Clinical outcome assessment in patients with epilepsy: the value of health-related quality of life measurements

Reijneveld, J.C.; Thijs, R.D.; Thuijl, H.F.V.; Appelhof, B.A.; Taphoorn, M.J.B.; Koekkoek, J.A.F.; ... ; Dirven, L.

Epilepsy Research 200 (2024) 107310

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Clinical outcome assessment in patients with epilepsy: The value of health-related quality of life measurements

Jaap C. Reijneveld [a,b,*], Roland D. Thijs [a,d], Hinke F. van Thuijl [a], Bente A. Appelhof [a], Martin J.B. Taphoorn [c], Johan A.F. Koekkoek [c], Gerhard H. Visser [a], Linda Dirven [c]

[a] Department of Neurology, SEIN, Heemstede, the Netherlands
[b] Department of Neurology, Amsterdam University Medical Center, Amsterdam, the Netherlands
[c] Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands
[d] Department of Neurology, University College, London, United Kingdom

ARTICLE INFO

Keywords:
Epilepsy
Quality of life
Patient-reported outcome
Clinical
Review

ABSTRACT

This narrative review provides an overview of the current knowledge on health-related quality of life (HRQOL), a relevant clinical outcome in patients with epilepsy. It shows that the most important factor determining HRQOL in this patient group is seizure frequency. In particular, seizure-freedom is associated with better HRQOL scores. Many other factors may impact perceived HRQOL aspects, but their interrelation is complex and requires further research. Novel analytical approaches, such as hierarchical cluster and symptom network analyses might shed further light on this, and may result in recommendations for interventions on the most 'central' factors influencing different aspects of HRQOL in patients with epilepsy. Next, an overview of the HRQOL tools and analytical methods currently used in epilepsy care, with a focus on clinical trials, is provided. The QOLIE-31 is the most frequently applied and best validated tool. Several other questionnaires focusing on specific aspects of HRQOL (e.g., mood, social impact) are less frequently used. We show some pitfalls that should be taken into account when designing study protocols including HRQOL endpoints. This includes standardized statistical analysis approaches and predefined reporting methods for HRQOL in epilepsy populations. It has been shown in other patient groups that the lack of such standardisation negatively impacts the quality and comparability of results. We conclude with a number of recommendations for future research.

1. Introduction

Epilepsy is one of the most frequent neurological disorders in adults, affecting over 70 million people worldwide (Thijs et al., 2019). Historically, the primary treatment goal is the achievement of seizure-freedom. In general, seizure-freedom is reached in approximately 50% of patients through the first appropriately chosen anti-seizure medication (ASM), and in another 20% through second- or third-choice ASM, or with a combination of two or more ASM (Janmohamed et al., 2020). The remaining 30% so-called drug-resistant patients might be eligible for epilepsy surgery or other invasive treatment options (e.g., vagus nerve stimulation), but unfortunately many will never reach seizure freedom.

For many patients, epilepsy is a life-long condition, or at least impacts on decades of their lifespan. Although patients with epilepsy (PWE) might lead a relatively normal life, the impact of the constant awareness of being at risk for seizures and having to take medication on a daily basis, which can have side-effects, often severely impacts patient everyday functioning and well-being. This can relate to different levels, including work, family and social life. Currently, the most commonly used primary outcome measure in clinical trials and clinical practice is some type of quantification of seizure frequency. However, seizure control does not directly nor consistently translate into improved perceived health for PWE (Cramer et al., 2019). Possible drug toxicity or other treatment- or disease-related factors may result in a net negative impact on PWEs health status, even when seizure freedom is achieved. Several studies have demonstrated that assessment of quality of life based on seizure frequency reduction (SFR) does not show consistent results across different ASMs, at either the 50% or 75% SFR thresholds. Therefore, it remains to be determined whether the currently most frequently used outcome measures in both clinical practice and clinical research are the most relevant for all PWE, and if other patient-centred

* Corresponding author at: Department of Neurology, SEIN, Heemstede, the Netherlands.
E-mail address: JReijneveld@sein.nl (J.C. Reijneveld).

https://doi.org/10.1016/j.eplepsyres.2024.107310
Received 19 May 2023; Received in revised form 20 December 2023; Accepted 22 January 2024
Available online 24 January 2024

outcome measures should be included more widely for a more holistic view on possible benefit for PWE health and functioning.

In this review, we will evaluate the value of clinical outcome assessments reflecting the patients' functioning and wellbeing, in particular health-related quality of life (HRQOL), as outcome measure.

2. Clinical Outcome Assessments

The US Food and Drug Administration (FDA) has defined four types of patient-centred outcome measures, reflecting how a patient feels, functions or survives, which are collectively called clinical outcome assessments (COAs) (for more information see {Dirven, 2018 #2006}): (1) patient-reported outcome (PRO) measures, (2) clinician-reported outcome (ClinRO) measures, (3) observer-reported outcome (ObsRO) measures, and (4) performance outcome (PerfO) measures. Patient-reported outcomes (PROs) are important measurements for quantifying symptoms, function, and overall HRQOL. The FDA and the European Medicines Agency (EMA) have defined PROs as 'a measurement directly reported by patients that reflects patients' perception of a disease and its treatment'. Clinician-reported outcome (ClinRO) measures are based on a report that comes from a healthcare professional, whereas ObsRO measures are based on reports from someone other than the patient or healthcare professional (e.g., another proxy). In some patients, the same concept can be measured with different COAs, e.g., cognitive symptoms, which can be measured objectively with a PerfO (i.e., neurocognitive tests) or subjectively with a PRO measure (i.e., questionnaires). Clinical outcome assessments (COAs) can provide additional information about the beneficial and adverse effects of a new treatment strategy, adding context to information on response assessed through biomarkers (e.g., imaging, blood tests), clinical response (e.g., SFR) or, progression-free or overall survival (Dirven et al., 2018).

2.1. Patient-reported outcomes

Patient-reported outcomes can be measured either through a self-report or in an interview, and might cover symptoms, functioning, and overall HRQOL (see for more information (Dirven et al., 2018)). In clinical trials, information from PROs can be used to assess the net clinical benefit of a particular experimental treatment, combined with disease-oriented measures such as SFR and toxicity. In clinical practice, information from PROs can be applied to shared decision-making in which patients, their primary caregivers, and their physicians jointly make a treatment decision based on the best available evidence. Results of PROs assessed over time might also be used in clinical practice for needs assessment, and to monitor a patient's symptoms or functioning during the disease trajectory. With treatment effects monitored, opportunities for better symptom management can be identified, so that patients can be referred to another healthcare professional (e.g., a patient with depression can be referred to a psychiatrist), or to identify potential warning signs that might trigger preventive additional care (e.g., psychotherapy in case of a high risk for depression) (Dirven et al., 2013).

2.2. Health-related quality of life for epilepsy patients

Health-related quality of life (HRQOL) is a multidimensional concept covering different aspects of patients' perception of his/her quality of life. HRQOL is a PRO, and reflects the three different levels of functioning as specified by the World Health Organisation (WHO) International Classification of Functioning, Disability, and Health: it covers functioning on the level of impairment, activity limitations, and participation restrictions. There is a wide range of PRO instruments focusing on HRQOL, from unidimensional measures (assessing one specific aspect of HRQOL, such as fatigue) to multidimensional HRQOL measures (Ware and Sherbourne, 1992). Currently, there is no single gold standard tool to measure HRQOL in epilepsy patients.

2.2.1. Generic

The first scales that were used to assess HRQOL in epilepsy patients were generic measures, suitable for the general population and/or multiple disease sites. An example is the SF-36 questionnaire, a short-form health survey consisting of 36 questions that looks at functioning on eight different domains, being vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health (Ware and Sherbourne, 1992).

Another generic PRO measure used in the epilepsy patient population is the PROMIS-10 (also called PROMIS-Global Health (GH)), developed from the National Institute of Health's sponsored PROMIS question banks (Hays et al., 2009). It was designed and validated to measure mental and physical health within and across healthy subjects, as well as patients with multiple conditions such as heart disease, cancer, rheumatoid arthritis, and psychiatric disorders. In PWE, PROMIS-10 met the ideal criteria for patient input, literature review and clinician input, and construct validity (Jones et al., 2020), and was therefore considered relevant for this patient population.

2.2.2. Disease-specific questionnaires

Disease-specific HRQOL measurement tools have also been developed. For example, in the cancer field, a frequently used tool is the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (Aaronson et al., 1993) in conjunction with site-specific questionnaires, such as the brain tumour module QLQ-BN20 (Osoba et al., 1996; Taphoorn et al., 2010) or the breast cancer module QLQ-BR45 (Bjelic-Radisic et al., 2020). Regarding neurological diseases, disease-specific questionnaires also have been developed for Parkinson's disease (for an overview see (Berardi et al., 2021)) and multiple sclerosis (Khurana et al., 2017), amongst others.

2.2.3. Epilepsy-specific questionnaires

The QOLIE-31 questionnaire is a validated 31-item PRO measure that evaluates HRQOL in PWE specifically (Cramer et al., 1998). The SF-36 was used as the foundation for the creation of this epilepsy-specific scale (Devinsky et al., 1995), as the same research group demonstrated the relevance for an epilepsy-specific HRQOL questionnaire when comparing HRQOL in different patient groups (Hermann et al., 1996). Seven subscales cover domains evaluating the impact of epilepsy on cognitive functioning (problem-solving, memory, concentration), emotional well-being (mood), energy/fatigue, medication effects (worry over physical/mental effects of medication), overall QOL, seizure concern (worry/fear of seizures and their manifestations), and social functioning (social and leisure impact, driving, work limitations). Each domain includes two to six items, and has a total score that ranges from 1 to 100, with higher values indicating a better HRQOL. The QOLIE-31 total score is calculated as a weighted average of the domain scores. The QOLIE-31 also has an abbreviated (QOLIE-10) (Cramer et al., 1996) and the original, longer version (QOLIE-89), the latter consisting of 17 scales (Devinsky et al., 1995). In addition to the scales covered by the QOLIE-31, the QOLIE-89 covers language, attention/concentration, memory, physical function, pain, role limitations due to physical problems, role limitations due to emotional problems, health discouragement, and health perceptions.

The Seizure Severity Questionnaire (SSQ) is also specifically developed for PWE, and includes questions related to frequency and helpfulness of warning signs, as well as frequency, severity, and burden of ictal and postictal effects (Borghs et al., 2014). As the name suggests, it is mainly designed for further detailing seizure severity and its impact on HRQOL, and less on generic HRQOL. There are several other scales in use for generic HRQOL assessment in PWE, including the Veterans Administration scale and the Chalfont-National Hospital Scale NHS3 version, the Occupational Hazard scale, the Liverpool Seizure Severity Scale, and the Hague Seizure Severity (HASS) scale for children (for an overview comparison see (Avila et al., 2017). The NEWQOL is meant for

patients with new-onset epilepsy that experienced a first seizure within the last 6 months (Abetz et al., 2000), while the LQOL is designed for patients with refractory epilepsy (Baker et al., 1994 #2009). The Washington Psychosocial Seizure Inventory (WPSI) was specifically developed to identify psychological and social problems among PWE (Dodrill et al., 1980).

In a recent, very informative systematic review, Jones et al. concluded that, based on time for completion (i.e. $\leq$3 min), costs (charge), coverage of HRQOL domains, as well other psychometric properties, the QOLIE-10 and PROMIS-10 questionnaires were most feasible for implementation into adult epilepsy clinics, but that further studies assessing the responsiveness over time are needed (Jones et al., 2020). Remarkably, whereas QOLIE-10 is a disease-specific instrument, PROMIS-10 is not. To our knowledge, no formal comparison regarding the feasibility and validity of the abovementioned tools has been done.

3. The main determinants of HRQOL in epilepsy patients

The main determinant of overall HRQOL in epilepsy patients is, not unexpectedly, the occurrence of seizures. Many studies have shown that for seizure-free patients, the level of HRQOL is comparable to healthy controls (Spencer et al., 2007; Vickrey et al., 1994; Boylan et al., 2004; Markand et al., 2000; Vickrey et al., 1992; Luoni et al., 2011). The exact nature of the correlation between HRQOL and seizure frequency, however, is unclear (Spencer et al., 2007; Vickrey et al., 1994; Luoni et al., 2011). There seems to be no linear correlation between seizure frequency and HRQOL, though it is assumed that a seizure-reduction of $>$ 75% is correlated with improvement in HRQOL. In patients with multiple seizures per month, however, the exact seizure frequency does not appear to correlate with HRQOL scores (Blond et al., 2016).

Several other factors also impact on aspects of HRQOL. Psychiatric comorbidities, such as depression, anxiety, and suicidal ideation play an important role (Boylan et al., 2004), as do side-effects of ASM which may include said psychiatric comorbidities. Furthermore, many PWE suffer from neurocognitive deficits (Gauffin et al., 2021), that may also have an impact on perceived HRQOL. The interplay between all these factors is complex. For instance, mood disorders are more prevalent in PWE who are not seizure-free, but are also frequently-reported side--effects of ASM. Moreover, underlying brain pathology related to the epilepsy, seizure frequency, ASM, and mood can all impact on cognitive functioning, which in itself also has a complex interaction with aspects of HRQOL. The correlation between objective cognitive (test) performance and subjective cognitive (complaints) performance, which are generally considered separate concepts, and perceived HRQOL (of which subjective cognitive functioning is part) is far from linear (Caramanna et al., 2021). Furthermore, sleep disorders and migraine, which are more prevalent in PWE than in the general population, and social impairment might have a negative impact on HRQOL (Blond et al., 2016). In a systematic review, Baranowski found no clear difference in overall HRQOL of older PWE in comparison to younger age groups. Participants reported energy/fatigue to have the most negative effect on HRQOL. As stated before, seizure frequency was a strong predictor of HRQOL, and comorbidity and depression were moderate predictors (Baranowski, 2018). There is substantial global variation in HRQOL of PWE, and country income level may play a role (Saadi et al., 2016).

Though seizure freedom seems to be the hierarchically most important determinant of HRQOL in PWE, the interactions between contributing factors are complex. Still, despite advances in treatment options (e.g. surgery, newer ASM with presumed fewer side effects), HRQOL does not seem to improve over the years on group level; Wassenaar et al. found no significant differences in HRQOL (overall QOLIE-31 scores) when comparing two cross-sectional community-based samples that were obtained from the same Dutch suburban region 10 years apart (n = 344 and n = 248 PWE, respectively) (Wassenaar et al., 2013). Further insight in how all contributing factors interact might reveal which factors are most crucial and should be interventional targets. For example, if mood has the highest impact on other contributing factors, future research efforts might focus on more frequent application of antidepressants in PWE suffering from mood disorders, which is nowadays hampered by (sometimes exaggerated) concerns about the risk of seizures or drug-drug interactions (Craig and Osborne, 2020).

A relatively novel way to determine these dependencies is to analyse systematically assessed aspects of HRQOL (i.e., functioning and/or symptom scores) of large patient populations through hierarchical cluster analyses. Previously, we found four symptom clusters in a cohort of over 4000 glioma patients (Coomans et al., 2019), in which seizures were included. Two of these symptom clusters were found to have a negative association with certain aspects of functioning, including physical, role and/or social functioning. Even more sophisticated is the use of network analyses techniques, which have the added benefit that they can also provide information on the strength and direction of correlations between different factors (Oreel et al., 2019). To our knowledge, these approaches have not been applied to HRQOL data of PWE so far. These methods might provide more insight into the interdependencies between different factors influencing aspects of HRQOL, and reveal central targets for intervention to more effectively enhance HRQOL.

4. HRQOL integration in clinical trials for PWE

To our knowledge, there is no complete overview of the quality of patient-centred evidence presented in RCTs for PWE, as has been done in other disease groups (e.g., {Dirven, 2014 #1806}). That is certainly a task to be performed in the near future. For now, we focus on a couple of practice-determining recent studies, such as the Standard and New Antiepileptic Drugs (SANAD)-II studies. The SANAD-II studies are open-label, non-inferiority, multicentre randomised phase IV studies on both focal (Marson et al., 2021a), and generalised epilepsy (Marson et al., 2021b). In SANAD-II, the long-term clinical effectiveness and cost-effectiveness of established first-line treatment and newer ASM were compared in a real-world setting. For both studies, the primary endpoint was 12 month remission of seizures, and HRQOL was a secondary outcome. For adults, HRQOL outcomes were assessed using subscales of NEWQOL (Abetz et al., 2000) and the Impact of Epilepsy Scale (Jacoby et al., 1993). HRQOL questionnaires were completed at baseline and annually thereafter. Jn addition, adults and parents completed a subset of HRQOL measures at 3 months and 6 months. In the generalised epilepsy SANAD-II study, 221/520 (42.5%) participants returned a baseline questionnaire and at least one follow-up questionnaire. Based on this high proportion of missing data, the authors stated that HRQOL results could not be considered reliable, and that data imputation was not considered reasonable. The response percentage was slightly higher in the focal epilepsy SANAD-II trial, being 49.8% (593/990) and this was considered sufficient for analysis. The latter trial report concluded that for adults, lamotrigine was associated with a better profile on self-reported measures of HRQOL than levetiracetam or zonisamide. A comparison of the treatment effects showed negative treatment effects for levetiracetam compared with lamotrigine for patient-reported anxiety, depression, stigma, epilepsy impact, and overall QOL. Compared with lamotrigine, zonisamide had a negative effect for depression, epilepsy impact, and overall QOL. In another recent report on a practice-changing RCT on the addition of cannabidiol in tuberous sclerosis complex patients with drug-resistant epilepsy (Thiele et al., 2021), results on QOL assessment were only reported under the subheading ‘other secondary outcome measures’ in the supplementary material.

5. Pitfalls in the assessment and collection of HRQOL-data in epilepsy trials

Although the fact that HRQOL assessments are integrated in the above mentioned clinical trials in PWE is to be applauded, problems

with compliance prevented the authors from drawing solid conclusions. Unfortunately, despite big efforts, large-scale HRQOL data collections in PWE have thus far not generally paid off in terms of valid and informative results. In general, several factors might negatively impact both the quantity and quality of HRQOL data collected, such as the representativeness of the study population, appropriateness of applied time windows for assessment, cognitive deficits within the population, and handling of missing data.

First of all, baseline trial populations are not typically representative of real-world patients asthe strict inclusion criteria lead to selection of patients with relatively high performance scores, and thus higher HRQOL scores. During the course of the trial, patients with poorer health status might drop out more frequently, resulting in an even further overestimation of HRQOL in the remaining, relatively fit sample (Dirven et al., 2013). This last issue also applies to measuring HRQOL in clinical practice; deteriorating patients might not complete their questionnaires. Secondly, the quantity and quality of collected HRQOL data in clinical trials can also depend on appropriate completion-time windows for assessments (e.g., week 4–6 after randomisation). The timing of HRQOL assessments should fit with the purpose of the trial. If the main objective is to determine the long-term net clinical benefit of a new ASM, it does not make sense to measure HRQOL early after the start. When the objective is to determine the immediate burden of the treatment (e.g., toxicity), HRQOL assessments should be done shortly after baseline. Handling deviations from the planned window of data collection also impact the quality and quantity of the data. Allowing larger completion-time windows might improve the validity of the results by having more complete HRQOL information, thereby facilitating statistical modelling, but might negatively impact the quality of the data, depending on the specific research question (Ediebah et al., 2013). In all cases, it is important to perform a baseline measurement before randomisation and thus before the start of treatment. Thirdly, many PWE suffer from cognitive deficits (Li et al., 2020). Cognitive dysfunction might hamper self-reported HRQOL, as patients might not be able to provide valid feedback about their own level of functioning or symptom experience (Caramanna et al., 2021). This may subsequently hamper a reliable interpretation on the impact of a new treatment or routine care on PWEs' HRQOL.

6. Pitfalls in the analysis and interpretation of HRQOL-data in epilepsy trials

Missing data might seriously hamper the analysis of longitudinal HRQOL data. Walker et al. (2003) previously showed that the major source of missing data was administrative failure, divided into patient-related factors and researcher-related factors. Patient-related factors included intentional or non-intentional non-attendance of study visits, poor patient motivation, misunderstanding of instructions, and incorrect completion of questionnaires. Researcher-related factors included administrative failure (e.g., questionnaires not being administered or being administered at the wrong time), lack of explanation, or reluctance to assess a patient who is deteriorating clinically. Patients who had been compliant during the follow-up period lived significantly longer than patients who were not compliant (Walker et al., 2003). There are many ways to correct for missing data, depending on the data characteristics, see {Dirven, 2013 #1760} for more extensive and in-depth information.

When good quality data with satisfying response rates are available, the next challenge is to do a proper data analysis. A lack of a consistent approach to analysing and interpreting PRO endpoints makes it difficult to compare results across various clinical trials in most disease fields. This lack of standardisation of PRO analysis approaches hampers the likelihood of findings informing policy and treatment decisions, and makes inefficient use of increasingly finite research funding (Bottomley et al., 2016). In the oncology field, this increased awareness has inspired the formation of the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) consortium aiming to develop guidelines for standardised analysis methods {Coens, 2020 #1950}. Depending on the diversity of PRO analysis methods in the epilepsy field, a similar effort might be necessary.

When subsequently combining outcome measures into a net clinical benefit, difficult trade-off issues may arise when interpreting findings. When both the primary (seizure) outcome measure and the HRQOL analysis point in the same direction (e.g., both improve or both decline) when comparing experimental and standard treatment arms, there is no issue. Trade- off discussions may arise, however, when the primary seizure outcome improves in the experimental treatment arm compared with the standard treatment, but HRQOL declines significantly, or vice versa (Dirven et al., 2014a). At that point, there is no consensus on the optimal treatment strategy for that specific patient population. Moreover, for some patients a reduction of seizure frequency is most important, while maintenance or improvement of HRQOL might be more relevant for others. It thus seems that there is need for a more personalised approach. Based on the patient's characteristics and preferences, physicians must advise the patient which treatment strategy might best meet their needs.

7. Recommendations for future research

First, novel analytical methods, such as cluster and symptom analysis, of large HRQOL datasets of preferably combined clinical epilepsy trials, might shed further light on the causal interaction and/or hierarchical order of prevalent symptoms and HRQOL issues. Such analyses might result in the definition of targets for interventions, which can ultimately result in improved HRQOL in PWE. Second, more insight is needed into the current level of PRO analysis and reporting in randomised controlled trials of PWE, similar to previous efforts in other patient groups (Dirven et al., 2014b), in order to assess whether PRO evidence is of sufficiently high quality to rely on when determining the net clinical benefit. Subsequently, recommendations on the further improvement of (better alignment of) study design, data analysis and reporting of results might be necessary.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

van Thuijl Hinke: Writing – review & editing. **Appelhof Bente:** Writing – review & editing. **Taphoorn Martin JB:** Writing – review & editing, Conceptualization. **Koekkoek Johan AF:** Writing – review & editing, Conceptualization. **Reijneveld Jacob C:** Writing – original draft, Supervision, Investigation, Conceptualization. **Thijs Roland:** Writing – review & editing, Conceptualization. **Visser Gerhard H:** Writing – review & editing, Supervision, Conceptualization. **Dirven Linda:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

References

Aaronson, N.K., et al., 1993. The European Organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J. Natl. Cancer Inst. 85 (5), 365–376.

Abetz, L., et al., 2000. Patient-based assessments of quality of life in newly diagnosed epilepsy patients: validation of the NEWQOL. Epilepsia 41 (9), 1119–1128.

Avila, E.K., et al., 2017. Seizure control as a new metric in assessing efficacy of tumor treatment in low-grade glioma trials. Neuro Oncol. 19 (1), 12–21.

Baker 1, G.A., et al., 1994. Development of a novel scale to assess life fulfillment as part of the further refinement of a quality-of-life model for epilepsy. Epilepsia 35 (3), 591–596. https://doi.org/10.1111/j.1528-1157.1994.tb02479.x.

Baranowski, C.J., 2018. The quality of life of older adults with epilepsy: a systematic review. Seizure 60, 190–197.
Berardi, A., et al., 2021. Tools to assess the quality of life in patients with Parkinson's disease: a systematic review. Expert Rev. Pharm. Outcomes Res 21 (1), 55–68.
Bjelic-Radisic, V., et al., 2020. Corrigendum to an international update of the EORTC questionnaire for assessing quality of life in breast cancer patients: EORTC QLQ-BR45: Ann Oncol 2020; Volume 31, Issue 2, Pages 283-288. Ann. Oncol. 31 (4), 552.
Blond, B.N., Detyniecki, K., Hirsch, L.J., 2016. Assessment of treatment side effects and quality of life in people with epilepsy. Neurol. Clin. 34 (2), 395–410 (viii).
Borghs, S., et al., 2014. Sensitivity testing of the seizure severity questionnaire (SSQ). Epilepsy Behav. 31, 281–285.
Bottomley, A., et al., 2016. Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards. Lancet Oncol. 17 (11), e510–e514.
Boylan, L.S., et al., 2004. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. Neurology 62 (2), 258–261.
Caramanna, I., et al., 2021. Objective neurocognitive functioning and neurocognitive complaints in patients with high-grade glioma: Evidence of cognitive awareness from the European Organisation for research and treatment of cancer brain tumour clinical trials. Eur. J. Cancer 144, 162–168.
Coomans, M.B., et al., 2019. Symptom clusters in newly diagnosed glioma patients: which symptom clusters are independently associated with functioning and global health status. Neuro Oncol. 21 (11), 1447–1457.
Craig, D.P., Osborne, C., 2020. Risk of seizures with antidepressants: what is the evidence? Drug Ther. Bull. 58 (9), 137–140.
Cramer, J.A., et al., 1996. A brief questionnaire to screen for quality of life in epilepsy: the QOLIE-10. Epilepsia 37 (6), 577–582.
Cramer, J.A., et al., 1998. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. Epilepsia 39 (1), 81–88.
Cramer, J.A., et al., 2019. Health-related quality of life in patients treated with eslicarbazepine acetate monotherapy: pooled analysis from two registered clinical trials. Epilepsy Behav. 92, 31–35.
Devinsky, O., et al., 1995. Development of the quality of life in epilepsy inventory. Epilepsia 36 (11), 1089–1104.
Dirven, L., et al., 2013. Health-related quality of life in patients with brain tumors: limitations and additional outcome measures. Curr. Neurol. Neurosci. Rep. 13 (7), 359.
Dirven, L., et al., 2014b. The level of patient-reported outcome reporting in randomised controlled trials of brain tumour patients: a systematic review. Eur. J. Cancer 50 (14), 2432–2448.
Dirven, L., et al., 2018. Working plan for the use of patient-reported outcome measures in adults with brain tumours: a response assessment in neuro-oncology (RANO) initiative. Lancet Oncol. 19 (3), e173–e180.
Dirven, L., Reijneveld, J.C., Taphoorn, M.J., 2014a. Health-related quality of life or quantity of life: a difficult trade-off in primary brain tumors? Semin. Oncol. 41 (4), 541–552.
Dodrill, C.B., et al., 1980. An objective method for the assessment of psychological and social problems among epileptics. Epilepsia 21 (2), 123–135.
Ediebah, D.E., et al., 2013. Effect of completion-time windows in the analysis of health-related quality of life outcomes in cancer patients. Ann. Oncol. 24 (1), 231–237.
Gauffin, H., et al., 2021. Similar profile and magnitude of cognitive impairments in focal and generalized epilepsy: a pilot study. Front Neurol. 12, 746381.
Hays, R.D., et al., 2009. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual. Life Res 18 (7), 873–880.
Hermann, B.P., et al., 1996. A comparison of health-related quality of life in patients with epilepsy, diabetes and multiple sclerosis. Epilepsy Res 25 (2), 113–118.
Jacoby, A., et al., 1993. Measuring the impact of epilepsy: the development of a novel scale. Epilepsy Res. 16 (1), 83–88.
Janmohamed, M., et al., 2020. Pharmacoresistance - Epidemiology, mechanisms, and impact on epilepsy treatment. Neuropharmacology 168, 107790.
Jones, F.J.S., et al., 2020. A feasibility assessment of functioning and quality-of-life patient-reported outcome measures in adult epilepsy clinics: a systematic review. Epilepsy Behav. 102, 106704.
Khurana, V., et al., 2017. Patient-reported outcomes in multiple sclerosis: a systematic comparison of available measures. Eur. J. Neurol. 24 (9), 1099–1107.
Li, N., et al., 2020. One-year analysis of risk factors associated with cognitive impairment in newly diagnosed epilepsy in adults. Front Neurol. 11, 594164.
Luoni, C., et al., 2011. Determinants of health-related quality of life in pharmacoresistant epilepsy: results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments. Epilepsia 52 (12), 2181–2191.
Markand, O.N., et al., 2000. Health-related quality of life outcome in medically refractory epilepsy treated with anterior temporal lobectomy. Epilepsia 41 (6), 749–759.
Marson, A., et al., 2021a. The SANAD II study of the effectiveness and cost-effectiveness of levetiracetam, zonisamide, or lamotrigine for newly diagnosed focal epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. Lancet 397 (10282), 1363–1374.
Marson, A., et al., 2021b. The SANAD II study of the effectiveness and cost-effectiveness of valproate versus levetiracetam for newly diagnosed generalised and unclassifiable epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. Lancet 397 (10282), 1375–1386.
Oreel, T.H., et al., 2019. The dynamics in health-related quality of life of patients with stable coronary artery disease were revealed: a network analysis. J. Clin. Epidemiol. 107, 116–123.
Osoba, D., et al., 1996. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. Qual. Life Res 5 (1), 139–150.
Saadi, A., Patenaude, B., Mateen, F.J., 2016. Quality of life in epilepsy-31 inventory (QOLIE-31) scores: a global comparison. Epilepsy Behav. 65, 13–17.
Spencer, S.S., et al., 2007. Health-related quality of life over time since resective epilepsy surgery. Ann. Neurol. 62 (4), 327–334.
Taphoorn, M.J., et al., 2010. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. Eur. J. Cancer 46 (6), 1033–1040.
Thiele, E.A., et al., 2021. Add-on cannabidiol treatment for drug-resistant seizures in tuberous sclerosis complex: a placebo-controlled randomized clinical trial. JAMA Neurol. 78 (3), 285–292.
Thijs, R.D., et al., 2019. Epilepsy in adults. Lancet 393 (10172), 689–701.
Vickrey, B.G., et al., 1992. A health-related quality of life instrument for patients evaluated for epilepsy surgery. Med. Care 30 (4), 299–319.
Vickrey, B.G., et al., 1994. Quality of life of epilepsy surgery patients as compared with outpatients with hypertension, diabetes, heart disease, and/or depressive symptoms. Epilepsia 35 (3), 597–607.
Walker, M., et al., 2003. Practical problems with the collection and interpretation of serial quality of life assessments in patients with malignant glioma. J. Neurooncol. 63 (2), 179–186.
Ware, J.E., Sherbourne, C.D., 1992. The MOS 36-itme short-form health survey (SF-36). I. Conceptual framework and item selection. Med. Care 30 (6), 473–483.
Wassenaar, M., et al., 2013. Treatment of epilepsy in daily clinical practice: have outcomes improved over the past 10 years? J. Neurol. 260 (11), 2736–2743.