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Health-Related Quality of Life in Children and Adolescents with Epilepsy: A Systematic Review

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1. Introduction

With the patients' preferences in the centre of contemporary medicine, it was developed the patient-reported outcome (PRO) concept that represents the patient's report of a health condition and its treatment regimen (Acquadro et al., 2003). This general term includes different sources of information coming directly from patients about their health; each providing a unique and valuable perspective like well-being, functional status, health-related quality of life (HRQOL), and others. The primary values of PROs are considered as indicators of the impact of disease, essential parts for evaluating treatment efficacy and interpreting clinical outcomes, and key elements in decision-making. Coming directly from a patient about his health, PROs are equally valuable as other reports coming from the observations of that patient, e.g. physiological or clinical data.

Nowadays, the concept of the HRQOL appears as the most significant PRO, frequently reported in prevention, treatment, and rehabilitation. This concept represents the patient's evaluation of the impact of a health condition and its treatment on daily life (Acquadro et al., 2003). HRQOL is a multidimensional, changing construct that covers physical, emotional, mental, social, and behavioral components of well-being and functioning as perceived by patients (Ravens-Sieberer et al., 2006). Although a subjective construct, HRQOL is conceptualized through objective indicators as well, and from a measurement perspective, qualitatively and quantitatively observed (Verdugo et al., 2005). The term is separated from its "parent", quality of life (QOL), which implies on an evaluation of the impact of all non-health-related aspects of life on general well-being (FDA, 2006).

Systematizing the current pediatric literature, HRQOL is defined as "functioning, feelings about functioning, health, and value assigned to duration of life" (Davis et al., 2006). The main identified components in the construct are physical and psychological well-being, energy and vitality, self-perception, cognitive functioning, social functioning and support, autonomy and independence, psychological relations to the material environment, and general health perception and life quality (Ravens-Sieberer et al., 2006). Adolescents' HRQOL is a separated construct, with maturation, intimacy, and sexuality as important components added to its assessment (Frisein, 2007). Considering the methodology of

HRQOL assessment, important issues are age, developmental characteristics, self-rating and proxy responding, generic and disease specific approaches, psychometric considerations, and cross-cultural settings (Erling, 1999; Christakis et al., 2001; Barnes & Jenney, 2002; Matza et al., 2004; De Civita et at., 2005; Ravens-Sieberer et al., 2006). First, HRQOL assessment should consider relevant age groups (mainly up to 3, 4-7, 8-12, and 13-16 year-olds), with developmental characteristics specified; physical, psychological, and social. Then, it must be determined an age-appropriate rating, whether a child can rate own HRQOL, or a proxy should be considered. Finally, based on the aims of assessment, appropriate questionnaire should be selected respectfully of type (generic or specific, profile or index, and utility measure), psychometrical characteristics (reliability, validity, responsiveness, and interpretability), and an emphasis put on the cultural settings. Therefore, the evaluation of HRQOL in a group of children or adolescents should include all relevant domains to that group and it should be performed applying appropriate methodology, taking into account sophisticated measures developed and regulations asserted (De Civita et at., 2005; Ravens-Siebere et al., 2006; Davis et al., 2006).

Pediatric epilepsy is a very complex neurological condition primarily characterized by unexpected, episodic, and chronic nature of variety of seizures, but also by different developmental, psychological, behavioral, educational, and social difficulties. As such, pediatric epilepsy has pervasive impacts on all aspects of a child's life (Ronen et al., 2003). Over the past 25 years or more, an extensive literature has examined the impacts of pediatric epilepsy and its co-morbidities on children's lives. A number of studies evaluated the impact of epilepsy on general health, emotional well-being, psychosocial functioning, family, and so on. Epilepsy impact was far more frequently evaluated considering HRQOL, which includes the perceived impact of epilepsy and its treatment on everyday living and functioning. Only with HRQOL, it has become possible to perceive how a child/adolescent with epilepsy lives from day to day, considering his/her well-being and functioning in a variety of domains (physical, cognitive, psychological, social, school, etc.).

The findings of studies from two past decades generally showed that HRQOL in pediatric epilepsy is significantly affected in many domains, primarily cognitive, psychological, and social. Nevertheless, a number of studies that evaluated HRQOL had methodological shortcomings (like not defining domains of interest, age-inappropriate assessments, inappropriate questionnaires used, cross-sectional design, etc.) and findings of different studies were often contradictory (Ronen et al., 2003; Lach et al., 2006). Considering this, it is not possible to draw general conclusions about specific domains of HRQOL affected in children and adolescents with epilepsy and to understand the nature and dynamics of epilepsy and its treatment impacts on everyday living and functioning in this population.

Therefore, this review was organized with the aims to identify in a systematic way the domains of HRQOL affected in children and adolescents, the predictors of HRQOL, and the impacts on HRQOL of specific and non-specific epilepsy treatments (antiepileptic drugs (AEDs), epilepsy surgery, vagus nerve stimulation, and others).

2. Methods

2.1 Search strategy

Three independent computerized searches of the literature for the period 1st January 1996 to 31st January 2011 were performed in Pubmed, Scopus, and Web of Science. Besides, a detailed search of main relevant journals was performed: epilepsy (Epilepsia, Epilepsy & Behavior, Epilepsy Research, Seizure, Epileptic Disorders, Epilepsy Abstracts, Epilepsy

Currents, and Epilepsies), child neurology (Developmental Medicine and Child Neurology, Journal of Child Neurology, and Pediatric Neurology), and patient outcome assessment (Value in Health, Health and Quality of Life Outcomes, and Quality of Life Research). The term "epilepsy" was combined with other key terms: children, adolescents, quality of life, QOL, health-related quality of life, and HRQOL. The reference lists of all identified publications were checked to retrieve other relevant publications, which were not identified by means of the searches.

2.2 Selection criteria

The following selection criteria were set: (1) the study population was children and/or adolescents up to 18 years of age; (2) HRQOL was the primary or secondary endpoint of the study; (3) HRQOL was assessed with an epilepsy specific and/or generic questionnaire/s previously validated; (4) the data for overall and/or domains of the questionnaire/s used were reported; and (5) the study was published in a peer-review journal. Based on the previous analyses of epilepsy specific questionnaires for HRQOL assessments in children and adolescents, eleven questionnaires were available (Ronen et al., 2003a; Waters et al., 2009) - Impact of Childhood Neurologic Disability Scale – ICND (Camfield et al., 2003), Quality of Life in Epilepsy for Adolescents questionnaire – QOLIE-AD 48 (Carmer et al., 1999), HRQOL in Pediatric Epilepsy Scale (Arunkumar et al., 2000), Quality of Life in Childhood Epilepsy Questionnaire – QOLCE (Sabez et al., 2000), HRQOL Instrument for Children with Epilepsy – CHEQOL-25 (Ronen et al. 2003), Epilepsy and Learning Disabilities Quality of Life Scale – ELDQOL (Buck et al., 2007), DISABKIDS Chronic Generic Measure, with Epilepsy Specific Module (Simeoni et al., 2007), Glasgow epilepsy outcome scale for young persons – GEOS –YP (Townshend et al., 2008), Epilepsy and children questionnaire – ECQ (Coda et al., 2001), Escala de calidad de vida del niño con epilepsia – CAVE (Herranz & Casas, 1996), and HRQOL for Brazilians – QVCE-50 (Maia Filho et al., 2007). Lists of different generic HRQOL questionnaires were provided in (Davis et al., 2006; Solans et al., 2008).

The described inclusion criteria were applied to the initial 1208 hits. Based on titles and abstracts of articles, 155 articles were potentially applicable from all three searches. When PDF files were obtained for these 155 articles, the selection criteria were applied again to the full articles' text and 44 remained to be included in this review.

2.3 Quality assessment

Two investigators (Stevanovic and Tadic) assessed the methodological quality of all 44 selected studies using a 17-item standardized checklist of predefined criteria (Table 1). The checklist was a modified version of an established criteria list for systematic reviews (Kuijpers et al., 2004; Mols et al., 2005; Den Oudsten et al., 2007). Each item of a selected study that met the criterion was assigned one point. If an item did not meet a particular criterion or was described insufficiently or not at all, no point was assigned. The highest possible score was 17. Studies scoring 70% or more of the maximum attainable score (i.e. ≥12 points) were rated to be of "high quality", studies scoring between 50% and 70% (i.e. 8-11 points) were rated as "moderate quality", and studies scoring lower than 50% (i.e. ≤ 7 points) were rated as "low quality" studies.

Positive if:
QOL assessment
A. A psychometrically sound questionnaire used
B. A reason given for choosing a certain questionnaire
Study population
C. Children and/or adolescents and parents/caregivers included
D. Inclusion and/or exclusion criteria considered (at least age, duration of symptoms, and relevant comorbidity)
E. Participation rates for patient groups described and these rates exceeded 75%
F. A description of the sample included socio-demographic (at least age, gender, and educational status) and epilepsy variables (at least type, age at onset, duration, and treatment)
G. Information is given about the ratio non-responders versus responders or no selective response
H. The setting of requirement given (i.e. general practice, hospital, occupational setting, etc)
I. The process of data collection described (e.g., interview or self-assessment, etc.)
Study design
J. The data prospectively gathered
K. The follow-up period of at least 6 months
L. Drop-out/loss to follow-up < 20%
HRQOL Results
M. The sample size (the number of cases equaled at least ten times the number of variables in the multivariate analysis)
N. The results reported overall and specific HRQOL domains (at least mean and standard deviations)
O. The results compared between two or more groups (e.g., health population, groups with different severity of epilepsy or age) and/or compared with at least two time points (e.g., longitudinally or pre- versus post-treatment)
P. The data for children and adolescents presented separately
Q. Predictors described using regression analyses or structural equation modeling

Table 1. List of criteria for assessing the methodological quality of HRQOL studies

2.4 Data extraction and synthesis

Data were extracted of the selected studies regarding a study population, design, HRQOL questionnaire/s used, HRQOL domains and predictors studied, and treatment reported. All measures used for HRQOL assessments in the selected, besides holding the title of quality of life of HRQOL, are very different from each other on several aspects despite having adequate psychometric properties, especially in epilepsy (Ronen et al., 2003). Therefore, in order to facilitate interpretation and comparison of the results of the studies that used different questionnaires, the following HRQOL domains were considered: general health, physical, cognitive, psychological, general behavior, social, family, school, and epilepsy specific domain. Where appropriate, to the domains were added specific subdomains evaluated by the questionnaires used (i.e. psychological domain (emotional well-being,

anxiety, etc.) or cognitive domain (attention, memory, etc)). HRQOL predictors were considered as demographic, social, psychological, and epilepsy specific. For epilepsy treatment, AEDs, epilepsy surgery, vagus nerve stimulation, and others interventions/drugs were considered relevant.

The domains of HRQOL affected in children and adolescents were identified from the synthesis of consistent findings from the studies that compared HRQOL between children and adolescents and controls or from the synthesis of consistent findings from the studies using the same questionnaire. Next, HRQOL predictors were identified from the synthesis of consistent findings from the studies that used regression models to evaluate predators of HRQOL. Finally, the impacts on HRQOL of specific and/or non-specific treatments were identified from the synthesis of consistent findings from the studies that consider some treatment.

Findings were considered consistent if ≥ 75% of the studies that investigated a domain/predictor showed the same direction of the association. Five levels of evidence were defined as modified according to the study of Mols and colleagues (Mols et al., 2005) (Table 2).

Strong	Consistent findings (≥75%) in at least two high-quality studies or one high-quality study and at least two moderate studies
Moderate	Consistent findings (≥75%) in one high-quality study and one moderate- or low-quality study or at least three moderate studies
Weak	Findings of one high-quality study or consistent findings of two moderate studies or at least three low-quality studies
Inconclusive	Inconsistent findings or less than three low-quality study

Table 2. Level of evidence

3. Results

3.1 Study characteristics and methodological quality

Forty-four analyzed studies were published after 1999 and mostly in the USA, Canada, and Australia (Table 3). Thirty-one studies were cross-sectional, 12 follow-up, and one randomized clinical trial (RCT). In 15 studies, HRQOL was compared between children and adolescents and controls (general population or chronic illnesses), while a specific and/or non-specific treatment was considered in 15. Nine studies evaluated HRQOL in adolescents and nine evaluated HRQOL as self- (child/adolescent) and parent-rated. The study samples included between 9 and 474 participants.

There was disagreement between the two reviewers when scoring the articles, mainly due to differences in applying the criteria B, E, G, and M. These disagreements were solved through discussion in a consensus meeting. The quality scores ranged from 7 (low) to 14 points (high), with the mean score of 10. Methodological shortcomings mainly concerned the reason given for choosing a certain questionnaire (B), the rater, children and/or adolescents and parents (C), the participation rates (E), the follow-up period (K), the sample size (M), the data presentation, children and adolescents (P), and the predictors (Q).

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
Children and adolescents with epilepsy				
Ronen et al., 2010, Canada	12 (E, K, M, P, O)	CHEQOL-25, children, adolescents, parents,	Design: cross-sectional Number (m/f): 131 (NA) Age (years): 7.8-16 Epilepsy type: different types	• Predictors : duration of epilepsy, age at epilepsy onset, number of AEDs, side effects of AEDs, attention and conduct problems, anxiety, intelligence, autonomy, social support, family structure, social skills, parent mood, and victimization
Yam et al., 2008, China	12 (B, E, K, P, Q)	CHEQOL-25 children, adolescents, parents,	Design: cross-sectional Number (m/f): 266 (NA) Age (years): 8-18 Epilepsy type: different types Control group: 381 CAWE from Canada	• CAWE from Hong Kong had lower levels of HRQOL in the interpersonal, secrecy, and worries domain compared to CAWE from Canada • There was acceptable agreement between children and parents, but parents tended to underestimate the HRQOL of their children
Verhey et al., 2009, Canada	11 (B, G, K, P, Q)	CHEQOL-25, children, adolescents, parents,	Design: cross-sectional Number (m/f): 391 (189/202) Age (years): 8-17 Epilepsy type: different types	• Lower levels of parent–child agreement on the more abstract domains of HRQOL in CAWE (secrecy and concerns) • Parent perspectives alone are insufficient to measure their child's HRQOL
Mathiak et al., 2010, Poland	11 (B, C, K, M, P, Q)	QOLCE, parents	Design: cross-sectional Number (m/f): 31 (19/12) Age (years): 6-15 Epilepsy type: different types	• CAWE with right-hemispheric foci had lower levels in emotional (including anxiety) and social (including stigma) domains
Clary et at., 2010, USA	10 (B, C, E, K, M, O, P)	QOLCE, parents	Design: cross-sectional Number (m/f): 132 (69/63) Age (years): 6-17 Epilepsy type: different types	• Predictors: age at onset (emotional well-being), intelligence (cognitive functioning), depression, withdrawal, attention problems, atypicality, and aggression (cognitive function, emotional well-being, and behavior)
Ferro et al., 2011, Canada	10 (B, C, G, K, P, O, N)	QOLCE, parents	Design: 24-month-follow-up Number (m/f): 339 (177/162) Age (years): 4-12 Epilepsy type: newly diagnosed, different types	• Maternal depressive symptoms had significant negative impacts on HRQOL in CAWE. This relationship was moderated by family resources and partially mediated by family functioning and demands
Yong et al., 2006, China	8 (A, B, C, D, E, K, N, O, P)	QOLCE, parents	Design: cross-sectional Number (m/f): 418 (241/177) Age (years): 4-18	• Predictors: child's educational degree, mental development, age at onset and diagnosis, seizure frequency, number of

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
			Epilepsy type: different types	AEDs, economic status, parental health (depression and anxiety)
Li et al., 2008, China	7 (A, B, C, D, E, K, N, O, P, Q)	QOLCE, parents	Design: cross-sectional Number (m/f): 340 (203/137) Age (years): 4-18 Epilepsy type: different types	• Parental anxiety is inversely correlated to HRQOL in CAWE
Wirrell et at., 2005, Canada	7 (A, B, C, G, K, M, N, O, P, Q)	QOLCE, modified version, parents	Design: cross-sectional Number (m/f): 57 (27/28) Age (years): 4-16 Epilepsy type: different types Control group: 55 healthy and controls with chronic conditions	• Sleep problems correlated with lower levels of overall HRQOL and in physical, social, and cognitive functioning and behavior domain
Haneef et al., 2010, USA	11 (D, E, G, K, P, Q)	PedsQL, children, adolescents, parents	Design: cross-sectional Number (m/f): 100 (59/41) Age (years): 2-18 Epilepsy type: different types Control group: literature data	• CAWE had lower physical, emotional, social, and school functioning compared to the normative data • CAWE had significantly lower physical and school functioning compared to other chronic illnesses as self-rated, and lower physical, emotional, and social functioning as parent-rated • Children with well-controlled epilepsy and a neuropsychiatric comorbidity had lower HRQOL in all domains than those without a neuropsychiatric comorbidity • Lower levels of HRQOL were observed in refractory than in well-controlled epilepsy
Ingerski et al., 2010, USA	9 (B, D, E, F, G, K, P, Q)	PedsQL, children, adolescents, parents,	Design: cross-sectional Number (m/f): 105 (71/34) Age (years): 2-18 Epilepsy type: NS Control group: different chronic conditions (7)	• Children and adolescents with epilepsy had similar or better levels of HRQOL than others with chronic conditions
Modi et al., 2010, USA	7 (B, C, D, E, G, J, K, M, P, Q)	PedsQL, parents	Design: cross-sectional Number (m/f): 53 (27/26) cases with a single seizure and 56 (35/21) cases with a newly diagnosed epilepsy Age (years): 2.1-17.9 Epilepsy type: different types Control group: normative data	• Children with a single seizure and newly diagnosed epilepsy had lower physical, emotional, social, and school functioning compared to the normative data • No significant differences were found between children with a single seizure and children with newly diagnosed epilepsy

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
Lagunju et al., 2009, Nigeria	7 (A, B, C, D, E, F, K, O, P, N)	PedsQL, children, adolescents, parents,	Design: cross-sectional Number (m/f): 66 (33/33) Age (years): 5-15 Epilepsy type: different types	• Predictors : seizure severity and family disruption
Baca et al., 2010, USA	12 (B, G, K, P, Q)	CHQ-CF87, CHQ-PF50, children, adolescents, parents	Design: cross-sectional Number (m/f): 279 (149/130) Age (years): NS (mean 13 (2.6)) Epilepsy type: different types Control group: 143 healthy siblings	• CAWE had lower levels of physical function and physical role limitations as self-rated than their siblings • Patents of CAWE reported lower levels of physical and psychosocial functioning than for their siblings and as compared to the normative data • There is significant differences in child self-report versus parent report of HRQOL for CAWE compared with sibling controls
Miller et al., 2003, USA	10 (B, C, D, E, K, M, P)	CHQ-PF 50, parents	Design: cross-sectional Number (m/f): 41 (23/18) Age (years): 4-19 Epilepsy type: different types Control group: 41 age- and sex-matched healthy controls	• CAWE had lower levels of global health, physical functioning, roles (physical, emotional, and behavioral), mental health, self-esteem, parent impact, and family activities compared to healthy controls • Predictors : comorbid neurological impairments and number of AEDs
Tse et al., 2007, Canada	11 (B, C, K, O, P, Q)	ICND, parents	Design: cross-sectional Number (m/f): 101 (52/49) Age (years): 3-17 Epilepsy type: different types Control group: 101 siblings	• CAWE with better social skills had better HRQOL (in overall and impact of epilepsy on behavior, cognition, and physical/neurological disability domain)
Montanaro et al., 2005, Italy	9 (B, C, D, E, F, K, P, Q)	ECQ, children, adolescents	Design: cross-sectional Number (m/f): 140 (70/70) Age (years): 7-16 Epilepsy type: different types Control group: healthy controls	• CAWE had lower levels of psychological and social functioning than healthy controls, but similar levels of school functioning
• ***Adolescents with epilepsy***				
Devinsky et al., 1999, USA	13 (C, E, K, O)	QOLIE-AD 48, adolescents	Design: cross-sectional Number (m/f): 197 (96/101) Age (years): 11-17 Epilepsy type: different types	• Attitudes toward epilepsy domain with the lowest score • Predictors : age, epilepsy severity, side effects of AEDs (neurotoxicity), and socioeconomic status

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
Stevanovic, 2007, Serbia	12 (C, E, G, K, M)	QOLIE-AD 48, adolescents	Design: cross-sectional Number (m/f): 71 (39/32) Age (years): 11.5-18 Epilepsy type: different types	• Males and females had similar levels of HRQOL, except that female perceived grater epilepsy impacts • Attitudes toward epilepsy and social support domain with the lowest scores • Predictors : number of AEDs, epilepsy concern, and female gender
Adewuya, 2006, Nigeria	10 (A, B, C, K, M, N, O)	QOLIE-AD 48, adolescents	Design: cross-sectional Number (m/f): 86 (50/36) Age (years): 12-18 Epilepsy type: different types	• Attitudes toward epilepsy domain with the lowest score • Predictors : number of AEDs, duration of illness, side effects of AEDs, general psychopathology, and parent mood (depression)
Benavente-Aguilar, et al., 2004, Spain	10 (B, C, E, K, M, O, P)	QOLIE-AD 48, adolescents	Design: cross-sectional Number (m/f): 66 (36) Age (years): 10-19 Epilepsy type: different types	• Attitudes toward epilepsy domain with the lowest score • Predictors : epilepsy severity and side effects of AEDs
Turky et al., 2008, UK	10 (C, E, G, K, M, N, O)	QOLIE-AD 48, adolescents	Design: cross-sectional Number (m/f): 56 (25/31) Age (years): 11-17 Epilepsy type: different types	• Predictors : seizure frequency and the presence of special educational needs
Wu et al., 2010, China	12 (B, C, E, K, M)	QOLIE-AD 48, adolescents	Design: cross-sectional Number (m/f): 47 (26/21) Age (years): 11-17 Epilepsy type: different types Control group: 47 age- and sex-matched healthy controls	• No differences between males and females • Social support domain with the lowest score • AWE had more impaired aspects of memory, concentration, physical functioning and social support compared to normal controls • Predictors : seizure worry, age at epilepsy onset, and fear of injury
• ***Specific epilepsy types or specific populations with epilepsy***				
Connoly et al., 2006, Australia	13 (C, K, M, P)	CHQ-PF 50, QOLCE, parents	Design: cross-sectional Number (m/f): 30 (22/8) Age (years): 7-12 Epilepsy type: benign rolandic epilepsy (BRE)	• Children with BRE had lower levels of self-esteem, anxiety, depression, and impact of the illness on the family compared to normative data, but similar levels of physical functioning • Predictors : general intellectual ability and parental emotional impact

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
Northcott et al. , 2007, Australia	10 (B, C, G, K, M, P, Q)	QOLCE, parents	Design: cross-sectional Number (m/f): 40 (16) Age (years): 6-12 Epilepsy type: BRE Control group: 40 age- and sex- matched healthy controls	• Children with BRE had lower levels of cognition, attention, memory, anxiety, self-esteem, and general health compared to healthy controls
Sabaz et al., 2001, Australia	12 (B, C, K, P, Q)	QOLCE, parents	Design: cross-sectional Number (m/f): 94 (46/48) Age (years): 4-18 Epilepsy type: different types with and without intellectual disability	• Intellectually normal CAWE had higher levels on physical restrictions, attention, language, control/helplessness, social interactions, social activities, and behavior than CAWE and intellectual disability (IQ < 70)
Sabaz et al., 2003, Australia	12 (C, G, K, P, Q)	CHQ-PF 50, QOLCE, parents	Design: cross-sectional Number (m/f): 119 (63/56) Age (years): 4-18 Epilepsy type: epilepsy syndromes	• Symptomatic epilepsy syndromes had lower levels of physical function, social limitations due to behavioral difficulties and physical health, self-esteem and emotional impact compared to idiopathic epilepsy syndromes
Wanigasinghe et al., 2010, Australia	7 (B, C, E, I, K, M, N, O, P, Q)	PedsQL, parents	Design: cross-sectional Number (m/f): 63 (41/22) Age (years): 4-20 Epilepsy type: epilepsy in hemiplegic cerebral palsy (CP) Control group: hemiplegic CP without epilepsy	• Emotional, school, and social functioning were significantly lower in children with CP and epilepsy than in those without epilepsy
Wake et al., 2003, Australia	7 (B, C, D, E, F, G, K, M, P, Q)	CHQ-PF 50, parents	Design: cross-sectional Number (m/f): 80 (45/35) Age (years): 5-18 Epilepsy type: different types in CP Control group: children with CP, but without epilepsy	• Children with CP and epilepsy had lower levels of self-esteem and difficulty getting along in the family
• ***Antiepileptic drugs (AEDs)***				
Jakovljevic et al., 2008, Serbia	10 (B, C, D, E, K, M, N)	QOLIE-AD-48, adolescents	Design: 3-months-follow-up Number (m/f): 21 (NA) Age (years): 8-20 Epilepsy type different types Frequency of assessments: two Drug: valproate	• Memory/concentration and physical functioning domain inversely correlated with the serum concentrations of valproate

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
Gupta et al., 2004, India	10 (A, B, C, K, M, P, Q)	QOLCE, parents	Design: randomized, double-blind, placebo-controlled trail Number (m/f): 31 (18/12) Age (years): 3-12 Epilepsy type: different types Frequency of assessments: two Drug: melatonin and valproate	• Significant improvement on attention, memory, language, other cognitive processes, anxiety, and behavior after adding melatonin to valproate
Jung et al., 2010, Korea	9 (B, C, E, G, P, Q, H, I)	K-QOLCE, parents	Design: 6-month-follow up Number (m/f): 474 (276/198) Age (years): 4-17 Epilepsy type: different types Frequency of assessments: two Drug: topiramate	• Significant improvement after 6 months was observed in energy/fatigue, anxiety, self-esteem, concentration, memory, language, social activities, and behavior domain • CAWS receiving only topiramate showed a greater improvement with regard to the cognition and behavior domain than those taking polytherapy
Vovk et al., 2010, Serbia	7 (B, C, D, E, F, K, M, N, O, P)	QOLIE-AD-48, adolescents	Design: 3-month-follow-up Number (m/f): 26 (11/15) Age (years): 8-54 Epilepsy type: different types Frequency of assessments: two Intervention or drug: topiramate	• Topiramate plasma concentration did not correlate with HRQOL
Ficker et al., 2005, USA	10 (B, C, G, H, K, N, Q)	QOLIE-AD-48, adolescents	Design: 3-month-follow-up Number (m/f): 39 (NA) Age (years): 12-17 Epilepsy type: partial epilepsy Frequency of assessments: two Intervention or drug: carbamazepine	• There were significant improvements in epilepsy impact and health perception domain in CAWE taking carbamazepine
• *Epilepsy surgery*				
Van Empelen et al., 2005, The Netherlands	14 (D, M, Q)	HAY, children, adolescents, parents	Design: 24-month-follow-up Number (m/f): 21 (4/17) Age (years): 6.2-16.8 Epilepsy type: symptomatic	• Improvement in physical, cognitive, and social activities after 6 months • CAWE felt less bothered at 24 months about the seizures; cognitive and social activities, as

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
			Control group: reference data for healthy children Frequency of assessments: four Intervention: epilepsy surgery	well as feelings about seizures and epilepsy treatment improved, while the frequency of concerns and feelings of inferiority because of having a chronic illness decreased • No significant differences were found between children (6–12 years) and adolescents (older than 12 years) • Before surgery, children felt less bothered with respect to physical, cognitive, and social activities than their parents did. Two years after surgery, they still felt less bothered than their parents did about cognitive activities. Additionally, their feelings with respect to general physical complaints and to seizures were more positive than those of the parents
Zupanic et al., 2009, USA	12 (B, J, K, P, Q)	QOLCE, QOLIE-AD-48 parents/care givers, adolescents	Design: cross-sectional Number (m/f): 83 (35/48) Age (years): 0-21 Epilepsy type: symptomatic Frequency of assessments: once Intervention: epilepsy surgery	• Physical activity, cognition, social activity, and general health were significantly better in children with seizure-free outcomes than in children who were not seizure-free (parents rates) • There was no difference in levels of HRQOL (QOLIE-AD 48 domains) between adolescents who were seizure free and adolescents who were not after surgery
Sabaz et al., 2006, Australia	12 (B, C, D, M, P)	QOLCE, parents	Design: 18-month-follow up Number (m/f): 35 (NA) Age (years): 6-18 Epilepsy type: symptomatic Frequency of assessments: three Intervention: epilepsy surgery	• CAWE who were seizure free postoperatively showed improvements in social interactions, social activities, anxiety, control-helplessness, physical restrictions, and general health • Predictors : seizure outcome (seizure freedom) and baseline levels of HRQOL
Mikati et al., 2010, Lebanon	8 (A, B, C, D, H, K, M, P, Q)	QOLCE, parents	Design: cross-sectional Number (m/f): 19 (11/8) Age (years): 2-14 Epilepsy type: symptomatic	CAWE who underwent surgery had higher levels of behavior than non-operated CAWE, but similar levels of physical activates, emotional, cognitive and social

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
			Control groups: 19 non-surgery partial epilepsy matched controls; 19 matched healthy controls Intervention: epilepsy surgery	functioning CAWE who underwent surgery had lower levels of physical functioning and general health than healthy controls
Mikati et al., 2008, Lebanon	8 (A, B, C, D, H, K, M, P, Q)	QOLCE, parents	Design: cross-sectional Number (m/f): 17 (10/7) Age (years): 4-16 Epilepsy type: symptomatic Control group: 12 non-surgery epilepsy matched controls Frequency of assessments: once Intervention: epilepsy surgery	CAWE who underwent surgery had higher levels of physical activities, emotional well-being, and general health than non-operated CAWE Type of surgery (temporal vs. extratemporal) was not associated with HRQOL
Vagus nerve stimulation (VNS)				
Sherman et al., 2008, Canada	11 (B, C, M, N, P, Q)	ICND, parents	Design: 1-year-follow-up Number (m/f): 34 (10/14) Age (years): 3-18 Epilepsy type: different types Control group: 19 children with chronic epilepsy Frequency of assessments: two Intervention: VNS	Pre-implantation, VNS children as a group had significantly poorer HRQOL compared with the chronic epilepsy group in terms of epilepsy-specific and global domains During the follow-up, the children in both groups showed no changes in epilepsy-specific quality of life A greater number of children in the VNS group had meaningful increases in HRQOL compared with the chronic epilepsy group, but this difference did not reach statistical significance
You et al., 2007, Korea	9 (B, C, D, E, M, N, P, Q)	QOLCE parents	Design: 6-year-follow-up Number (m/f): 28 (16/12) Age (years): 2y5m – 17y10m Epilepsy type: different types Frequency of assessments and timing: four Intervention: VNS	VNS improved memory, mood, behavior, alertness, achievement, and verbal skills as HRQOL domains
Mikati et al., 2009. Lebanon	8 (A, B, C, D, K, M, N, P, Q)	QOLCE, parents,	Design: 0.4-3.9-year follow-up Number (m/f): 11 (NA) Age (years): 5-18 Epilepsy type: different	CAWE with VNS had improvement in social domain only

Reference, country	Study quality (unsatisied criteria)	HRQOL instrument/s, rater	Study method	General HRQOL findings
			types Frequency of assessments: two Intervention: VNS	
Epilepsy - nonspecific pharmacological treatments or interventions				
Yoo et al., 2009, Korea	9 (B, C, D, E, G, K, M, P)	QOLCE, parents	Design: 2-month-follow-up Number (m/f): 25 (17/8) Age (years): 6-17 Epilepsy type: different types Frequency of assessments: two Drug: osmotic-controlled release oral delivery system (OROS) methylphenidate	After two months of OROS methylphenidate treatment, levels of physical restriction, self-esteem, memory, language, other cognition, social interaction, behavior, and general health domain improved
Conant et al., 2008, USA	8 (B, C, D, E, G, K, M, P, Q)	QOLCE, parents	Design: 10-week-follow up Number (m/f): 9 (NA) Age (years): 8-16 Epilepsy type: different types Frequency of assessments: two Intervention: karate program	Significant improvement on memory after passing the karate program
CAWE – children and adolescents with epilepsy, CHEQOL-25 – HRQOL Instrument for Children with Epilepsy, QOLCE – Quality of Life in Childhood Epilepsy Questionnaire, QOLIE-AD 48 – Quality of Life in Epilepsy for Adolescents questionnaire, PedsQL – Pediatric quality of life inventory (Varni et al., 2001), CHQ-CF87 and CHQ-PF50 – Child Health Questionnaire (Landgraf, 1996), ICND – Impact of Childhood Neurologic Disability Scale, ECQ – Epilepsy and children questionnaire, HAY – How Are You (Bruil, 1999), NA – not available, AEDs – antiepileptic drugs				

Table 3. Overview of the studies included in the analyzes

3.2 Health-related quality of life

Children and adolescents with epilepsy had significantly lower levels of functioning and well-being in physical, psychological (including emotional, general mental health, and self-esteem), social, school, and family domain compared to healthy controls, siblings, and/or the normative data (Miller et al., 2003; Montanaro et al., 2004; Modi et al., 2009; Haneef et al., 2010; Baca et al., 2010). One study reported that children and adolescents had significantly lower physical and school functioning compared to other chronic illnesses as self-rated, and lower physical, emotional, and social functioning as parent-rated (Haneef et al., 2010). Nevertheless, one study showed that children and adolescents had similar or better levels of HRQOL as others with chronic conditions (Ingerski et al., 2010). Finally, children and adolescents with refractory epilepsy or neuropsychiatric co-morbidities had low levels of physical, emotional, social, and school functioning (Haneef et al., 2010).

Six cross-sectional studies evaluated HRQOL in adolescents with epilepsy using the QOLIE-AD 48 (Devinsky et al., 1999; Benavente-Aguilar et al., 2004; Adewuya, 2006; Stevanovic, 2007; Turky et al., 2008; Wu et al., 2010). In these studies, the attitudes towards epilepsy and social domain were with the lowest scores, when the scores of all eight QOLIE-AD 48 domains were compared in-between. Only one study reported that AWE had more impaired aspects of memory/concentration, physical and social functioning compared to normal controls (Wu et al., 2010). There were no differences between males and females in the social, health perception, memory/concentration, physical functioning, stigma, attitudes toward epilepsy, and school behavior domain evaluated by the QOLIE-AD 48 (Stevanovic, 2007; Wu et al., 2010).

Several studies evaluated HRQOL in specific epilepsy groups. In two studies, HRQOL was evaluated in children with benign rolandic epilepsy and psychological domain (including anxiety, depression, and self-esteem) was more affected than others were (Connolly et al., 2006; Northcott et al., 2007). Further, one study reported that intellectually normal CWE had higher levels on physical, cognitive (attention, language), psychological (control/helplessness), social and general behavior than CWE and intellectual disability (IQ < 70) (Sabaz, 2001). One study reported that symptomatic epilepsy syndromes had lower levels of physical, psychological, and social compared to idiopathic epilepsy syndromes (Sabaz, 2003). Finally, two studies analyzed HRQOL in epilepsy in cerebral palsy and reported decreased levels of functioning and wellbeing in different domains (Wake et al., 2003; Wanigasinghe et al. 2010).

Finally, four studies reported that there was acceptable agreement between children/adolescents and parents, but parents tended to underestimate the HRQOL of their children (Miller et al., 2003; Van Empelen et al. 2005; Yam et al., 2008; Verhey et al., 2009). The level of agreement between child self-report's and parent proxy was lower on the more abstract domains of HRQOL (feeling, secrecy, concerns, etc.) (Van Empelen et al. 2005; Yam et al., 2008).

3.3 Predictors

Different demographic, social, psychological, and epilepsy specific variables were investigated as predictors of HRQOL in children and adolescents and all were summarized in Table 4 according to the levels of evidence found.

3.3.1 Impacts of AEDs on HRQOL

Two studies evaluated the impact of topiramate (Jung et al., 2010) and carbamazepine (Ficker et al., 2005) on HRQOL in children and adolescents. Topiramate treatment led to significant improvements after 6 months in psychological (including energy/fatigue, anxiety, and self-esteem), cognitive (including memory and language), social, and general behavior domain. Adolescents with partial epilepsy treated with carbamazepine had significant improvements in epilepsy impact and health perception domain.

In one RCT, the impact of adding melatonin to valproate on HRQOL was evaluated (Gupta et al., 2004). The findings suggest that significant improvements were found on cognitive (including attention, memory, language, and other cognitive processes) and general behavior after adding melatonin to valproate.

Two studies evaluated the relationship between the serum concentrations of valproate and topiramate and HRQOL (Jakovljevic et al., 2008; Vovk et al., 2010). For valproate, it was

reported that memory/concentration and physical domain were inversely correlated with the serum concentrations, while for topiramate, the correlation between the serum concentrations and HRQOL was not observed.

Strong	Moderate	Weak	Inconclusive
Children and adolescents			
Age at epilepsy onset, number of AEDs, parental depression (Miller et al., 2003; Yong et al., 2006; Ronen et al, 2010; Clary et al., 2010; Ferro et al., 2010)	Attention problems, intelligence, family including, structure, parental anxiety, etc. (Yong et al., 2006; Li et al., 2008; Lagunju et al., 2009; Ronen et al, 2010; Clary et al., 2010)	Social skills, duration of epilepsy, side effects of AEDS, conduct problems, autonomy, social support, victimization (Ronen et al, 2010; Tse et al., 2007)	Seizure frequency, seizure severity, comorbid neurological impairments, psychological problems (conduct, anxiety, depression, withdrawal, atypicality, aggression), child's educational degree, mental development, economic status (Miller et al., 2003; Yong et al., 2006; Lagunju et al., 2009; Clary et al., 2010)
Adolescents			
Seizure worry/concern, side effects of AEDs (Devinsky et al., 1999; Benavente-Aguilar et al., 2004; Adewuya, 2006; Stevanovic, 2007; Wu et al., 2010)	Epilepsy severity, number of AEDs (Devinsky et al., 1999; Benavente-Aguilar et al., 2004; Adewuya, 2006; Stevanovic, 2007)	Age, socioeconomic status, fear of injury, age at epilepsy onset, female gender (Devinsky et al., 1999; Stevanovic, 2007; Wu et al., 2010)	Duration of epilepsy, seizure frequency, general psychopathology, special education needs, parent mood (depression) (Benavente-Aguilar et al., 2004; Adewuya, 2006; Turky et al., 2008)

Table 4. Predictors of HRQOL in children and adolescents with epilepsy

3.3.2 Impacts of epilepsy surgery on HRQOL

Five studies, two follow-ups, evaluated HRQOL in children and adolescents with symptomatic epilepsy who underwent epilepsy surgery (Van Empelen et al., 2005; Sabaz et al., 2006; Mikati et al., 2008; Mikati et al., 2010; Zupanc et al., 2010). All studies reported that epilepsy surgery improved different HRQOL domains in children and adolescents compared to non-operated children and adolescents or healthy controls. However, there were no differences in HRQOL between adolescents who were and who were not seizure free after surgery (Zupanc et al., 2010). No differences were found between children and adolescents (Van Empelen et al., 2005), while seizure outcome (seizure freedom) and baseline levels of functioning strongly predicts HRQOL in this population (Sabaz et al., 2006).

3.3.3 Impacts of vagus nerve stimulation on HRQOL

Three follow-up studies evaluated HRQOL in children and adolescents with implemented vagus nerve stimulation (VNS) (You et al., 2007; Sherman et al., 2008; Mikati et al., 2009). In general, VNS improved different HRQOL domains in children and adolescents, mainly cognitive, psychological, and social (You et al., 2007; Sherman et al., 2008). However, there was no statistical difference between those children with and without VNS (You et al., 2007).

3.3.4 Miscellaneous

One follow-up study reported that after two months of OROS-methylphenidate treatment added to AEDs improved physical, psychological (including self-esteem), cognitive (including memory and language), social interaction, general behavior, and general health domain (Yoo et al., 2009). One follow-up study reported that a 10-week karate program for children and adolescents significantly improved memory in cognitive HRQOL domain (Conant et al, 2008).

4. Discussion

This is the first systematic review synthesizing different studies that evaluated HRQOL in children and adolescents with epilepsy over 12 past years. The affected domains, predictors, and impacts on HRQOL of specific and non-specific treatments were reviewed. Previous reviews evaluated methodological issues in HRQOL assessment, components of theoretical model, and determinants of HRQOL in pediatric epilepsy (Ronen et al., 2003a; Cowan & Baker, 2004; Maia Filho et al., 2004; Lach et al., 2006; Waters et al., 2009).

4.1 Summary of evidence

Combining the selected studies, the following evidence was found for different aspects of HRQOL in children and adolescents with epilepsy.

First, strong evidence was found that children and adolescents have more affected HRQOL in physical, psychological, and social domain than healthy children and adolescents, while the findings were inconclusive for the findings for other HRQOL domains or when children and adolescents were compared to other chronic conditions. When only adolescents with epilepsy were considered, strong evidence was found that specific HRQOL domains affected were attitudes toward epilepsy (negative epilepsy perceptions) and social domain, while there were no differences between males and females. Additionally, weak evidence exists that adolescents with epilepsy had more impaired aspects of memory, concentration, physical functioning and social compared to normal controls. The above findings were based on comparisons between children and adolescents and healthy children and adolescents, including siblings, and/or the normative data for the questionnaires, and only a few studies included other chronic conditions as controls. Therefore, the affected domains, physical, psychological, and social, could be also affected in other chronic conditions to different degrees and it does not mean that these domains are specifically affected in epilepsy. It would be necessary to include different chronic conditions to study domains specifically affected in this population.

Second, strong evidence was found that parent perspectives alone are insufficient to measure their child's HRQOL. In pediatric epilepsy, parents tended to underestimate the HRQOL of their children and perceived differently domains that are more abstract. Although the child and parent perspectives may be different, resulting in different scores,

both are potentially valid and need to be considered in HRQOL assessments (Eiser & Morse, 2001a; Eiser & Morse, 2001b).
Third, in specific groups of children and adolescents with epilepsy, only moderate evidence was found that in benign rolandic epilepsy psychological domain (including anxiety, depression, and self-esteem) was more affected than others were. For others, the findings are inconclusive and no evidence could be found.
Forth, considering HRQOL predictors, strong evidence was found for age at epilepsy onset (younger age), a number of AEDs (more AEDs), and parental depression as the predictors when children and adolescents were considered together. Moderate evidence was found for attention problems, overall intelligence (lower) and family (including its structure, parental anxiety, etc.). Specific to adolescents only, seizure worry/concerns and side effects of AEDs were found as strong predictors and epilepsy severity, while a number of AEDs as moderate. The predictors of HRQOL were not studied in children only. Other predictors were with weak to moderate evidence or the findings are inconclusive. The previous narrative review showed that different aspects of epilepsy and its co-morbidity affect HRQOL (Lach et al., 2006). The results of this review showed that epilepsy variables affect HRQOL to different degrees, as well as psychological and sociodemographic variables. Nevertheless, strong predictor is parental depression, especially maternal. One study demonstrated that maternal depressive symptoms had significant negative impacts on HRQOL and this relationship was moderated by family resources and partially mediated by family functioning and demands (Ferro et al., 2010).
Finally, considering the impact of antiepileptic drugs or vagus nerve stimulation on HRQOL domains, the findings are inconclusive and no evidence could be found. Strong evidence was found that significant postoperative improvement was observed in physical, cognitive, social, and general health domain. However, this might not be the real picture about impacts of antiepileptic treatments on HRQOL, because there are no data from clinical trials that use HRQOL and other PRO as clinical endpoints. Therefore, this finding need to be taken with some reserve.

4.2 Strengths and limitations

There are several obvious methodological shortcomings in the set of the studies available for this review.
First, in most of the studies, there was small sample size and none of the studies calculated the number of subjects needed. Considering that HRQOL is a highly variable characteristic, there is a need for much more subjects in order to analyze differences between different groups or different times of assessment (Cramer, 2002; Fayers & Machin, 2007). Second, in most of the studies, HRQOL was evaluated for both, children and adolescents, and only one study separately reported the findings. However, it was demonstrated that HRQOL has specific characteristics and dynamics in childhood and adolescents and it has to be evaluated separately (Ravens-Siebere et al., 2006; Davis et al., 2006). Third, nine studies evaluated HRQOL as self- (child/adolescent) and parent-rated thus, comparing their results could be a source for type II error. Forth, most of the studies failed to state why particular HRQOL questionnaire was used. Stating that the reason for selecting a measure was its sound psychometric characteristics is of smaller value, because one of the basic principal in HRQOL assessment is using a psychometrically sound measure. A questionnaire should be selected considering the underlying theoretical model of assessment, objectives of assessment, population of interest, and so on (Ronen, 2003; Lach et al., 2006; Waters et al.,

2009). Fifth, HRQOL was analyzed mostly determining statistical significance between the groups or assessments. Any parameter for detecting a clinical significance or clinically meaningful change was not included, except by Sabaz and his colleagues who applied multivariable statistics for detecting subtle changes in HRQOL after epilepsy surgery (Sabaz et al., 2003).

The review itself has some limitations. First, the review included enough studies to extract the findings considering the specific HRQOL domains affected in children and adolescents when healthy controls were included. However, small number of studies compares children and adolescents and children with other chronic conditions. Additionally, small number of studies evaluated HRQOL in specific antiepileptic treatment, so the findings from the analyzed studies might prevent from drawing valid evidence. Second, as mentioned above combining the results of different studies that used parent or child reports for HRQOL could be a source for type II error. Third, there could be language bias, whereas only studies in English were included, besides that language was not exclusion criteria for selecting studies.

5. Conclusion

Based on the findings and evidence found, it could be concluded that children and adolescents have more affected HRQOL in physical, psychological, and social domain than healthy children and adolescents. In adolescence, attitudes toward epilepsy and social domain are the most affected. Age at epilepsy onset, a number of AEDs, and parental depression are important HRQOL predictors, but specific to adolescents only, seizure worry/concerns and side effects of AEDs were found as strong predictors. Further, the parent perspectives alone are insufficient to measure their child's HRQOL. Finally, epilepsy surgery improves HRQOL in physical, cognitive, social, and general health domain. For the other epilepsy treatments, no valid evidence was found.

Undoubtedly, the results indicate that more research on HRQOL in this population is needed. General recommendations for future research should include the following. First, more studies are needed that compare HRQOL in epilepsy and other chronic conditions. Second, more data should be available from clinical trials that used HRQOL. Third, HRQOL predictors need to be evaluated with structure equation models in order to demonstrate the role of possible risk, moderators, and mediating factors. Finally, the methodological shortcomings of the available studies stated in the limitations of the review have to be avoided following epilepsy specific and general recommendations for patient-outcome assessments (Leidy et al., 1998; Scientific Advisory Committee of the Medical Outcomes Trust, 2002; Terwee et al., 2007; Fayers & Machin, 2007).

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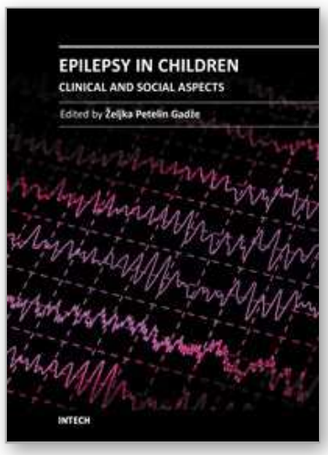

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Epilepsy is a neurological condition that accompanies mankind probably since its inception. About 400 years before Christ, the disease was already known by Hippocrates, who wrote the book â€œOn The Sacred Diseaseâ€. Classically, epilepsy has been defined as a chronic condition characterized by an enduring propensity to generate seizures, which are paroxysmal occurring episodes of abnormal excessive or synchronous neuronal activity in the brain. Out of all brain disorders, epilepsy is the one that offers a unique opportunity to understand normal brain functions as derived from excessive dysfunction of neuronal circuits, because the symptoms of epileptic seizures are not the result of usual loss of function that accompanies many disease that affect the brain. I am therefore extremely honoured to present this book. The 15 very interesting chapters of the book cover various fields in epileptology â€“ they encompass the etiology and pathogenesis of the disease, clinical presentation with special attention to the epileptic syndromes of childhood, principles of medical management, surgical approaches, as well as social aspects of the disease.

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