Longitudinal analyses of QoL outcomes over 2 years by treatment group for Arm A (99% CIs)

	CBZ	GBP	LTG	TPM	OXC
Continuous QoL outcomes					
Anxiety (measurements made at 0, 3-, 12-, and 24-month time points)					
CBZ	–	−0.40 (−1.42, 0.62)	−0.61 (−1.65, 0.43)	−0.08 (−1.09, 0.92)	0.28 (−1.05, 1.62)
GBP	0.40 (−0.62, 1.42)	–	−0.20 (−1.24, 0.83)	0.33 (−0.67, 1.33)	0.67 (−0.64, 1.98)
LTG	0.61 (−0.43, 1.65)	0.20 (−0.83, 1.24)	–	0.54 (−0.48, 1.56)	0.73 (−0.60, 2.07)
TPM	0.08 (−0.92, 1.09)	−0.33 (−1.33, 0.67)	−0.54 (−1.56, 0.48)	–	0.25 (−1.06, 1.56)
OXC	−0.28 (−1.62, 1.05)	−0.67 (−1.98, 0.64)	−0.73 (−2.07, 0.60)	−0.25 (−1.56, 1.06)	–
Depression (measurements made at 0, 3-, 12-, and 24-month time points)					
CBZ	–	−0.05 (−0.93, 0.84)	0.16 (−0.70, 1.03)	−0.64 (−1.50, 0.22)	0.82 (−0.32, 1.96)
GBP	0.05 (−0.84, 0.93)	–	0.22 (−0.67, 1.11)	−0.58 (−1.46, 0.30)	0.57 (−0.56, 1.70)
LTG	−0.16 (−1.03, 0.70)	−0.22 (−1.11, 0.67)	–	−0.83 (−1.69, 0.03)	0.68 (−0.46, 1.82)
TPM	0.64 (−0.22, 1.50)	0.58 (−0.30, 1.46)	0.83 (−0.03, 1.69)	–	**1.27 (0.13, 2.41)**
OXC	−0.82 (−1.96, 0.32)	−0.57 (−1.71, 0.57)	−0.68 (−1.81, 0.46)	**−1.27 (−2.41, −0.13)**	–
Mastery (measurements made at 0, 12-, 24-month time points)					
CBZ	–	0.09 (−0.79, 0.97)	0.14 (−0.69, 0.97)	0.24 (−0.60, 1.09)	−0.50 (−1.63, 0.63)
GBP	−0.09 (−0.97, 0.79)	–	*−0.02 (−0.88, 0.84)*	0.14 (−0.73, 1.02)	−0.14 (−1.35, 1.08)
LTG	−0.14 (−0.97, 0.69)	*0.02 (−0.84, 0.88)*	–	0.12 (−0.70, 0.94)	−0.37 (−1.49, 0.76)
TPM	−0.24 (−1.09, 0.60)	−0.14 (−1.02, 0.73)	−0.12 (−0.94, 0.70)	–	−0.05 (−1.27, 1.16)
OXC	0.50 (−0.63, 1.63)	0.14 (−1.08, 1.36)	0.37 (−0.76, 1.49)	0.05 (−1.16, 1.27)	–
AEP (measurements made at 0, 3-, 12-, 24-month time points)					
CBZ	–	−0.58 (−2.91, 1.76)	0.09 (−2.29, 2.46)	−0.46 (−2.80, 1.88)	0.65 (−2.46, 3.76)
GBP	0.58 (−1.76, 2.91)	–	0.73 (−1.63, 3.10)	0.16 (−2.19, 2.51)	1.45 (−1.55, 4.45)
LTG	−0.09 (−2.46, 2.29)	−0.73 (−3.10, 1.63)	–	−0.51 (−2.89, 1.86)	0.80 (−2.29, 3.88)
TPM	0.46 (−1.88, 2.80)	−0.16 (−2.51, 2.19)	0.51 (−1.86, 2.89)	–	1.31 (−1.87, 4.48)
OXC	−0.65 (−3.76, 2.46)	−1.45 (−4.45, 1.55)	−0.80 (−3.88, 2.29)	−1.31 (−4.48, 1.87)	–
ABNAS (measurements made at 0, 12-, and 24-month time points)					
CBZ	–	−0.31 (−4.18, 3.55)	1.58 (−2.30, 5.46)	0.67 (−3.26, 4.60)	2.13 (−2.81, 7.07)
GBP	0.31 (−3.55, 4.18)	–	1.88 (−1.84, 5.61)	0.98 (−2.81, 4.76)	2.82 (−1.94, 7.58)
LTG	−1.58 (−5.46, 2.30)	−1.88 (−5.61, 1.84)	–	−0.94 (−4.73, 2.85)	1.17 (−3.66, 6.01)
TPM	−0.67 (−4.60, 3.26)	−0.98 (−4.76, 2.81)	0.94 (−2.85, 4.73)	–	2.33 (−2.72, 7.38)
OXC	−2.13 (−7.10, 2.84)	−2.82 (−7.58, 1.94)	−1.17 (−6.04, 3.69)	−2.33 (−7.38, 2.72)	–
Stigma (measurements made at 0, 12-, and 24-month time points)					
CBZ	–	−0.21 (−0.70, 0.27)	0.02 (−0.46, 0.49)	−0.06 (−0.55, 0.44)	0.25 (−0.35, 0.84)
GBP	0.21 (−0.27, 0.70)	–	0.26 (−0.22, 0.73)	0.17 (−0.33, 0.66)	0.39 (−0.20, 0.97)
LTG	−0.02 (−0.49, 0.46)	−0.26 (−0.73, 0.22)	–	−0.07 (−0.56, 0.41)	0.24 (−0.34, 0.81)
TPM	0.06 (−0.44, 0.55)	−0.17 (−0.66, 0.33)	0.07 (−0.41, 0.56)	–	0.16 (−0.45, 0.78)
OXC	−0.25 (−0.84, 0.35)	−0.39 (−0.97, 0.20)	−0.24 (−0.81, 0.34)	−0.16 (−0.77, 0.44)	–
Binary QoL outcomes					
Fair/poor health perception (measurements made at 0, 12-, and 24-month time points)					
CBZ	–	0.95 (0.50, 1.81)	0.92 (0.47, 1.79)	1.15 (0.59, 2.22)	*2.43 (0.78, 7.59)*
GBP	1.05 (0.55, 2.01)	–	*1.41 (0.57, 3.52)*	1.21 (0.64, 2.30)	**3.44 (1.17, 10.09)**
LTG	1.09 (0.56, 2.11)	*0.71 (0.28, 1.77)*	–	1.27 (0.65, 2.45)	*3.13 (0.83, 11.82)*
TPM	0.87 (0.45, 1.68)	0.83 (0.43, 1.57)	0.79 (0.41, 1.53)	–	*2.94 (0.94, 9.23)*
OXC	*0.41 (0.13, 1.28)*	***0.26 (0.07, 0.93)***	*0.32 (0.08, 1.20)*	*0.34 (0.11, 1.07)*	–
Worse health transition (measurements made at 0, 12-, and 24-month time points)					
CBZ	–	1.19 (0.77, 1.85)	*1.08 (0.70, 1.68)*	*1.07 (0.69, 1.66)*	1.20 (0.61, 2.37)
GBP	0.84 (0.54, 1.30)	–	*0.88 (0.56, 1.39)*	*0.87 (0.55, 1.37)*	0.95 (0.52, 1.75)
LTG	*0.92 (0.59, 1.43)*	*1.14 (0.72, 1.79)*	–	0.95 (0.60, 1.50)	1.27 (0.69, 2.36)
TPM	1.04 (0.67, 1.63)	*1.15 (0.73, 1.80)*	1.06 (0.67, 1.68)	–	1.15 (0.61, 2.15)
OXC	0.83 (0.42, 1.64)	1.05 (0.57, 1.93)	0.79 (0.42, 1.46)	0.87 (0.47, 1.63)	–
Worry about past seizure (measurements made at 0, 12-, and 24-month time points)					
CBZ	–	0.51 (0.21, 1.22)	**0.35 (0.13, 0.94)**	0.74 (0.32, 1.70)	0.55 (0.18, 1.64)
GBP	1.97 (0.82, 4.73)	–	*1.26 (0.34, 4.71)*	*1.73 (0.71, 4.20)*	*0.90 (0.35, 2.34)*
LTG	**2.86 (1.06, 7.71)**	*0.79 (0.21, 2.97)*	–	*1.42 (0.40, 5.05)**	*0.97 (0.18, 5.21)*
TPM	1.35 (0.59, 3.12)	*0.58 (0.24, 1.41)*	*0.71 (0.20, 2.51)**	–	0.53 (0.19, 1.53)
OXC	1.83 (0.61, 5.46)	*1.11 (0.43, 2.89)*	*1.04 (0.19, 5.59)*	1.89 (0.65, 5.45)	–
Worry about future seizures (measurements made at 0, 12-, and 24-month time points)					
CBZ	–	0.62 (0.18, 2.11)*	*0.78 (0.18, 3.39)*	*0.76 (0.21, 2.69)*	*0.51 (0.06, 4.50)*
GBP	1.61 (0.47, 5.44)*	–	*1.34 (0.31, 5.75)*	*1.33 (0.39, 4.51)*	*0.65 (0.08, 5.36)*

Continued

Table 3. Continued.

	CBZ	GBP	LTG	TPM	OXC
LTG	1.91 (1.30, 2.82)	*0.75 (0.17, 3.21)*	–	*0.99 (0.24, 4.04)*	*0.58 (0.06, 5.66)**
TPM	*1.32 (0.37, 4.67)*	*0.75 (0.22, 2.55)*	*1.01 (0.25, 4.15)*	–	0.57 (0.18, 1.86)
OXC	*1.97 (0.22, 17.39)*	*1.54 (0.25, 9.27)**	*1.73 (0.18, 16.92)**	1.75 (0.54, 5.71)	–
Feels socially restricted (measurements made at 0, 12-, and 24-month time points)					
CBZ	–	*0.88 (0.50, 1.56)*	*1.22 (0.68, 2.19)*	1.02 (0.60, 1.73)	*1.76 (0.86, 3.61)*
GBP	*1.13 (0.64, 2.00)*	–	*1.45 (0.73, 2.90)*	*1.21 (0.65, 2.27)*	*1.32 (0.57, 3.05)*
LTG	*0.82 (0.46, 1.46)*	*0.69 (0.35, 1.37)*	–	*0.86 (0.45, 1.63)*	*1.19 (0.52, 2.74)*
TPM	0.98 (0.58, 1.67)	*0.83 (0.44, 1.55)*	*1.17 (0.61, 2.22)*	–	*1.27 (0.59, 2.72)*
OXC	*0.57 (0.28, 1.16)*	*0.76 (0.33, 1.76)*	*0.84 (0.37, 1.94)*	*0.79 (0.37, 1.68)*	–
Poor global QoL (measurements made at 0, 12-, and 24-month time points)					
CBZ	–	1.19 (0.90, 1.57)	1.08 (0.82, 1.43)	0.99 (0.75, 1.32)	1.17 (0.80, 1.71)
GBP	0.84 (0.64, 1.11)	–	0.91 (0.69, 1.20)	0.84 (0.63, 1.11)	0.96 (0.66, 1.39)
LTG	0.93 (0.70, 1.23)	1.10 (0.83, 1.45)	–	0.92 (0.69, 1.22)	1.11 (0.75, 1.62)
TPM	1.01 (0.76, 1.34)	1.20 (0.90, 1.59)	1.09 (0.82, 1.45)	–	1.09 (0.74, 1.60)
OXC	0.85 (0.58, 1.24)	1.04 (0.72, 1.51)	0.90 (0.62, 1.33)	0.92 (0.63, 1.35)	–

CBZ, carbamazepine; GBP, gabapentin; LTG, lamotrigine; TPM, topiramate; OXC, oxcarbazepine; AEP, adverse events profile; ABNAS, Aldenkamp-Baker Neuropsychological Assessment Schedule; QoL, quality of life; CI, confidence interval.

Tables present coefficients (with 99% CIs) for continuous QoL measures over 2 years by treatment group, and odds ratios (with 99% CIs) for binary QoL measures over 2 years by treatment group. Columns represent the baseline comparator, e.g., CBZ column represents the scores for the other groups compared with CBZ, so the first cell in the first column is the comparison of GBP_ versus _CBZ, where CBZ is treated as the baseline.

Results not in italics were for longitudinal models with random intercept and slope; results in italics indicate a longitudinal model with random intercept only was used. Results with an asterisk indicate possible model convergence issues, but with reasonable standard errors reported. Results in bold highlight those that achieved statistical significance at 1% level.

For continuous QoL measures Anxiety, Depression, AEP, ABNAS and Stigma, higher scores were indicative of worse QoL, whereas for continuous QoL measure Sense of Mastery, higher scores were indicative of better QoL. For continuous QoL measures, a significant positive result indicates that those assigned to the comparator treatment experience higher QoL scores than those assigned to the baseline treatment, and significant negative results indicate that those assigned to the comparator treatment experience lower QoL scores than those assigned to the baseline treatment.

For binary QoL measures, seizure worry about past seizures, seizure worry about future seizures, social restrictions, responses were recorded as yes (1) versus no (0). For binary QoL measure general health perception, responses were recorded as excellent/very good/good (0) versus fair/poor (1). For binary QoL measure health transition, responses were recorded as better/same (0) versus worse (1). For binary QoL measure Global QoL responses were recorded as poor (1) versus good (0). For binary QoL measures, an odds ratio significantly >1 indicates that individuals assigned to the comparator treatment are more likely to experience the event coded 1 compared to those assigned to the baseline treatment (for odds ratios significantly <1, individuals assigned to the comparator are less likely to experience the event coded 1 than those assigned to the baseline).

and minimize harm, as in usual clinical practice. At this policy level, the QoL data did not favor initiating treatment with any one drug over any other. In relation to this point, it is worth noting that the adverse event profiles of the different drugs, as reported by patients, were not significantly different; and this corresponded with the clinician-based reports of only small differences in rates of adverse events, at least for Arm A.[6,7] Nonetheless, by the time of 2-year follow-up, a sizeable number of patients (around 45%) were no longer taking the drug to which they were originally randomized, having switched to another because of adverse effects, lack of efficacy, or both. Overall, however, the QoL findings suggest that individual response to a drug is more important for QoL than the type of drug given, and emphasizes that an iterative approach to clinical practice is required, wherein drug adjustments are instigated in a timely and responsive manner.

The clinical findings from SANAD supported use of lamotrigine as first-line treatment in partial epilepsies,[6,7] since lamotrigine emerged as the drug with the least number of patients failing due to adverse effects. However, the QoL findings provide little additional evidence to support this conclusion: rather, they suggest that in relation to QOL outcomes, there is little to choose between the different drugs under scrutiny. Our findings for QoL are also in contrast to previous reports of improvements in overall and domain-specific QoL with use of lamotrigine,[31–34] potentially attributable to its documented mood-enhancing properties.[4,35,36] These apparently discrepant findings may be related to differences in study populations, sample size, and length of follow-up.

Inevitably, there are limitations to this study. One is that SANAD was conducted prior to UK licensing of some newer AEDs shown to have more benign side effect profiles. Had these drugs been included in the analysis, between-drug differences for QoL might have been more apparent.

A second limitation is that because of the greater costs of using other methods, we opted to collect QoL information using mailed questionnaires. In doing so, we adopted an approach used successfully in our previous randomized studies of treatment issues in epilepsy. As in these previous studies, patient response rates at successive data collection waves were high, but inevitably with this approach there were some nonresponders and hence loss to follow-up; and some patients who responded were slow to respond. In addition, a basic analysis indicated that age and gender may be linked to time taken to return a questionnaire. A full report on the QoL profiles of those completing the QoL assessment

Table 4. Longitudinal analyses of QoL outcomes over 2 years by treatment group for Arm B (99% CIs)

	VPS	LTG	TPM
Continuous QoL outcomes			
Anxiety (measurements made at 0, 3-, 12-, and 24-month time points)			
VPS	–	−0.80 (−2.34, 0.74)	−0.19 (−1.74, 1.36)
LTG	0.80 (−0.74, 2.34)	–	0.61 (−0.91, 2.12)
TPM	0.19 (−1.36, 1.74)	−0.61 (−2.12, 0.91)	–
Depression (measurements made at 0, 3-, 12-, 24-month time points)			
VPS	–	0.23 (−0.98, 1.43)	−0.10 (−1.39, 1.18)
LTG	−0.23 (−1.43, 0.98)	–	−0.39 (−1.55, 0.77)
TPM	0.10 (−1.18, 1.39)	0.39 (−0.77, 1.55)	–
Mastery (measurements made at 0, 12-, and 24-month time points)			
VPS	–	0.56 (−0.66, 1.77)	−0.03 (−1.26, 1.19)
LTG	−0.56 (−1.77, 0.66)	–	−0.64 (−1.89, 0.61)
TPM	0.03 (−1.19, 1.26)	0.64 (−0.61, 1.89)	–
AEP (measurements made at 0, 3-, 12-, and 24-month time points)			
VPS	–	0.02 (−3.62, 3.66)	0.77 (−2.75, 4.28)
LTG	−0.02 (−3.66, 3.62)	–	0.77 (−2.73, 4.26)
TPM	−0.77 (−4.28, 2.75)	−0.77 (−4.26, 2.73)	–
ABNAS (measurements made at 0, 12-, and 24-month time points)			
VPS	–	0.59 (−4.37, 5.55)	1.25 (−3.47, 5.98)
LTG	−0.59 (−5.55, 4.37)	–	0.62 (−3.83, 5.06)
TPM	−1.25 (−5.98, 3.47)	−0.62 (−5.06, 3.83)	–
Stigma (measurements made at 0, 12-, and 24-month time points)			
VPS	–	*−0.12 (−0.71, 0.46)*	−0.37 (−0.96, 0.21)
LTG	*0.12 (−0.46, 0.71)*	–	−0.25 (−0.89, 0.40)
TPM	0.37 (−0.21, 0.96)	0.25 (−0.40, 0.89)	–
Binary QoL outcomes			
Fair/poor health perception (measurements made at 0, 12-, 24-month time points)			
VPS	–	*1.15 (0.12, 10.72)*	*1.24 (0.12, 13.34)*
LTG	*0.87 (0.09, 8.15)*	–	*1.06 (0.13, 8.66)*
TPM	*0.81 (0.07, 8.65)*	0.82 (0.31, 2.18)	–
Worse health transition (measurements made at 0, 12-, and 24-month time points)			
VPS	–	1.07 (0.50, 2.28)	*0.95 (0.43, 2.08)*
LTG	0.94 (0.44, 2.01)	–	*0.90 (0.43, 1.87)*
TPM	*1.06 (0.48, 2.32)*	1.11 (0.52, 2.38)	–
Worry about past seizures (measurements made at 0, 12-, and 24-month time points)			
VPS	–	*0.90 (0.28, 2.90)*	*0.93 (0.29, 2.96)*
LTG	*1.11 (0.35, 3.56)*	–	*1.06 (0.38, 2.95)*
TPM	*1.08 (0.34, 3.44)*	*0.95 (0.34, 2.64)*	–
Worry about future seizures (measurements made at 0, 12-, and 24-month time points)			
VPS	–	*1.44 (0.16, 13.27)*	*1.06 (0.14, 8.14)*
LTG	*0.69 (0.08, 6.39)*	–	*0.69 (0.11, 4.46)*
TPM	*0.94 (0.12, 7.24)*	*1.44 (0.22, 9.27)*	–
Feels socially restricted (measurements made at 0, 12-, and 24-month time points)			
VPS	–	*0.59 (0.30, 1.17)**	*1.01 (0.49, 2.05)**
LTG	*1.68 (0.85, 3.33)**	–	1.72 (0.84, 3.51)
TPM	*0.99 (0.49, 2.02)**	0.58 (0.28, 1.19)	–
Poor global QoL (measurements made at 0, 12-, and 24-month time points)			
VPS	–	0.98 (0.63, 1.52)	0.96 (0.61, 1.50)
LTG	1.02 (0.66, 1.59)	–	0.98 (0.62, 1.54)
TPM	1.05 (0.67, 1.64)	1.02 (0.65, 1.61)	–

Continued

compared to those lost to QoL follow-up and of early compared to late responders is provided elsewhere.[6] However, the implications of such self-selection biases need to be acknowledged here. It is possible that important QoL outcomes associated with the drugs were not detected, because patients for whom QoL effects were most negative were those who opted not to respond at the various follow-ups; conversely, patients who responded may have been those with the most dramatic responses to therapy or marked drug side effects. The effect of these possibilities was investigated by performing a sensitivity analysis using best case and worst case assumptions, which demonstrated that

Table 4. Continued.

LTG, lamotrigine; TPM, topiramate; VPS, valproate; AEP, Adverse Events Profile; ABNAS, Aldenkamp-Baker Neuropsychological Assessment Schedule; QoL, quality of life; CI, confidence interval.

Tables present coefficients (with 99% CIs) for continuous QoL measures over 2 years by treatment group, and odds ratios (with 99% CIs) for binary QoL measures over 2 years by treatment group. Columns represent the baseline comparator, for example, CBZ column represents the scores for the other groups compared with CBZ, so the first cell in the first column is the comparison of GBP_ versus _CBZ, where CBZ is treated as the baseline.

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For binary QoL measures seizure worry about past seizures, seizure worry about future seizures, and social restrictions, responses were recorded as yes (1) versus no (0). For binary QoL measure general health perception, responses were recorded as excellent/very good/good (0) versus fair/poor (1). For binary QoL measure health transition, responses were recorded as better/same (0) versus worse (1). For binary QoL measure Global QoL, responses were recorded as poor (1) versus good (0). For binary QoL measures an odds ratio significantly >1 indicates that individuals assigned to the comparator treatment are more likely to experience the event coded 1 compared to those assigned to the baseline treatment (for odds ratios significantly <1, individuals assigned to the comparator are less likely to experience the event coded 1 than those assigned to the baseline).

some of the conclusions could change under different scenarios.

Similarly, given that there were some important differences with regard to the baseline clinical and demographic characteristics of responders to the QoL study compared with nonresponders, the results of the analysis need to be interpreted with caution. Our findings that women were more likely than men to be responders and, conversely, that the age of responders was higher than for nonresponders are all potentially important sources of bias, given our previous report[37] that gender and age are significant risk factors for both time to treatment failure and to a 12-month remission.

In addition, the fact that SANAD was an unblinded study raises the possibility of bias arising from patients' lack of willingness to acknowledge and report adverse effects of the newer drugs, given their psychological investment in the possible benefits over the older drugs.

Finally due to the number of comparisons made, the type I error rate may have increased. Because no clear strategy was suggested in the literature[38] for adjusting for multiple testing in data as complex as ours (with multiple arms, treatments and endpoints, and longitudinal data), we attempted to compensate for this by presenting 99% CIs. However, we accept that this is a basic solution to a complex problem, and so results should be interpreted with caution.

Despite these limitations, SANAD is the only large comparative drug study to our knowledge that includes QoL and health economic assessments alongside clinical assessments.

As indicated earlier, since completion of SANAD, additional new AEDs have been licensed in the United Kingdom for the treatment of epilepsy (e.g., levetiracetam and zonisamide); therefore, these drugs are currently being compared in a parallel trial, the SANAD-II trial, following the same design and utilizing the same QOL outcome measures, thus allowing for meta-analysis of study findings.

Acknowledgments

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Contributors: Julie Doughty (research associate at University of Newcastle Institute of Health and Society), Barbara Eaton (trial manager at Department of Neurosciences, University of Liverpool), and Virginia Swain (independent researcher) assisted with data collection, coding, and checking and data entry processes. Julie Doughty also contributed to previous trial outputs. A complete list of clinicians contributing patients to the SANAD trial and the QoL Study, can be found in the report to the UK Health Technology Assessment Programme (HTA, 2007, 11: 37).

Co-investigators: R Appleton (pediatric neurologist, Royal Liverpool Children's Hospital Trust, Alder Hey) was the paediatric neurology coordinator for the SANAD Trial, sat on the management committee, and contributed to outputs reporting the clinical findings; DW Chadwick (Professor of Neurology, University of Liverpool) jointly coordinated the SANAD Trial, with AG Marson; C Gamble (Professor in Medical Statistics, University of Liverpool, Department of Biostatistics) was predecessor to J Crossley for the QoL study; P Shackley (Senior Lecturer in Health Economics, University of Newcastle Institute of Health and Society) was responsible for analysis of health economic data, sat on the management committee, and contributed to outputs reporting the health economic findings; DF Smith (Consultant Neurologist, Walton Centre for Neurology and Neurosurgery NHS Trust, Liverpool) sat on the management committee and contributed to outputs reporting the clinical findings; A Vanoli (Lecturer in Health Economics, University of Newcastle) was predecessor to P Shackley, sat on the management committee, and contributed to outputs reporting the health economic findings; PR Williamson (Professor of Statistics, University of Liverpool, Department of Biostatistics) was statistical team leader, sat on the management committee, and contributed to outputs reporting the clinical findings.

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Additional Contributors

AJ was responsible for study concept and design, coordination of data collection and management, data interpretation, and revision of the manuscript for content; JC, MS, and CTS were responsible for data analysis and drafting the manuscript for content; GAB was responsible for study concept and design and revising the manuscript for content; AGM was responsible for study concept and design and revising the manuscript for content. All authors had full access to the data reported herein. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Conflict of Interest

Prof A Jacoby has acted as a consultant on QoL studies for Eisai Pharmaceuticals in 2012. During the period of the study reported here she was in receipt of an educational grant from Pfizer Pharmaceuticals for a study of *Prevalence of Anxiety and Sleep Disorders in Epilepsy* (award of £100,000, 2008–2009). Dr J Crossley was supported by a grant from Epilepsy Research UK. Maria Sudell was supported by an NIHR Research Methods Fellowship. Prof AG Marson coordinates the UK National Audit of Seizure Management in Hospitals, which is joint funded by GlaxoSmithKline, UCB Pharma, and Eisai. Prof GA Baker received educational grants from Sanofi Aventis and UCB during the period of the study reported here. He acted as a consultant on QoL studies for Eisai Pharmaceuticals in 2012. 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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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. QoL study response rates (all questionnaires over the first 2 years after randomization).

Table S2. Sensitivity analysis—longitudinal analyses of QoL outcomes over 2 years by treatment group for Arm A (best case data, 99% CIs).

Table S3. Sensitivity analysis—longitudinal analyses of QoL outcomes over 2 years by treatment group for Arm A (worst case data, 99% CIs).

Table S4. Sensitivity analysis—longitudinal analyses of QoL outcomes over 2 years by treatment group for Arm B (best case data, 99% CIs).

Table S5. Sensitivity analysis—longitudinal analyses of QoL outcomes over 2 years by treatment group for Arm B (worst case data, 99% CIs).

Table S6. Treatment comparison output from joint models for continuous QoL measures only.

Table S7. Association between the time-to-event and longitudinal components of the joint models for the continuous QoL measures.