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Targeted Review

Psychobehavioral therapy for epilepsy

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ABSTRACT

Growing evidence suggests a bidirectional interaction between epileptic seizures and psychological states, fuelling the interest in the development and application of psychobehavioral therapy for people with epilepsy (PWE). The objective of this article is to review the various psychobehavioral therapies in regard to their application, hypothesized mechanisms, and effectiveness. Most psychobehavioral therapy aims at improving psychological well-being and seizure control. Behavioral approaches, cognitive–behavioral therapy (CBT), and mind–body interventions are the most widely applied approaches for PWE. Cognitive–behavioral therapy, mind–body approaches, and multimodel educative interventions have consistently demonstrated positive effects on enhancing well-being. Nevertheless, the effects on seizure control remain inconsistent, partly attributable to small clinical trials and inadequate control groups. Assessor-blinded randomized controlled trials with sufficient power and carefully defined therapeutic components corresponding with objective and subjective outcome measures are recommended for future trial designs.

Key questions

1. What psychobehavioral therapies are/may be useful in epilepsy?
2. What are the hypothesized mechanisms of action of psychobehavioral therapy for epilepsy?
3. Is psychobehavioral therapy effective in epilepsy?
4. What are the methodological challenges associated with the scientific study of psychobehavioral therapies and the proposed strategies for meeting those challenges?

1. Introduction

Accumulating evidence from animal models and clinical studies suggests a bidirectional relation between seizures and psychological states [1–3]. This understanding has been coupled with increasing research effort in incorporating psychobehavioral therapy in epilepsy care to improve psychological well-being and seizure control. This article aims to review the application and efficacy of psychobehavioral therapy for people with epilepsy (PWE) and to draw conclusions regarding the implications for future trial designs and clinical practice. The hypothesized mechanisms of these therapies are also discussed, which complement existing reviews [4,5]. For the purpose of this review, psychobehavioral interventions are defined as those based on theory of psychotherapy. Alternative remedies for epilepsy such as spirituality, energy healing, and aromatherapy, although they appear to be psychological in nature, will not be considered.[1]

2. What psychobehavioral therapies are/may be useful in epilepsy?

Therapeutic elements in psychobehavioral therapies that are most extensively applied include behavioral approaches, cognitive–behavioral therapy, and mind–body approaches. The majority of therapies are based

[1] All literature published in English before August 4, 2013 is included. Inclusion criteria regarding sample size and study design are not defined. Relevant studies are identified by search in MEDLINE (Ovid) and PsycINFO database with the following keywords: epilepsy or seizure or convulsion and one of the following keywords: alternative therapy, aura interruption, behavioral therapy, biofeedback, breathing, conditioning, cognitive–behavioral therapy, counseling, countermeasure, desensitization, education, mind–body, mindful, psychological, psychotherapy, relaxation, self-control, and self efficacy.

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on a primary therapeutic approach with a correspondent conceptualization of the psychological mechanism that underlies seizure activity [6–8]. However, some interventions employed a composition of therapeutic elements from different approaches, which are delivered as multimodel interventions [9–11].

These therapies may be delivered through individual-based therapy and/or group-based sessions, although most prospective clinical trials employed a multiple-session group therapy design. The number of sessions varied from brief interventions consisting of 2 sessions to comprehensive therapy with up to more than 40 sessions [9,12,13]. Some therapies also involved caregivers of PWE [14,15]. Most interventions include an evaluation of the individual's psychological stressors which could potentially increase seizure activity. An assessment of environmental and behavioral obstacles that prevent the individual from regulating lifestyle-related physiologic seizure risk factors, including drug noncompliance and sleep deprivation, are emphasized.

This section describes the application of the various techniques. Discussion on their hypothesized mechanisms and critical evaluations of their efficacy will follow.

2.1. Behavioral approaches

The behavioral approach for epilepsy is based on one of the earliest paradigms of psychotherapy and remains an essential element in many protocols. It operates by applying countermeasures upon seizure triggers and early stages of seizure activity to abort or reduce the likelihood of developing a seizure from the outset. Techniques such as conditioning, aura interruption, systematic desensitization, and EEG biofeedback are the major therapeutic components [16–18].

Aura interruption and systematic desensitization operate similarly based on the recognition of preictal and early ictal phenomena, with specific emphasis on the correlating psychosocial and emotional contexts. Countermeasures to interrupt the behavioral chain are applied when these preictal or early ictal phenomena arise. The most common techniques are relaxation, abdominal breathing, attention shifting, and inward monolog [6,12,19].

Operant conditioning by pairing an epileptic seizure with punishment and a seizure-free period with reward was mainly found in the early literature [20]. This method is used in conjunction with EEG biofeedback later on. Individuals are trained to increase 11- to 15-Hz EEG activity localized to the sensorimotor cortex to resemble a state of mental relaxation [21–24]. Electroencephalographic activities are explicitly displayed on a computer screen. Rewards (games and token) appear on the screen when the desirable EEG patterns occur and disappear when the EEG patterns fall beyond the range.

2.2. Cognitive–behavioral therapy (CBT)

Cognitive–behavioral therapy emphasizes the examination of the relationship between thoughts and emotions in the context of a specific event. Individuals learn to identify maladaptive patterns of thought and to establish alternative improved habitual cognitive and behavioral response patterns in order to enhance subjective emotional well-being. It is applied on a wide range of psychiatric disorders in systematized approaches. Therapeutic elements for PWE include psychoeducation on disease knowledge, mood regulation techniques, behavioral and cognitive countermeasures to auras, the resolution of cognitive dissonance that may result in intense emotional distress, stress management, as well as elements that facilitate lifestyle modification.

Most CBT protocols emphasize the individual's perception of health locus of control and aim at empowering individuals to establish subjective control over their seizures. Further, their role and participation in treatment are promoted with motivational techniques [10,15,25,26]. Journaling as a tool to record contextual seizure characteristics, relaxation logs, and self-affirmation statements is commonly used. Some include structured workbooks that guide and involve individuals through the exploration of their seizure experiences. Andrews and Reiter pioneered with the development of a systematic, semidirective, step-by-step counseling technique that is based on the workbook "Taking Control of Your Epilepsy" as an ongoing guideline for individual sessions. It comprises 12 sessions and includes detailed behavioral and cognitive restructuring techniques, lifestyle recommendations, assertive communication skills, and goal setting exercises [27]. Since an increased awareness of the capacity for taking control of seizure precipitants may lead to a tendency to react with self-blame and guilt in some individuals, alternative behavioral responses and cognitive reframing strategies are offered in case such feelings should arise.

Some interventions for PWE are specifically designed to treat or prevent psychiatric comorbidities and to decrease the build-up of seizure activities [7,28–31]. For example, Goldstein and colleagues described using a 12-session standardized CBT individually for adults PWE with psychiatric comorbidity [7]. Similarly, Macrodimitris et al. developed group-based CBT for PWE with comorbid depression and anxiety [30].

2.3. Mind–body approaches

Mindfulness and acceptance-based meditation have become one of the most common mind–body approaches used in PWE in recent years. Although meditation styles vary, all practices involve self-observation of mental and bodily activity, attention training, and the cultivation of process-oriented awareness. The therapeutic component of mindfulness is to acquire attention control by focusing on internal processes (breath, bodily sensations, thoughts, and emotions) and external stimuli (sights, sounds, smells, and textile) at the present moment ("here-and-now"), with nonelaborative attitude and nonjudgmental acceptance. These techniques have been formalized into standardized psychotherapy such as Mindfulness-Based Stress Reduction (MBSR), Mindfulness-Based Cognitive Therapy (MBCT), and Acceptance and Commitment Therapy (ACT). Mindfulness-Based Cognitive Therapy and Acceptance and Commitment Therapy have been applied among individuals with seizures. Various skills are involved; basic techniques include mindful breathing, mindful eating, mindful awareness on sensations, and thought and emotional labeling [8,32–35].

Generic stress reduction techniques, such as relaxation exercises and breathing, are widely employed in conjunction with other psychobehavioral approaches for epilepsy. Most breathing techniques utilize awareness of breathing rate, rhythm, and volume to achieve a state of calmness and to minimize physiological reactions to stress [36–38]. Moreover, they are often used jointly with muscle relaxation exercises, such as Jacobson's progressive muscular relaxation (PMR) and yoga exercises.

3. What are the hypothesized mechanisms of action of psychobehavioral therapy for epilepsy?

The application of psychobehavioral therapy to epilepsy as a chronic neurological disease does not necessarily aim at resolving psychopathology as in the traditional psychiatric setting. Instead, therapies aim at assisting individuals to increase their ability of coping with their disorder on a psychological level with possible underlying neurobiological alterations that might contribute to improved seizure control and psychological well-being.

Despite their diverse approaches, all psychobehavioral therapies for epilepsy operate with the aim to increase the individual's ability to prevent the build-up of seizure activity. In general, therapies aim to reduce both nonspecific seizure precipitants (e.g., sleep deprivation, stress, and physiologic risks) and specific internal (e.g., emotional distress and cognitive distortion) and/or external (e.g., sensory and environmental) contextual seizure precipitants, as illustrated in Figs. 1 and 2. Several hypothesized mechanisms of action are discussed below.

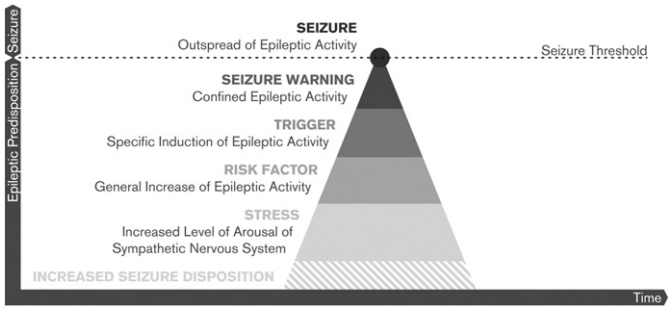

Fig. 1. The seizure event as the end-point of seizure precipitating factors. Fig. 1 conceptualizes the hypothesized interaction between the seizure threshold and the accumulation of seizure activity in the brain of an individual with an increased epileptic disposition. The seizure event is pictured as the end-point of proceeding factors that appear in the schematic order of temporal proximity to the actual seizure event. The proceeding factors can be correlated with various stages of the electrophysiological build-up of seizure activity: The disposition to experience epileptic seizures may increase due to alterations on a cellular or macroscopic level that can originate from various etiologies, e.g., traumatic brain injury and genetic mutations. Stress is conceptualized to act as a nonspecific seizure precipitant that corresponds with various neuroendocrinologic changes. Seizure risk factors are nonspecific seizure precipitants that affect the brain as a whole, e.g., missed sleep, missed meal, omitted medication. Seizure triggers are specific seizure precipitants that induce epileptic activity by being physiologically processed in an area adjacent to or overlapping with epileptogenic neurons. The nature of the neuronal network in which the seizure trigger is processed may be simple (e.g., visual stimuli) or complex (e.g., cognitive or emotional triggers). Seizure warning signs include all subjective phenomena that are reported by individuals to occur reliably prior to a generalized or complex partial seizure event. Those seizure warning signs may appear days and hours (usually referred to as "prodrome") or minutes to seconds (usually referred to as "aura") prior to the seizure. The latter is usually regarded as the subjective correlate of the initial appearance of confined epileptic activity in the brain. If the accumulated seizure activity crosses the seizure threshold, a seizure occurs. All or some of these factors may operate for a given seizure in an individual.

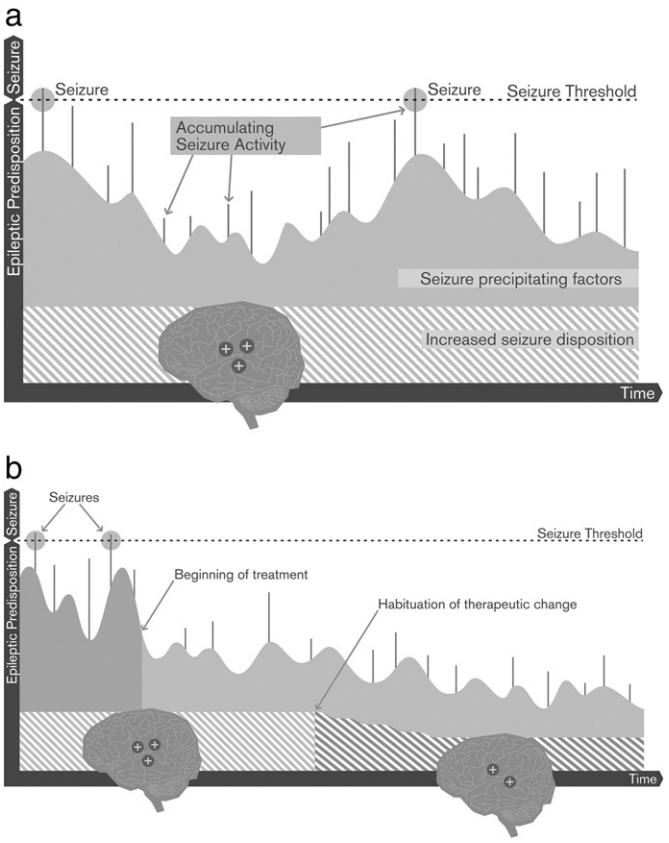

Fig. 2. a: Model of interaction between multifactorially conditioned accumulation of seizure activity, seizure threshold, and seizure occurrence. Panel a shows the conceptualized interaction between the seizure threshold and fluctuating levels of seizure activity in the brain of an individual with an increased epileptic disposition. The rising and falling levels of seizure activity are hypothesized to depend on the individual's reactions to multiple seizure precipitating factors as well as to seizure warning signs. b: Model of hypothesized effects of psychobehavioral interventions for epilepsy. Panel b illustrates the hypothesized short-term and long-term effects of psychobehavioral interventions. Individuals with an increased epileptic disposition learn to proactively avoid the build-up of seizure activity per various strategies that are being employed by psychobehavioral interventions. This is hypothesized to reduce nonspecific seizure precipitants and some specific seizure precipitants in the short-term. Long-term practice of the psychobehavioral strategies leads to habitualization results in use-dependent changes of neuronal circuits. This change of brain structure is hypothesized to correlate with a decrease of the epileptic disposition of the individual's brain.

3.1. Stress hypothesis

Stress is widely accepted as a risk factor for seizures and can exacerbate seizure manifestation in humans and animal models [1,39–41]. Since stress may alter autonomic nervous system functioning by increasing sympathetic activity, stress reduction techniques are possibly effective by increasing the parasympathetic response. The restoration of balance within the autonomic nervous system can, hence, import beneficial effects for patients with epilepsy by reducing the physiological correlates of psychological stress, thereby preventing the build-up of seizure activity. Besides, hyperventilation could be an acute stress reaction towards the emergence of a seizure and consequentially a trigger of a seizure in itself. Stress reduction breathing such as deep abdominal breathing might reverse this effect by increasing partial pressure of carbon dioxide (PCO_2) and, thus, lowering seizure activity [42]. Evidence is found in approaches that utilize a stress reduction model, e.g., relaxation training, mindfulness meditation, and yoga exercises. Most of them demonstrated a reduction of seizure occurrence [8,32,36,43–46].

3.2. Psychiatric comorbidity hypothesis

Multiple studies have revealed a high prevalence of psychiatric disorders in PWE. The prevalence is fairly consistent across studies suggesting that around 1 in 4 PWE have a psychiatric comorbidity [47,48]. The high prevalence of comorbidity is attributed to a variety of factors including reactive processes, iatrogenic causes, genetic predisposition, and seizure-related endogenous changes impacting neurochemical and neurophysiological processes.

Furthermore, the relation between epilepsy and psychiatric disorder has been demonstrated to be bidirectional, whereby the latter can be a risk factor for the former [2,3,49]. There is evidence that individuals who have a history of a formal psychiatric diagnosis have a higher risk of developing seizures at a later time [50]. Patients with a history of a psychiatric disorder have seizures that are less responsive to antiepileptic drug treatment and worse seizure outcome following epilepsy surgery [51,52]. It has been hypothesized that both disorders share common pathogenic and psychogenic mechanisms that, in turn, explain their high comorbidity [53–55].

According to this hypothesis, treating psychiatric disorders and psychological symptoms in PWE has the potential to improve not only psychological well-being but also seizure manifestation. This has become the rationale that underpins several CBT protocols that aim at resolving psychological complications and improving well-being.

3.3. Self-efficacy hypothesis

Health locus of control is the degree of an individual's subjective sense of control over personal health. Lacking or externalization of control is associated with health-compromising behaviors such as drug noncompliance and psychiatric comorbidity [56,57]. Patients with epilepsy suffer from persistent worries about seizure recurrence, probably arising from a sense of unpredictability of the course of the disorder as well as subjective helplessness. Evidence suggests that the level of depression and anxiety at one year following the diagnosis of epilepsy

correlates with the degree to which a patient senses a lack of self-control but not with the actual number of seizures [57]. This indicates that the assumed uncertainty towards having a seizure could be more disabling than the seizure itself.

Hence, the individual's role and participation in their own epilepsy condition are emphasized in many psychobehavioral protocols [10,25–27]. The understanding that seizure occurrence might not be entirely random and unpredictable, but could be triggered by multiple risk factors that are highly controllable, is a motivating insight for many patients since it increases their sense of control over their health condition. This possibly increases the likelihood and openness for them to engage in psychobehavioral therapy, in which their cooperation and practice are central to treatment efficacy.

3.4. Learning hypothesis

Learning to stop the progression of seizure activity is the central idea of most behavioral approaches for PWE. In behaviorism, it is believed that desirable behaviors can be learned and unlearned a strengthened and weakened by applying structural behavioral modification, whereby the process of long-term potentiation (LTP) underlies the synaptic mechanism that correlates with and eventually facilitates the behavioral change [16,58]. Behaviorists regard seizures as a learned action resulting from a habitual chain of seizure-related behaviors. According to their idea, damaged neurons create only a predisposition for the occurrence of seizures, and it is the individual's response to the dysfunction that is more critical to trigger seizure activity [19,59]. The learning hypothesis is supported by the observation that the detection of seizure triggers can be facilitated by eliciting the biographical context of the first seizure events [60]. The underlying psychological theme will often resurface in the individual's life and trigger seizures even though the psychological stimulus might be less intense than prior to the first seizure events.

Behavioral approaches for PWE are applied based on this mechanism of action. Aura interruption and systematic desensitization allow individuals to learn new sets of reactions to preictal and early ictal phenomena, which probably lead to neurobiological changes. Presumably, newly learned actions could be able to engage neurons adjacent or contralateral to the area of hyperexcitable neurons in order to prevent further recruitment and, hence, the spread of seizure activity. Another hypothesis is that these new behaviors might be able to engage neurons of complex networks in order to prevent loss of consciousness [61–64]. In operant conditioning and EEG biofeedback, desirable EEG patterns were learned by positive reinforcement and negative reinforcement. These learning processes are presumably established through LTP [22].

3.5. Generic adjustment hypothesis

Adjustment issues may arise when an individual starts to have seizures or becomes seizure-free after treatment. Research even suggests that the de novo development of psychogenic nonepileptic seizures might be an underestimated entity in adults after epilepsy surgery, particularly in female patients with preoperative psychiatric comorbidity [65]. Problems with psychosocial adjustment were prominent in PWE in various areas including education, employment, interpersonal relationships, treatment options, and even pregnancy. Some psychobehavioral therapies enhance adjustment by providing educational materials, introducing adaptive coping, communication skills, general problem-solving skills, and nonjudgmental awareness [8,10,32–35,66]. These processes are supposed to allow a psychologically healthy transition of an individual's sense of self-identity from being “chronically ill” to being “normal”. These forms of interventions might also reduce one's sense of helplessness, as well as secondary gain issues, and could promote psychological well-being, which might in turn prevent the increase of seizure activity.

4. Is psychobehavioral therapy effective in epilepsy?

Although many individual trials have reported beneficial effects of psychobehavioral therapy in terms of psychological well-being and seizure control, robust evidence is scarce. This section assesses the published evidence from prospective trials in regard to its effectiveness. Table 1 presents a summary of evidence from randomized controlled trials (RCTs).

4.1. Behavioral approaches

Behavioral therapies for PWE, which aimed at reducing seizures, were mainly found in the early literature, and many of them had significant methodological deficiencies. Although a clinically significant seizure reduction was reported in case studies, the findings were often based on observations or unsophisticated counting without reliable statistical bases [6,20,67]. There were also biases in patient selection; therapies were applied on institutionalized patients with mental retardation [20,67], and the positive changes were difficult to generalize. The only RCT was conducted by Dahl et al. in 18 PWE. This unblinded study reported a significant reduction of seizure frequency only in those who received behavioral therapy [45].

The most promising behavioral approach appeared to be EEG biofeedback. Tan and colleagues conducted a meta-analysis on 10 studies using EEG biofeedback on PWE [24]. All studies reported an overall mean reduction of seizures after treatment and 64 (74%) out of 87 patients reported fewer weekly seizures following EEG biofeedback training.

4.2. CBT

In general, the effects of CBT on enhancing psychological well-being are more established than its role on seizure control as evidenced by a handful of RCTs and multiple single trials.

A RCT ($n = 37$) showed a significant seizure reduction in CBT group (number of seizure per month at baseline = 6.33; posttreatment = 3.68; 3-month posttreatment = 1.39) compared with no change in control (4.95, 5.00, and 4.42, respectively) [68]. The achievement of complete seizure freedom was reported between 13% and 80% of the patients by a few uncontrolled studies [13,69–71]. The approach that based on a 12-session multimodel CBT-like intervention protocol, developed by Andrews and Reiter, and is one of the most effective and widely studied CBT approaches for improving seizure control [12,13,71]. Despite the positive findings, some studies suggested otherwise and did not demonstrate a significant effect of CBT on seizure control [7,72].

The effects of CBT on improving psychological states have been consistently demonstrated by RCTs [26,31,73–77]. Patients reported reduction of anxiety and depression symptoms and improvement on adjustment, social functioning, as well as quality of life (QOL).

4.3. Mind–body approaches

Studies using mind–body approaches consistently revealed a clinical improvement of both seizure control and psychological well-being in PWE [8,30,32,35]. Among various approaches, mindfulness-based ACT has been studied in two RCTs and showed significant effects on improving QOL and seizure control in patients with drug-resistant epilepsy; these positive results were sustained for one year after interventions [8,32]. A similar finding was reported by Thompson et al. using mindfulness- and cognitive–behavioral-based interventions delivered via telephone conference [32].

4.4. Multimodel educative interventions

Some multimodel interventions include a combination of education and skill-based training with or without cognitive–behavioral elements.

Many of them have been formalized into standardized program and are the most extensively and systematically studied psychobehavioral approach for PWE. Despite the heterogeneity of therapeutic content, length of intervention, and mode of delivery, these approaches have shown consistent effects on enhancing knowledge and management of seizures. Significant positive effects include improvement of psychological states [9,10,15,78,79], epilepsy knowledge [9,14,15,78,79], self-management [9,10,79,80], self-efficacy [80,81], perceived competencies and social skills [15,79], contentedness with therapy [10], drug compliance [9,81,82], and seizure control [9,10].

4.5. Summary of effects using psychobehavioral therapy for PWE

Cognitive–behavioral therapy, mind–body approaches, and multimodel educative interventions have consistently demonstrated significant effects on improving psychological well-being, and enhancing epilepsy knowledge and adjustment as compared with controls. However, the effects on seizure control remain inconsistent across studies; thus, no reliable conclusion can be drawn.

5. Challenges in research methodology and way forward

5.1. Deficiencies in study design

One of the most common shortcomings of these studies relates to the lack of control groups [4,83]. There was precedence for "significant" findings in uncontrolled studies to fail reproducibility when the intervention was subjected to a controlled trial as reported by Mittan in a comprehensive review [5]. Most RCTs were, however, compromised by the inadequate statistical power, which critically affected the validity of the results.

Many psychotherapy protocols consist of a mixture of therapeutic components, each of which could be considered as an independent variable. For instance, a multimodel educative program, Modular Service Package Epilepsy (MOSES), was designed with multiple aims spread over nine separate modules of interventions; each module was featured by a specific topic spanned from imparting knowledge to the adjustment and emotional aspects [10]. Although this form of intervention often demonstrates beneficial effects, it is difficult to clearly delineate the therapeutic components. Moreover, because of the nonspecific therapeutic target, an adequate control group and corresponding outcome measures are difficult to define. In addition, the lack of standardized protocols and intervention goals across studies, even within the same therapeutic approach, made the comparison difficult. For instance, some CBT protocols emphasize on establishing the patient's health locus of control [26,27]; while others are designed to prevent psychiatric comorbidities [7,30].

The outcome measures employed constitute a third problem. Most studies depend primarily on subjective self-report inventories with a set of yes–no questions or Likert scale ratings to ascertain constructs that are more complicated than a total score can represent, e.g., "depression", "quality of life" and "self management" [89]. Whether these inventories are measuring what they are intended to measure may be questionable, even if the inventory has undergone elaborate validation. It is also doubtful whether statistically significant changes actually carry clinical significance. Moreover, measures are not standardized across studies. For example, a widely measured construct, "depression", was measured by different scales in different studies. This makes any comparisons across studies difficult.

Most studies assessed therapeutic outcomes immediately after intervention or within short-term follow-up duration; long-term response data were lacking. The sustainability of therapeutic effects, thus, remains uncertain.

Finally, although double-blinded design is not practical because patients' active participation is required, with only a few exceptions, most of them were not even assessor-blinded. Investigators who conducted both the intervention and the outcome assessments are subject to potential biases in regard to subject selection, implementation of interventions, as well as the interpretation of results. To date, only the two studies using the Seizures and Epilepsy Education (SEE) program intervention paradigm were conducted, analyzed, and reported by individual third parties [9,14].

5.2. Common confounding factors

The internalization and application of the therapeutic principles are active processes that differ among individuals and require continuous motivation and compliance. These factors, however, are difficult to measure. These variations often become a major confounding variable that affect the sustainability of therapeutic effects and the correlation of results with the actual therapeutic mediator.

Moreover, concomitant AED usage was not described in most studies; hence, it remains unclear if it may have acted as a confounder of the effects of psychobehavioral therapy in regard to both psychological and seizure outcomes. Even if AED usage was statistically controlled, the long-term effects of psychotherapy could be difficult to determine if simultaneous changes of drug regimens occur. Likewise, progressive syndromes and fluctuations of seizure manifestation affect the interpretation of long-term effects of psychobehavioral therapy.

5.3. Proposed research strategies

Assessor-blinded randomized controlled trials with sufficient statistical power appear to be a necessary design to evaluate the efficacy of specific psychobehavioral paradigms. Collaboration across sites is important to improve recruitment and enhance generalizability [89]. Control groups should be carefully designed to delineate the nonspecific effects of the target therapy to be evaluated. The use of wait list control, nonspecific supportive treatment, or treatment as usual is recommended, which resemble the trial designs used in psychotherapy research conducted in traditional psychiatric settings that have demonstrated consistent validity. The relative efficacy of different interventions or their respective components can be separately compared in a second step [83–85].

The measurement approach of outcomes should be optimized. Objective measures of neurobiological correlates following psychobehavioral therapy should be used. For instance, serum levels as a measure of drug compliance could be utilized. Salivary cortisol level may be used as an objective neurobiological correlate of stress [86]. Magnetic resonance imaging or functional magnetic resonance imaging could be included as a morphological evidence of the hypothesis of neuroplasticity following psychobehavioral therapy [87–89]. These objective measures are important to determine the extent and mechanisms of psychological agents on PWE in a so called "top-down" process of how our mind changes our brain. Furthermore, confounding factors should be statistically controlled, including changes of clinical characteristics. Patients' application and practices of the therapeutic skills should be objectively monitored, for instance by journaling and obtaining logs of practices [13,71].

Randomized controlled trials could be supplemented by other types of research designs such as qualitative studies that could potentially facilitate the correlation of subjective qualia of seizure self-control phenomena and objective measurements and case reports that might explore specific psychological mediators of seizure self-control [90].

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Table 1
Summary of randomized controlled trials (RCTs) on effectiveness of psychobehavioral therapy for PWE.

Author	Trial size (n) Treatment vs. control	Intervention method Treatment vs. control	Outcome measures 1. Psychological and QOL 2. Seizure index	Psychological outcome[a] Results of treatment group vs. results of control group	Seizure outcome[a] Results of treatment group vs. results of control group
Behavioral approaches					
Dahl [44]	6 vs. 1) 6 2) 6	6-week contingent relaxation vs. 1) 6-week attention control 2) No treatment	1. – 2. Seizure frequency record	–	↓ Seizure frequency at immediate posttreatment and 30-week posttreatment vs. 1) No change 2) No change
CBT					
McLaughlin [68]	18 vs. 19	6-session CBT vs. 6-session relaxation	1. CIDI, GDS, and WPSI 2. Seizure frequency record	No change vs. no change	↓ Seizure frequency at immediate posttreatment and 3-month posttreatment vs. no change at all time point
Ciechanowski [74] and Chaytor [75]	40 vs. 40	8 50-mintue sessions of home-based sessions vs. no treatment	1. HSCL-20, QOLIE-31, Cornell Services Index, self-report on nonepilepsy cormorbidity, 2. Seizure frequency record	↓depression, ↓suicidal ideation and ↑emotional well-being at 6-month, 12-month and 18-month posttreatment vs. no change at all time point	No change vs. no change
Martinovic [31]	15 vs. 15	8 sessions of CBT vs. 8 sessions with therapeutic counseling without CBT	1. BDI, HAMD, QOLIE-31, CES-D, risk factor for depression 2. –	↑ QOL ↓ Risk of depression ↓ Anxiety ↓ Depression vs. no change	–
Tan [72]	8 vs. 1) 10 2) 9	8 2-hour sessions of group CBT vs. 8 2-hour sessions of 1) Supportive counseling 2) Wait list control	1. MMPI, BDI, WPSI, GRPA-P, GRPA-N, and GRPA-T 2. Seizure frequency record, patient's self-rating of seizure control	↑ GRPA-T vs. 1) No change 2) No change	No change vs. 1) No change 2) No change
Davis [73]	8 vs. 7	6 2-hour sessions of CBT vs. other controls not stated	1. DACL, GCS, BDI, and CAQ 2. –	↑ Social activity ↓ Dysphoria and depression ↓ Anxiety, stress, and anger vs. no change	–
Mind-body approaches					
Thompson [35]	26 vs. 27	8-hour telephone or web-based intervention vs. wait list control	1. BDI, PHQ-9, knowledge and skill measure, DCSES, SWLS, and BRFSS 2. –	↓ Depressive symptoms ↑ Knowledge and skills ↑ QOL on physical health vs. no change	–

Lundgren [32]	10 vs. 8	4 sessions of ACT treatment vs. 4 sessions of yoga	1. SWLS and WHOQOL-BREF 2. Seizure index (seizure frequency × duration in seconds)	↑ QOL (WHOQOL-BREF) vs. ↑ QOL (SWLS)	↓ Seizure frequency ↓ Seizure index vs. ↓ seizure index
Lundgren [8]	14 vs. 13	4 sessions of ACT treatment vs. 4 sessions of supportive therapy	1. SWLS and WHOQOL-BREF 2. Seizure index (seizure frequency × duration in seconds)	↑ QOL vs. no change	↓ Seizure frequency ↓ Seizure index vs. no change
Multimodel educative interventions					
Modi [80]	4 vs. 3	4 sessions of adherence intervention and problem solving program to children patient and family vs. treatment as usual	1. – 2. MEMS 6 Track Cap	–	Large improvement in 2 out of 4 families vs. small improvement in 2 out of 3 families.
Dilorio [81]	70 vs. 78	WebEast internet-based self-management program for 6 weeks vs. waitlist control	1. PSS, ESI-R, PSQI, ESMS, ESES, EKP, QOLIE-10 2. MAS	↑self-efficacy vs. no change	↑medication adherence vs. no change
Dilorio [82]	11 vs. 11	5 sessions of nurse-led telephone-based motivational interview treatment vs. attention-placebo control	1. Epilepsy self-management, Epilepsy Self-Efficacy Scale, Outcome expectancy, EKQ 2. MEMS cap, AGAS	↑ self-efficacy, ↑seizure management, and ↑epilepsy knowledge vs. ↑information management	No change vs. no change
May [10]	113 vs. 129	9 units of MOSES educational treatment program on epilepsy knowledge, self-confidence, and illness management vs. wait list control	1. SF-36, RSES, Zerssen Depression Scale, restriction in daily life, epilepsy-related fears, coping with epilepsy, and adaptation 2. Seizure frequency record and satisfaction with therapy	↑ Knowledge and coping with epilepsy in treatment group only vs. no change	↑ Satisfaction with therapy ↑ Drug tolerability ↓ Drug-related side effect vs. no change
Olley [76]	15 vs. 15	2-day psychoeducational program vs. wait list control	1. BDI, knowledge, and Crown-Crisp experiential index 2. –	↑ Knowledge ↓ Depressed symptoms vs. no change	–
Helgeson [9]	18 vs. 20	2-day SEE educational program to patient/family vs. wait list control	1. STAI, BDI, DACL, WPSI, SES, and SEE 50 items 2. No. of AEDs, blood level, and seizure frequency	↑ Knowledge vs. no change	↑ Drug compliance vs. no change
Lewis [15]	123 vs. 113	4 1.5-hour weekly child centered family focused educational group vs. Traditional lectures	1. Knowledge and Harter's self-competency scale 2. –	For parents: ↑ Knowledge; ↓ Anxiety For children: ↑ Perceived competencies ↑ Social skills vs. no change for parents and children	–

ACT, Acceptance and Commitment Therapy; AGAS, Antiretroviral General Adherence Scale; BDI, Back Depression Inventory; BRFSS, Behavioral Risk Factor Surveillance System; CAQ, Community Adjustment Questionnaire; CBT, Cognitive–Behavioral Therapy; CES-D, Center for Epidemiological Study on Depression; CIDI, Composite International Diagnostic Interview; DACL, Depression Adjective Checklist, Form E; DCSES, Depression Coping Self-Efficacy Scale; EKQ, Epilepsy Knowledge Questionnaire; GCS, Hudson Generalized Contentment Scale; GDS, Geriatric Depression Scale; GRPA, Global Ratings of Psychological Adjustment; T—Therapist; N—Neurologist; P—Patient; HAMD, Hamilton Depression Scale; MEMS, Medication Event Monitoring System; MMPI, Minnesota Multiphasic Personality Inventory; MOSES, Modular Service Package Epilepsy; QOL, Quality of Life; QOLIE, Quality of Life in Epilepsy;RSES, Rosenberg Self-esteem Scale; SEE, Seizure and Epilepsy Education; SES, Sherer's Self-Efficacy Scale;SF-36, 36-Item Short Form Health Survey; STAI, State-Trait Anxiety Inventory; SWLS, Satisfaction with Life Scale; WHOQOL-BREF, World Health Organization Quality of Life Instrument; WPSI, Washington Psychosocial Seizure Inventory HSCL-20, Hopkins Symptom Checklist-20; PSS, Perceived Stress Scale; ESI-R, Revised Epilepsy Stressor Inventory; PSQI, Pittsburgh Sleep Quality Index; ESMS, Epilepsy Self-Management Scale; ESES, Epilepsy Self-Efficacy Scale; EKP, Epilepsy Knowledge Profile; MAS, Medication Adherence Scale.

[a] All changes as presented by ↑ (increase) and ↓ (decrease) were at statistically significant level according to the original article.

Summary response to key questions

1. What psychobehavioral therapies are/may be useful in epilepsy?
   Behavioral approaches, cognitive–behavioral therapy, and mind–body approaches are the most widely applied psychobehavioral approaches for PWE. Some interventions employ a combination of therapeutic elements from multiple approaches.
2. What are the hypothesized mechanisms of action of psychobehavioral therapy for epilepsy?
   The major hypothesized mechanisms of action include stress reduction, treating psychiatric comorbidity, self-efficacy promotion including the development of seizure interruption techniques, learning hypothesis and generic adjustment hypothesis.
3. Is psychobehavioral therapy effective in epilepsy?
   Most psychobehavioral therapies aim at enhancing psychological well-being and seizure control; evidences for the former are more established. Because of major methodological deficiencies, reliable evidence on its role on seizure control is scarce.
4. What are the methodological challenges associated with the scientific study of psychobehavioral therapies and the proposed strategies for meeting those challenges?
   Major methodological problems include deficiencies in study designs and multiple confounding factors. Blinded randomized controlled trials with sufficient power and carefully defined therapeutic components corresponding with objective and subjective outcome measures are advisable. Confounding factors should also be rigorously controlled. Supplementary types of research designs, such as qualitative research and case reports, could be employed to facilitate the correlation of subjective qualia of seizure self-control phenomena and objective measurements.

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