Epilepsy & Behavior 74 (2017) 104–113

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Review

Implementation of psychological clinical trials in epilepsy: Review and guide

Avani C. Modi [a,*], Janelle Wagner [b,c,d], Aimee W. Smith [a], Tanja S. Kellermann [e], Rosa Michaelis [f,g]

[a] Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave., Cincinnati, OH 45229-3039, USA
[b] College of Nursing, Medical University of South Carolina, Charleston, SC, USA
[c] Comprehensive Epilepsy Program, Medical University of South Carolina, Charleston, SC, USA
[d] Department of Pediatrics, Medical University of South Carolina, Charleston, SC, USA
[e] Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA
[f] Department of Psychiatry, St. Marien-Hospital, Hamm, Germany
[g] Integrative Curriculum for Anthroposophic Medicine (ICURAM), University Witten/Herdecke, Witten, Germany

ARTICLE INFO

Article history:
Received 31 May 2017
Accepted 11 June 2017
Available online xxxx

Keywords:
Trial design
Psychotherapy
Pediatric
Evidence-based interventions
Outcomes

ABSTRACT

The International League Against Epilepsy (ILAE) Neuropsychiatry commission and United States Institute of Medicine report both identified cognitive and psychological comorbidities as a significant issue for individuals with epilepsy, with rates as high as 60%. However, there is a paucity of evidence-based treatments for many psychological conditions (e.g., learning disorders, cognitive disorders, behavioral disorders). Because of inherent challenges in the implementation of psychological therapy trials and specific considerations for the population with epilepsy, the focus of the current review was to provide guidance and recommendations to conduct psychological trials for individuals with epilepsy. Several key areas will be discussed, including selection of patients, trial design, psychological intervention considerations, outcomes and evaluation of results, publication of trial results, and special issues related to pediatric clinical trials. Rigorously designed psychological therapy trials will set the stage for evidence-based practice in the care of individuals with epilepsy, with the goal of improving seizures, side effects, and HRQOL.

1. Introduction

In 2011, the International League Against Epilepsy (ILAE) Neuropsychiatry commission [1], and in 2012, the United States Institute of Medicine report both identified cognitive and psychological comorbidities as a significant issue for individuals with epilepsy [2], with rates as high as 60% [3–6]. While older epilepsy clinical trials excluded psychiatric/psychological comorbidities, the high prevalence of comorbidities in epilepsy necessitated the need not only to include patients with comorbidities, but also to have clinical trials solely focused on epilepsy-related comorbidities [7]. Psychological interventions to address these comorbidities typically focus on behavior change, such as reducing symptoms of depression and anxiety. In addition, psychological interventions may aim at improving coping with a new epilepsy diagnosis, adherence and self-management to treatment regimens, or executive and other cognitive functioning skills. Throughout this manuscript, the term "psychological" is used as an all-inclusive term related to the prevention and treatment of comorbidities. Psychological intervention strategies often include psychoeducation, cognitive-behavioral therapy (CBT), behavioral therapy, acceptance and commitment therapy, mind–body therapy, motivational interviewing, problem-solving therapy, and family systems therapy.

There are a limited number of evidence-based treatments for many epilepsy-related comorbidities, including learning disorders [8], autism spectrum disorder [9], attention-deficit hyperactivity disorder (ADHD) [10,11], psychosis [12,13], cognitive difficulties (i.e., memory and concentration difficulties) [14,15], substance abuse [16], and conversion disorders (i.e., nonepileptic events) [17–20]. There is a larger evidence base for psychological treatment for depression and anxiety in epilepsy [21,22], and consensus statements exist about treating depression in patients with epilepsy [23]. However, recent reviews of psychological treatments in epilepsy highlight the lack of scientific rigor of many of these trials [24,25], which limits the application of these research findings to clinical practice. The focus of the current review was to provide an overview of the challenges of conducting psychological trials in epilepsy and recommendations based on existing guidelines and practice in clinical trials [26].

Psychological therapy trials and drug trials have many similarities. Adherence to the clinical protocol is critical and may play a key role in outcomes. For example, if patients do not receive the appropriate treatment dose (i.e., drug or number of psychological intervention sessions),

* Corresponding author at: Cincinnati Children's Hospital Medical Center, Division of Behavioral Medicine and Clinical Psychology, Center for Adherence and Self-Management, 3333 Burnet Ave., MLC 7039, Cincinnati, OH 45229-3039, USA.
E-mail address: avani.modi@cchmc.org (A.C. Modi).

http://dx.doi.org/10.1016/j.yebeh.2017.06.016
1525-5050/

outcomes may be compromised, and subsequently, results of the clinical trial are difficult to interpret. Similarly, ensuring that the selection of candidates for both drug and psychological therapy trials provides an appropriate sample for the generalizability of the findings is important. Mediators and moderators must be identified prior to the initiation of both types of trials and are often similar (e.g., disease severity). The measurement of outcomes for epilepsy drug trials and psychological trials has limitations due to the subjectivity of reporting on variables, such as seizure frequency, side effects, and psychological symptoms. More objective measurement approaches may be available depending on the outcome of interest (e.g., blood serum levels, electronic monitoring of adherence, electroencephalogram findings).

Despite their similarities, there are some key differences between psychological trials and drug trials. Unlike drug trials, psychological therapy trials are unique because the mode of intervention is typically provided by trained mental health professionals, in which the relationship between therapist and patient is critical. Psychological interventions can also be time-intensive, subject to therapist drift from the protocol, and may be more affected by family and individual circumstances and beliefs (e.g., other psychological comorbidities not targeted by the intervention, life stress, transportation, cultural beliefs, and cognitive abilities) [27–29] than drug studies [30]. In contrast, psychological trials typically have fewer adverse events compared with drug trials and, thus, may be considered safer [31]. Certain trial designs, such as cross-over, cannot be used in psychological clinical trials, given that the focus of these interventions is to learn and apply skills for behavior change. These skills cannot be unlearned and typically carry over into other study arms with unpredictable effects. Finally, as will be discussed below, double-blind placebo-controlled trials are difficult to conduct for psychological interventions, as it is typically not feasible for the therapist to be blinded to condition. Because of inherent challenges in the implementation of psychological therapy trials and specific considerations for the population with epilepsy, the focus of the current review was to provide guidance and recommendations to conduct psychological trials for individuals with epilepsy.

Several key issues are discussed below, including selection of patients, trial design, psychological intervention considerations, outcomes and evaluation of results, publication of trial results, and special issues related to pediatric clinical trials. Each section provides an overview of the considerations specific to epilepsy and associated recommendations (See Table 1).

Table 1
Aspects to consider when developing and implementing a psychological therapy trial.

Broad topics	Subsections
Selection of patients	1. Source of recruitment 2. Seizure diagnosis and treatment ○ Seizure type ○ Seizure severity ○ Seizure frequency ○ Seizure onset ○ Seizure treatment 3. Age, development, and targets for intervention 4. Comorbidities
Trial design	1. Crossover versus parallel group designs 2. Control groups 3. Difficulties of conducting double-blind placebo-controlled psychological therapy trials
Psychological intervention considerations	1. Details of the psychological intervention 2. Interventionists training requirements 3. Modality and location of intervention 4. Dose and duration of interventions 5. Treatment fidelity/integrity 6. Participant adherence to treatment protocol
Outcomes and evaluation of results	1. Primary versus secondary outcomes 2. Generic versus epilepsy-specific outcome measures 3. Respondent for outcome measurement 4. Common data elements 5. Process variables 6. Treatment response rates 7. Timing of outcome measures 8. Moderators and mediators of outcomes
Publication of trial results	1. Use of the CONSORT guidelines for nonpharmacologic trials
Special issues related to pediatric trials	1. Multi-informant assessment 2. Family versus individual intervention

2. Selection of patients

The selection of patients plays a key role in the inclusion/exclusion criteria for psychological trials. Below, we provide information on critical aspects of patient selection that may influence psychological therapy trial results and outcomes in epilepsy. Many of the issues for inclusion/exclusion criteria for epilepsy trials apply to both drug and psychological therapy trials [7].

2.1. Source of recruitment

Recruitment for psychological therapy trials should ideally occur across several diverse sites and settings to increase generalizability of study findings. Patients can be recruited from various settings, including epilepsy centers, schools, communities (e.g., local or national epilepsy affiliate or voluntary associations), or a combination of these. When conducting psychological therapy trials, researchers need to identify a sufficient number of patients during the recruitment period for whom the treatment is ultimately intended (e.g., patients from subspecialty clinics versus community providers). For example, patients from urban areas are likely to have greater access to epilepsy resources [32] and psychological health interventions (e.g., psychologists, epilepsy advocacy group, support groups) compared with those from rural areas, with potential impact on clinical trial results (e.g., overrepresentation of participants without transportation difficulties). This may be particularly salient for face-to-face psychological trials in which patients are asked to return to the trial location on a regular basis to receive psychological treatment. In contrast, trials of mobile health (mHealth) interventions and electronically administered assessment protocols (e.g., online questionnaires) may recruit patients who have difficulties accessing treatment centers in person. It is important to note that studies involving technology (i.e., computer, mobile phone, Internet) may inadvertently exclude patient subgroups (i.e., those in rural areas without reliable internet coverage).

2.2. Seizure diagnosis and treatment

Epilepsy represents a complex spectrum of heterogeneous disorders with different etiologies and manifestations; therefore, seizure type(s), severity, frequency, and onset are relevant to the design and understanding of psychological treatment trials. Ideally, trials should include participants who differ in terms of seizure etiology, diagnosis, severity, and chronicity such that subgroups that are most likely to benefit from the psychological therapy can be identified.

2.2.1. Seizure type

Determination of seizures should follow the ILAE classification system for seizure type, etiology, and syndrome (if applicable) [33]. At a minimum, seizures should be classified into focal versus generalized, and if focal, the area of the brain involved, if known. Etiology may be indicated as genetic, structural, or unknown. If symptoms can be classified into epilepsy syndromes, inclusion of diagnoses, such as benign epilepsy with centrotemporal spikes, childhood absence epilepsy, and juvenile myoclonic epilepsy should be reported and taken into consideration, where possible. Seizure types and foci and epilepsy syndromes are associated with particular neuropsychological profiles [34], which could impact patients' engagement and outcomes in psychological interventions. Notably, the majority of patients with epilepsy have average intelligence; however, even patients with new-onset epilepsy