The prevalence rates of medication adherence and factors influencing adherence to antiepileptic drugs in children with epilepsy: A systematic review and meta analysis

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ABSTRACT

Objective: We conducted a systematic review to assess antiepileptic drug (AED) adherence rates, and to identify the characteristics associated with nonadherence in children.
Methods: We searched PubMed, EMBASE, and the Cochrane Library from inception to June 2017. Observational studies addressing medication adherence or examining factors influencing AED adherence were included.
Results: We included 22 studies, involving 3955 participants. The general quality of included studies were rated as high quality. Adherence rates were reported in 18 studies, varying between 22.1% and 96.5%. Meta analysis of 13 studies (n = 2051) revealed a pooled adherence rate assessed by objective methods of 58% (95% CI [0.46, 0.74]). Meta analysis of nine studies (n = 1217) revealed a pooled adherence rate assessed by subjective Methods of 73%, (95% CI [0.63, 0.85]). Family support, smaller family size, stable parental marriage status, support from healthcare providers and higher family socioeconomic status were associated with better medication adherence. However, contradictory results were found regarding the effects of age, the frequency of seizure, type of seizures, type of medication and the number of administered drugs.
Conclusions: Adherence to AEDs is challenging for pediatric patients with epilepsy. Few factors which influence adherence can be drawn because of differing variables and results. Future prospective research should be designed with longer study periods and larger samples in naturalistic settings.

1. Introduction

Adherence is the degree to which patients' treatment-related behaviors (e.g., taking medication, keeping follow-up medical appointments, changing dietary habits) are consistent with instructions or recommendations provided by health professionals (Cramer et al., 2008; Osterberg and Blaschke, 2005). However, nonadherence occurs when a patient fails to use the prescribed treatment correctly, such as administering an incorrect amount of medication, or administering medication at the wrong time (Hugtenburg et al., 2013). It is estimated that 33–69% of all medication-related hospitalizations are because of medication nonadherence, resulting in more than $100 billion spent annually on avoidable hospitalizations in US (Cutler and Everett, 2010; Viswanathan et al., 2012; Peterson et al., 2003). Epilepsy is one of the most common chronic neurological disorders, and antiepileptic drug

(AED) therapy is the primary treatment for epilepsy. Although AEDs offer effective seizure prevention in approximately 70% of patients with epilepsy when the most effective regimen is followed (Kwan and Brodie, 2000), a recent systematic review reported that AED non-adherence in adults is highly prevalent, with estimates ranging from 26 to 79% (Malek et al., 2017). In adults, AED non-adherence is associated with poor seizure control, increased morbidity and mortality along with increased time of hospitalization, worsened patient outcome, poor quality of life, and increased health care cost (Faught et al., 2008; Davis et al., 2008; Faught et al., 2009; Hovinga et al., 2008). AEDs non-adherence will also lead to increase burden of inpatient and emergency department services. Moreover, it also affects the family members socially, economically, and psychologically. (Faught et al., 2008; Getnet et al., 2016; Lin et al., 2016). Current evidence also indicates that adherence to AEDs among children with epilepsy is suboptimal (Nazziwa

et al., 2014; Shah et al., 2013). However, reported adherence rates and factors associated with non-adherence are inconsistent.

The aim of this study was to (1) determine rates of adherence by combining all relevant studies of pediatric patients with epilepsy; (2) identify the patient, medication, caregiver, and environment-related characteristics associated with nonadherence; (3) assess the quality of studies of adherence in pediatric epilepsy.

2. Methods

2.1. Search strategy

Electronic literature searches were conducted in the Cochrane Library (2017, Issue 6), PubMed (1966–2017.6), EMBASE (1974–2017, Issue 6), and the relevant reference lists. The search strategy was as follows: ("adherence" or "nonadherence" or "compliance" or "non-compliance") and ("epilepsy" or "seizure" or "epilepsies") and ("pediatrics" or "infant" or "neonate" or "newborn" or "child" or "adolescent"). The search was restricted to human studies, and the language was restricted to English. The search was independently carried out by two investigators, and any disagreements were discussed until consensus was reached.

2.2. Study selection

Observational studies were included if they addressed medication adherence or examined factors influencing adherence to AEDs. No restriction was applied regarding specific measurements of adherence, and the methods of measuring adherence included both objective and subjective clinician-based measures. We included all observational studies including patients under the age of 18 years with epilepsy, regardless of gender, nationality, inpatient or outpatient therapy.

Studies were excluded if they: (i) did not report the outcome of interest, or (ii) included both children and adults and the data of children could not be extracted separately.

2.3. Data extraction

Data were extracted by two reviewers using a standardized summary table and any disagreements were discussed until consensus was reached. The data extraction form included: (i) country of the first author, (ii) study design, (iii) patient demographics, (iv) the definition of adherence and the methods of measuring adherence, (v) adherence rate and factors associated with adherence.

2.4. Assessment of methodological quality

Two reviewers independently assessed the reliability of the results of the included studies using the quality checklist developed by the US Agency for Healthcare Research and Quality (AHRQ) (Rostom et al., 2004). The checklist included 11 items: (1) Define the source of information (survey, record review), (2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications, (3) Indicate time period used for identifying patients, (4) Indicate whether or not subjects were consecutive if not population-based, (5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants, (6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements), (7) Explain any patients exclusions from analysis, (8) Describe how confounding was assessed and/or controlled, (9) If applicable, explain how missing data were handled in analysis, (10) Summarize patient response rates and completeness of data collection, (11) Clarify what follow-up, if any, was expected and the percentage patients for which incomplete data or follow-up was obtained. An item was scored '0′ if it was labeled 'No' or 'Unclear'; and was scored '1′ if it was labeled 'Yes'. The maximum score

on the quality assessment scale was 11. In our review, a score of 8–11 indicated high quality, 4–7 indicated moderate quality, and 0–3 indicated low quality (Hu et al., 2015). Discrepancies in evaluations were discussed until consensus was reached.

2.5. Statistical methods

The adherence rates of AED use at the end of follow up were combined and reported as proportions with 95% Confidential Intervals (CI) based on the adherence measures and type of epilepsy. I^2 statistic were used to test heterogeneity and it was more than 50% were taken as indicators of heterogeneity, a random-effects model was used for statistical analysis, otherwise, a fixed-effects model was used (Higgins et al., 2003). We conducted the meta-analysis using Stata 12.0 software (STATA Corporation, College Station, TX). Because of statistical and clinical heterogeneity, a quantitative analysis of the factors associated with adherence was not conducted. Instead, we provide a narrative summary of the included studies.

3. Results

3.1. Search results

Our initial search identified 518 potentially relevant articles. After the removal of duplicates, screening of titles and abstracts, and reading the full text, 22 observational studies were included in the review (Fig. 1).

3.2. Characteristics of included studies (Tables 1 and 2)

This review included 22 studies, involving a total of 3955 participants, of which 2053 were male (51.9%). Participants ranged in age from 6 months to 18 years. All included studies were published in English, employed observational paradigms and were published between 1985 and 2015. Thirteen studies were cohort studies and the others were cross-sectional studies. The first authors of the included
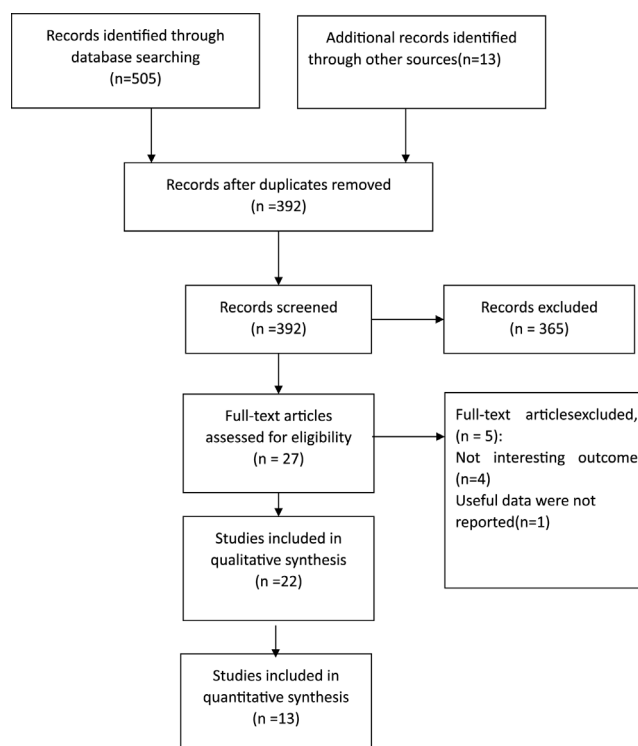

Fig. 1. Flowchart of the literature screening.