Effectiveness of Psychosocial Interventions for the Management of Psychogenic Non-Epileptic Seizures: A Systematic Review

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This report is submitted in partial fulfillment of the degree of Master of Psychology (Clinical)

School of Psychology
University of Adelaide

October 2023

Word Count: 6169

Contents

Statement of contribution.

The idea for the current project was developed in consultation with my supervisors. A research librarian at the University of Adelaide was consulted to determine the search terms for the review. I screened all studies for eligibility, with my supervisors additionally reviewing studies where eligibility was questionable, after which a consensus decision was made. I extracted the data from eligible studies and conducted analyses. My supervisors provided advice regarding the analyses. This thesis was written my myself and reviewed by my supervisors.

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This article is intended for submission to *Epilepsy & Behaviour,* which adheres to the Vancouver referencing style. At present, the article has been written to the Master of Psychology (Clinical) requirements of 6,000-8,000. This will not need to be edited prior to submission to meet the 8,000-word count specified by *Epilepsy & Behaviour*.

Abstract

Psychogenic non-epileptic seizures (PNES) are unexpected, involuntary occurrences that resemble an organic epileptic seizure, but are not accompanied by seizure activity in the brain. People with PNES are more likely to experience psychological, social, financial and physical difficulties compared to their healthy peers and people with organic epilepsy. Psychosocial interventions are the preferred treatment for PNES, although our understanding of how effective these treatments are remains limited and it is yet to be determined what specific intervention is best. This study builds on previous research by exclusively analysing randomised control trials, and measures the impact of psychosocial interventions on seizures, mental health and quality of life. The effectiveness of psychosocial interventions was examined post treatment and at approximately 6-month follow-up. A comprehensive search of three databases identified five studies that measured the effectiveness of psychosocial interventions in people with PNES. Hedges' *g* effect sizes were calculated for each psychosocial intervention for measures of seizure frequency, seizure severity, anxiety, depression and quality of life. Pooled effects were calculated for cognitive behaviour therapy and other types of intervention. Psychosocial intervention was most effective in reducing the frequency and severity of seizures, with the effects of mental health outcomes and quality of life diminishing over time. Cognitive behaviour therapy was the most effective type of intervention in the short term when all outcomes were pooled but was comparable to other types of therapies after time.

1. Introduction

Psychogenic non-epileptic seizures (PNES) are unexpected, involuntary occurrences that resemble an organic epileptic seizure, but are not accompanied by seizure activity in the brain [1]. PNES is a prevalent presentation in epilepsy clinics and affects approximately 108.5 people per 100,000 [2,3]. PNES can develop at any time across the lifespan, but onset is typically from late teenage years to early twenties [4]. PNES themselves are associated with low mortality, with most deaths in this patient population caused by factors external to PNES (e.g., substance abuse and comorbid psychiatric conditions) [5]. A complex interaction between genetic, environmental and psychological factors are reported to cause PNES, with a recent review finding increased rates of physical, sexual and psychological abuse and neglect as well as stressful life events, such as bereavement or illness in people with PNES [6]. In particular, a causal relationship between childhood sexual and physical maltreatment and PNES has been reported [7]. It has been proposed that PNES may be triggered by trauma cues and act as a means of suppressing intolerable memories or other distressing internal and external stimuli [8]. In this way, PNES may be considered as a type of dissociation whereby people can experience a disruption in consciousness, memory and/or perception [8]. The early age of onset, low mortality and psychological causation of PNES makes it a common condition in clinical settings [2,3].

PNES are classified as a mental health condition, however, there is no standalone diagnostic criterion in existing mental disorder classification manuals [9]. Most people with PNES fulfil the criteria of functional neurological symptom (Conversion) disorder in the Diagnostic and Statical Manual of Mental Disorders; Fifth Edition (DSM-5) or dissociative disorder in the International Classification of Diseases; Eleventh Revision (ICD-11) [9]. It is common for people with PNES to have additional psychological diagnoses and symptoms [6,9–11]. Unsurprisingly, given the increased likelihood of childhood trauma, post-traumatic stress disorder is particularly common occurring in 38% of people with PNES [11]. In addition, mood and anxiety disorders are very common, occurring in 72.7% and 54.5% (respectively) of people with PNES [10]. Underscoring the impact of these psychological difficulties, a large cohort study found suicide is the leading cause of death in individuals with PNES (18.8%) [12]. Other dissociative symptoms are also common in people with PNES, which is reflected on high scores on scales measuring dissociation (e.g., the Dissociative Experiences Scale) [13–15]. In addition to increased likelihood of psychological disorders, many people with PNES report cognitive complaints such as forgetfulness and difficulties in concentration [16]. The psychological and cognitive difficulties experienced by people with PNES highlight the complexity of the condition and therefore the importance of treatment for this group.

People with PNES also have poor health-related quality of life, with a recent review finding lower physical, mental and social wellbeing on self-report measures compared to their healthy peers [17]. Furthermore, people with PNES have lower scores on health-related quality of life measures compared to individuals with organic epilepsy [18]. Poor sleep, as characterised by reduced quantity of sleep, frequent awakenings and difficulty getting sleep, is one factor related to poor quality of life for people with PNES when compared to individuals with organic epilepsy [19]. In addition to poorer quality of life, people with PNES can experience financial hardship, with approximately 83% of affected individuals being unemployed and 57% relying on disability payments [20]. The impact of PNES extends beyond affected individuals, with carers of people with PNES reporting poorer quality of life than carers of people with organic epilepsy [18]. The poor psychological, cognitive, wellbeing and employment outcomes for people with PNES, and significant carer burden, further emphasises the importance of identifying effective treatments.

Difficulties in diagnosing PNES represent a significant barrier for people accessing treatment [21]. PNES are often mistaken for organic seizures, with an estimated 20-30% of patients referred to epilepsy units misdiagnosed with organic epilepsy [22]. Consequently, a correct diagnosis of PNES is typically delayed by seven to nine years [23]. During this delay, individuals may be exposed to the potentially harmful effects of redundant anti-epileptic drugs, including unwanted side effects, problematic interactions with other medications and costs associated with prescription medication [23–25]. For example, the medical costs associated with misdiagnosed PNES is high, and drop from approximately USD$4567 (approx. AUD$7093) per year to USD $2783 (approx. AUD$4322) per year following the correct diagnosis of PNES [26]. Furthermore, anti-epileptic medication may even exacerbate PNES [27]. Adding to the difficulty in diagnosis, organic epileptic seizures occur in 22% of people with PNES [28], and only 25% of individuals with PNES are able to correctly distinguish between organic seizures and PNES [29]. In response to the complexity around diagnosing PNES and poor outcomes associated with misdiagnosis, The International League Against Epilepsy (ILAE) highlighted the need for a clear and objective diagnostic approach [30]. They stated that the "gold standard" for diagnosing PNES involves the absence of epileptic brain activity on an EEG and the use of simultaneous video recording (vEEG) before, during, and after a seizure [30].

Psychological interventions are recommended by the ILAE as the first line treatment for people with PNES, however there is a disparity between this recommendation and what occurs in reality [30-33]. Only one third of patients are offered an appointment with a psychologist and 18% of patients are discharged after diagnosis with no treatment at all [30,31]. The lack of referrals for treatment may be due to negative attitudes of health care professionals who may believe treatment for PNES is "difficult" and "time consuming" and that people with PNES are "beyond help" [32]. In a recent study, 62% of health care professionals agreed that people with PNES arouse anger in medical staff and are viewed as "less urgent" than other patient presentations [33]. As a consequence, 60% of health care professionals believed that people with PNES are treated with disrespect [33]. Furthermore, many health care practitioners complain about having limited treatment options for PNES and state a perceived lack of efficacy and access to intervention [34]. Overall, barriers to receiving treatment for PNES may contribute to further psychological distress and feelings of helplessness for people with PNES [33].

Contrary to clinician beliefs, there is evidence supporting psychological interventions in the management of PNES [35–37]. A meta-analysis examining seizure outcomes found that 47% of people with PNES were seizure-free upon completion of a psychological treatment and 82% had a seizure reduction of at least 50% [35]. This study was limited however, as it only assessed seizure frequency. There is increasing evidence that suggests mental health and quality of life should also be assessed for intervention studies in PNES [38–40]. For example, despite reductions in seizures following psychological intervention, 43% of people with PNES remain unproductive (e.g., unable to attend work) due to concurrent psychiatric disorders. Consequently, more recent studies have investigated psychological and wellbeing outcomes in addition to seizures. A landmark randomised control study (RCT) study involving 368 participants diagnosed with PNES investigated the effectiveness of cognitive behaviour therapy (CBT) combined with standard medical care [36]. In addition to significantly improved seizure freedom, the study found better health related quality of life and reduced psychological distress [36].

CBT is the most common form of intervention for PNES and may support people with PNES by shifting maladaptive thinking (e.g., symptom focused attention) and unhelpful behaviours (e.g., avoidance) that maintain distress [41]. However, other interventions have also been found to provide benefit for people with PNES [35,37]. These interventions are not purely psychological (i.e., involve non-psychological aspects) or are not delivered by a psychologist, and are therefore collectively referred to as 'psychosocial' interventions. In this context, psychosocial interventions involve psychological, behavioural or social therapeutic approaches and aims to improve overall wellbeing and functioning [43]. For example, a manualised body focused therapy, CORDIS, was specifically designed to fill the gap in treatment options for people with PNES [42]. This therapy incorporates both psychological and psychosocial strategies such as psychoeducation, emotional regulation and improved body perception. In comparison to guided self-help, those who had CORDIS experienced more significant reductions in seizure severity six months post- treatment [42]. Further support for the effectiveness of psychosocial interventions was provided by a recent meta-analysis that found non-seizure outcomes (i.e., mental health outcomes, ability to function in everyday activities, quality of life, non-specific psychological factors such as anger and interoceptive awareness, dissociation, and somatoform symptoms) improved by a medium effect immediately post- intervention [37]. In sum, there is evidence that psychosocial interventions are beneficial in the management of PNES, not only in terms of seizure reduction, but also for mental health and wellbeing more broadly.

Research on the effectiveness of psychosocial interventions for PNES is quite extensive and the consensus of reviews that have collated this evidence have all supported psychosocial interventions for PNES. However, the reviews to date have the following limitations, which this study aims to address. First, they have relied on the inclusion of uncontrolled study designs, which can introduce bias and confounding variables [44]. Second, the studies did not use gold standard criteria to diagnose PNES or did not exclude comorbid epilepsy [29]. Third, the reviews did not collate evidence on the long-term effectiveness of psychosocial interventions for PNES. Follow-up analyses are essential for demonstrating consistency over time, uncovering the presence of delayed benefits or deterioration after intervention and evaluating the cost effectiveness of an intervention [36,45]. The current systematic review therefore exclusively analyses RCTs and employs a more stringent selection criteria where (1) participants with comorbid epilepsy were excluded and (2) diagnosis of PNES had to be confirmed via EEG or when unavailable, via clinician consensus with no doubt in diagnosis. The current systematic review provides an update on seizure frequency since Carlson et al. [35] given the more recent publication of the landmark study by Goldstein et al. [36] and provides insights into the effects of psychosocial intervention on seizure severity. Additionally, the current review provides further insights into mental health outcomes gained by Gaskell et al. [37] by distinguishing between measures of anxiety and depression. Finally, this systematic review is the first to investigate the effectiveness of psychosocial interventions for people with PNES at follow up, and therefore assess whether the preliminary positive findings of intervention generalise into longer-term outcomes.

2. Methods

2.1. Literature search

The protocol for this systematic review was pre-registered at Open Science Framework [*registration number removed for blind review*]. Eligible articles were identified from a search of the PubMed, PsycINFO and Medline databases. An expert Research Librarian assisted with the development of search terms that were tailored to each database (see Supplementary Material 2 for all logic grids). The database searches were limited to full-text articles published in English, with no date limits. The initial search was conducted on 10 October 2022 and a time-limited search was then conducted on 12 June 2023 to ensure the recency of results. Scopus citation searching was used and the reference lists all of included studies were manually searched, with no additional studies detected.

2.2. Eligibility criteria and selection

Study selection was completed by the author using Covidence software for systematic reviews [46]. A random selection of 50 studies were screened by a postgraduate researcher. To achieve randomisation, each study was automatically assigned a number by Covidence and a computer software [47] was then used to generate 50 random numbers between 1 and 1098 (i.e., total number of studies following removal of duplicates). Excellent inter-rater agreement was achieved (κ = 1.00 or 100% agreement).

A senior researcher reviewed studies where eligibility was questioned, after which a consensus decision was made. For a study to be eligible for inclusion in this review it had to: (1) target an adult sample (18 years and over) clinically diagnosed with PNES via EEG or where not possible, via clinician consensus with no doubt in diagnosis; (2) evaluate a psychosocial intervention; (3) employ a randomised control design, whereby the effectiveness of a psychosocial intervention was compared to an active control (i.e., standard medical care or guided self-help) and (4) administer validated functional (i.e., seizure severity, seizure frequency) or psychological (i.e., depression, anxiety, quality of life) outcomes measures pre- and post- intervention.

Studies were excluded if they: (1) included participants with co-morbid epilepsy; (2) did not quantitatively evaluate their psychosocial intervention (e.g., case studies, qualitative research, editorials); (3) evaluated a multidisciplinary program, whereby the psychosocial intervention formed one component; (4) did not provide sufficient data to calculate effect sizes; or (5) were not published/peer reviewed studies (i.e., dissertations).

2.3. Data collection and preparation

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses [48] methodological, sample and intervention characteristics were extracted from each study. These data included: (1) citation details (e.g., author, publication year); (2) recruitment sources (e.g. community, inpatient setting etc); (3) participant selection (e.g. random, consecutive, convenience, retrospective); (4) sociodemographic characteristics (i.e., age, gender, education); (5) intervention details (e.g., therapy framework, session duration and frequency); (6) outcomes measurements; and (7) data to calculate effect size estimates using Hedges' *g* (i.e., group means, standard deviations, change scores, exact *p* values or standard errors from a one-way ANOVA for each outcome at each assessment time point).

Authors of included studies were contacted for additional information, where required. Of three authors contacted, only one responded to requests for additional data [49]. Some data transformation was also required, whereby standard deviations were derived from standard errors [50] and means and standard deviations were estimated from medians and inter-quartile ranges [51].

Data extraction identified many different functional and psychological measures used by included studies. To ensure generalisability of the results, we only considered those pre-post outcomes examined by more than two studies. This resulted in a final group of five symptom domains: seizure frequency, seizure severity, depression, anxiety, and quality of life. Where studies provided subscale scores (e.g., physical and mental health quality of life) or multiple outcomes for the same domain, these were averaged to create a composite score to ensure data independence in the analysis [36,52].

2.4. Study risk-of-bias

Methodological bias was evaluated by the author and confirmed by a senior researcher using the 14-item Quality Assessment of Controlled Intervention Studies, developed by the National Heart, Lung and Blood Institute [53]. Each study was evaluated for potential flaws in methodology or implementation that are critical to validity, including: method of group assignment, potential sample confounds (e.g., demographics, concurrent interventions), study power, attrition and the degree to which causality could be inferred, based on the measured outcomes. Each study was rated on each criterion (‘yes’, ‘no’, ‘cannot determine’, ‘not applicable’ or ‘not reported’). The percentage of studies that met each assessment item was additionally calculated.

2.5. Publication bias

Given the limited number of studies identified in this review, statistical methods to detect and correct for publication bias (e.g., asymmetry tests such as funnel plot analysis) could not be performed [50]. Rather, Fail-safe N statistics (N_{fs}), which estimates the number of additional studies required to overturn the obtained effect size to a meaningless result ($g < 0.20$) was adopted [54]. A large N_{fs} suggests more confidence and robustness in findings. N_{fs} was deemed sufficient if it exceeded the number of studies that comprised of each outcome domain (that is, $N_{fs} > N$ studies per domain).

2.6. Data analysis

Hedges' *g* effect sizes, which correct for small sample bias, were calculated using Comprehensive Meta-Analysis Software [55] and forest plots were created using Microsoft Excel [56]. Both immediate effects (pre-to immediately post-intervention) and longer-term effects (i.e., pre- to follow up) were calculated. Effect sizes for each individual study were pooled using a random-effects model. To calculate *g*, a pre-post correlation is required [57]. As this statistic was not available for all measures, an intra-study correlation coefficient of 0.7 was assumed [58]. The results did not significantly alter when a sensitivity analysis that used prevalent correlations in applied contexts (i.e., 0.5, 0.7, 0.9) [59] was performed. The direction of *g* was standardised so that a positive value indicated benefit with the psychosocial intervention or larger improvement when compared to the control group. The magnitude of *g*, corresponded to the treatment effect, with values .2, .5, .8 and above 2.0 representing small, medium, large and very large effects respectively [60,61]. Statistical significance of each *g* value was assessed using *p* values. Between-study heterogeneity in effect estimates was investigated using I^2, which reflects the ratio of true effect to error variance and tau, which is an estimate of the standard deviation of the distribution of true effect sizes [62]. Effect sizes were grouped by outcome (i.e., seizure frequency, severity, anxiety, depression and quality of life) and by therapy framework (i.e., CBT or non-CBT).

3. Results

3.1. Study selection

Figure 1 details the search and study review process and outcome of each stage. The literature searches identified 1344 results, 246 of which were duplicates and 1042 of which were excluded after titles and abstracts were screened. The full-text articles of the remaining 56 studies were assessed for eligibility, to which the final sample comprised of 5 independent intervention studies [36,42,49,52,63].

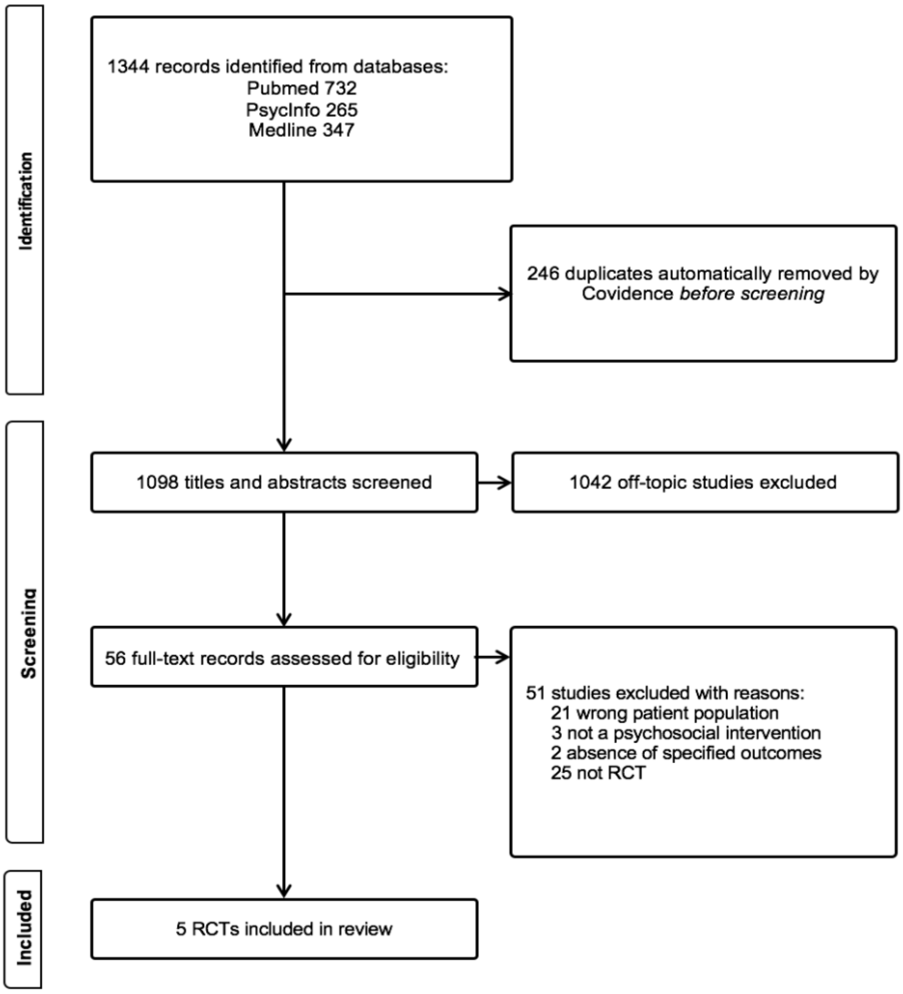


Fig. 1. Flowchart of study selection in line with PRISMA guidelines [48].

3.2. Study and sample characteristics

The five included RCTs were all published within the last two decades and consisted of participants from middle to high income countries (see Table 1). The combined sample of 520 participants (intervention = 265, control = 255) from these studies were predominately female (75%) with a mean age of 37 years (*SD* = 13.9). This pattern is reflective of global PNES prevalence studies which indicate a much higher occurrence of PNES in females (female to male ratio: 2.7-4.4) in early to mid-adulthood (i.e., 34.5 years for females, 37 years for males) [3,64]. Participants were recruited from a combination of inpatient [63], outpatient [42,52] and neuropsychiatric facilities [36,49].

Table 1
Study Characteristics.

Lead author (year)	Country	Sample size (I:C)	Mean age (SD)	Psychological intervention				
				Framework(s)	Duration	Format	Mental health measures	Control group
Ataoglu (2003)	Turkey	30 (15:15)	25 (4.9)[b]	Paradoxical Therapy	▪ 2x daily ▪ 3 weeks	Individual	HRSA	Diazepam
Goldstein (2010)	UK	64 (33:31)	36.7 (13.8)	Cognitive Behavioural Therapy	▪ 1 x weekly or fortnightly ▪ 12 weeks	Individual	Seizure frequency HADS	Standard care
Goldstein (2020)	UK	368 (186:182)	37.5 (14.3)	Cognitive Behavioural Therapy	▪ 9-12 sessions ▪ 4-5 months	Individual	Seizure frequency SSS GAD-7 PHQ-9 SF-12v2	Standard care
La France (2014)	USA	16 (9:7)	39.5 (10.1)	Cognitive Behavioural Therapy	▪ 12 sessions ▪ 60 minutes ▪ weekly	Individual	Seizure Frequency BAI HDS BDI-II QOLIE31+	Standard care
Senf-Beckenbach (2021)	Germany	42 (22:20)	34.8 (12.6)	Body-Focused Therapy	• 10 sessions ▪ 90 minutes ▪ weekly	Group	DES-20 LSSS PHQ-9	Self-help

Abbreviations. I: intervention group, C: control group, SD: standard deviation. [a] repeated measures relevant to this review. [b] calculated from estimated means [38].

Measure abbreviations: HRSA: Hamilton Rating Scale for Anxiety, HADS: Hospital Anxiety and Depression Scale, SSS: Seizure Severity Scale, GAD-7: Generalised Anxiety Disorder seven-item, PHQ-9: Patient Health Questionnaire nine-item, SF-12v2: Health-Related Quality of Life 12-item Short Form Survey version 2, BAI: Beck Anxiety Inventory, HDS: Hamilton Depression Scale, BDI-II: Beck Depression Inventory-II, QOLIE31+: Quality of Life in Epilepsy Inventory 31, DES-20: Dissociation Experience Scale, LSSS: Liverpool Seizure Severity Scale.

3.3. Psychosocial interventions

Table 1 summarises the psychosocial interventions, measures, and outcomes for each of the included studies. CBT for seizure control and to enhance psychological wellbeing was most evaluated [36,49,52]. One study examined paradoxical therapy [63] which encourages people to intentionally re-experience the triggers to their PNES, or purposely have a PNES, in a bid to become less distressed by them. A manualised body-focused psychotherapy, CORDIS, that incorporated psychoeducation, emotion-regulation and body perception was also evaluated [42]. These therapies were compared to standard medical care [36,49,52].

In this context, standard medical care refers to ongoing review by a medical clinician [36,49,52]. This may include supervision around the withdrawal of antiepileptic drugs as well as psychoeducation around the psychological basis of PNES. While standard medical care was described to be "supportive" in nature, psychosocial intervention was limited to the provision of psychoeducation. A self-care program involving weekly group discussion about seizure management and finding helpful resources to deal with seizures was also used as a form of control [42].

Psychosocial interventions were typically time-limited, ranging from a brief 3-week program [63] to five months of fortnightly CBT [36]. Most involved individually tailored therapy, with Senf-Beckenbach et al. [42] being the only evaluation of a small group program. All interventions were delivered by a trained mental health professional (i.e., psychiatrist, psychotherapist, CBT-trained nurse therapist).

Participation across the interventions was generally high, with dropout rates ranging from 0% to 31%. Study withdrawal, where reported, primarily involved the control groups - with participants expressing disappointment in their allocated treatment (e.g., self-care program) [42]. Whilst individual participants commented that the CBT content was 'too difficult' [49] aspects not related to the intervention were generally cited as a key barrier to participation - namely physical illness, social problems, or distance to the treatment centre [36,49].

Studies used a combination of thirteen self-report and one clinician-rated measures. Seizure frequency was measured by having participants keep a seizure diary [36,49,52] with the exception of Senf-Beckenbach et al. [42] where participants completed the self-reported Dissociative Experience Scale (DES-20). The DES-20 records the frequency of a broad spectrum of dissociative experiences, with a specific emphasis on interruptions to awareness and consciousness [42]. Seizure severity was measured via self-reported measures. In one of the studies, this was measured using the Liverpool Seizure Severity Scale. This scale asks participants to rate their most severe seizure in the last month and respond to statements about the nature and aftereffects of this seizure [42]. In the other study, seizure severity was rated using a seven-point scale from one (very mild) to seven (very severe) [36]. Mental health outcomes (i.e., anxiety and depression) and quality of life measures were all self-reported, with the exception of the clinician-rated Hamilton Rating Scale for Anxiety [63]. There was some overlap between mental health measures used, with two studies screening for depressive symptoms using the Patient Health

Questionnaire (PHQ-9) [36,42]. The PHQ-9 evaluates depressive symptoms occurring within the last two weeks in line with the DSM-5 criteria for Major Depressive Disorder and classifies symptoms as indicative of “minimal”, “mild”, “moderate”, “moderately severe” and “severe” depression [65].

3.4. Evaluation of study quality

Between-study quality ratings are illustrated in Figure 2 with individual study ratings listed in Supplementary Material 3. Key methodological strengths included the use of factorial designs, consistent with the review’s requirement that all studies use a randomised controlled design (randomised control trial; items 1 to 3; 100% criterion met). Due to the psychosocial nature of the intervention under evaluation, blinding only to outcome assessors was evaluated, to which three studies reported this (blinding; item 5). Almost all studies reported similar baseline characteristics between study groups (e.g., age, gender), confirming the validity of their randomisation procedure. In three of the studies, participants undergoing concurrent psychosocial therapy for PNES were purposefully excluded (selection; items 6 and 10). Attrition rates differed among the studies, but reasons for dropouts were provided when available (attrition; items 7 to 9). As per study criteria, all studies used standardised measures with reliable psychometric properties which were administered consistently across all participants (item 11). Although studies were typically described as feasibility or pilot trials, two included an a-priori or post-hoc power analysis to justify their sample size and all utilised intention-to-treat analysis, considered the ‘gold standard’ for evaluating RCTs (outcomes; items 11 to 14) [66].

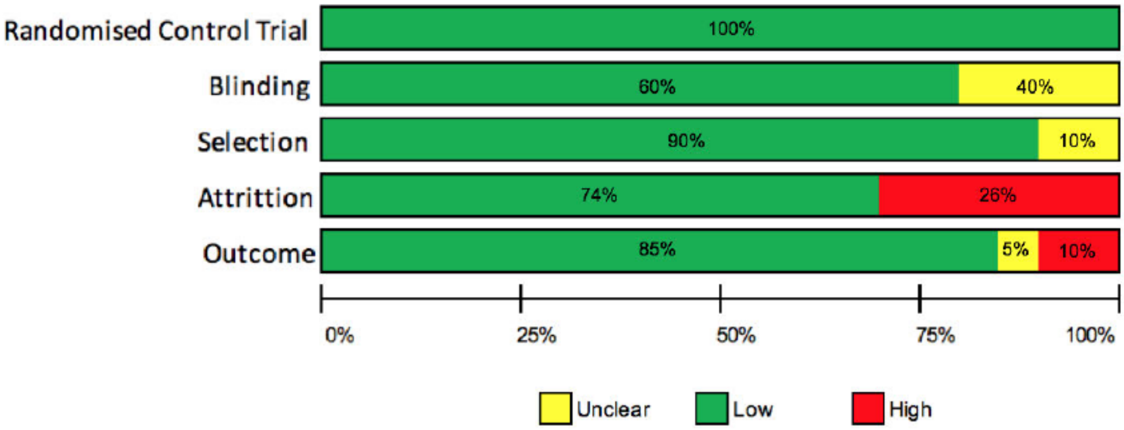
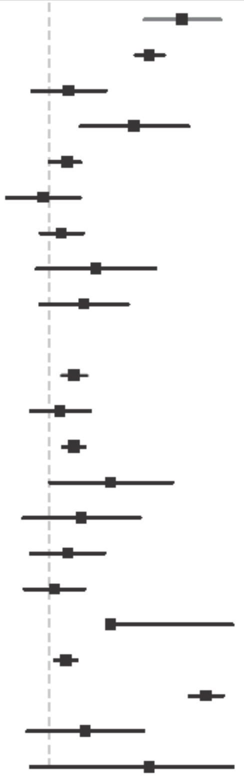


Fig. 2. Risk of Bias Across Studies

Table 2.

Immediate (pre-post) effects associated with psychosocial interventions.

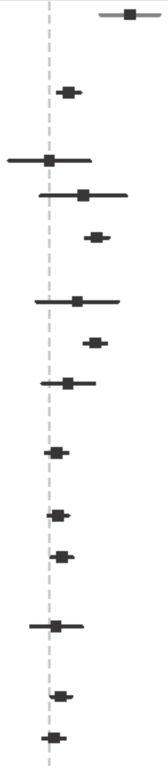
Category	Lead author (date)	Intervention	Measure	*N*	*g*	Forest plot *g* ± CI	*p*	Tau	I^2	N_{fs}	Control
Seizure frequency	Goldstein (2010)	CBT	Seizure count	64	2.17*		0.00				Standard care
	Goldstein (2020)	CBT	Seizure count	368	1.64*		0.00				Standard care
	Senf-Beckenbach (2021)	CORDIS	DES-20	42	0.32		0.29				Self-help
			Total g_w		**1.39***		**0.00**	**0.74**	**90.33**	**18**	
Seizure severity	Goldstein (2020)	CBT	LSSS	368	0.30*		0.00				Standard care
	Senf-Beckenbach (2021)	CORDIS	SSS	42	-0.10		0.73				self-help
			Total g_w		**0.20**		0.26	**0.18**	**0.00**	**0**	
Anxiety	La France (2014)	CBT	BAI	16	0.77		0.12				Standard care
	Ataoglu (2002)	Paradoxical therapy	HRSA	30	0.57		0.11				Diazepam
	Goldstein (2020)	CBT	GAD-7	368	0.41*		0.00				Standard care
	Goldstein (2010)	CBT	HADS	64	0.18		0.46				Standard care
			Total g_w		**0.40***		**0.00**	**0.00**	**0.00**	**4**	
Depression	La France (2014)	CBT	HDS	16	1.01*		0.05				Standard care
	La France (2014)	CBT	BDI-II	16	0.53		0.23				Standard care
	Senf-Beckenbach (2021)	CORDIS	PHQ-9	42	0.30		0.32				Self-help
	Goldstein (2020)	CBT	PHQ-9	368	0.26*		0.01				Standard care
	Goldstein (2010)	CBT	HADS	64	0.08		0.73				Standard care
			Total g_w		**0.27***		**0.00**	**0.00**	**0.00**	**1**	
Quality of life	Goldstein (2020)	CBT	SF-12v2	368	2.57*		0.00				Standard care
	La France (2014)	CBT	QOLIE31+	16	0.59		0.22				Standard care
			Total g_w		**1.64**		**0.10**	**1.35**	**93.38**	**14**	



Abbreviations = number of participants contributing to these data: *g* = Hedges' g effect size: g_w = weighted Hedges' g effect size: *p* = significance value associated with *g*: N_{fs} = fail-safe *N*:CBT Cognitive Behaviour Therapy: CORDIS: body-focused group therapy, DES-20: Dissociation Experience Scale, LSSS: Liverpool Seizure Severity Scale, SSS: Seizure Severity Scale, BAI: Beck Anxiety Inventory, HRSA: Hamilton Rating Scale for Anxiety, GAD-7: Generalised Anxiety Disorder seven-item,, HADs: Hospital Anxiety and Depression Scale, HDS: Hamilton Depression Scale, BDI-II: Beck Depression Inventory-II, PHQ-9: Patient Health Questionnaire nine-item, HADS: Hospital Anxiety and Depression Scale,SF-12v2: Health-Related Quality of Life 12-item Short Form Survey version 2, QOLIE31+: Quality of Life in Epilepsy Inventory 31. *denotes statistically significant effect estimate.

Table 3.

Longer-term effects (baseline to 6-month follow-up) associated with psychosocial interventions

Category	Lead author (date)	Intervention	Measure	*N*	*g*	Forest plot *g* ± CI	*p*	Tau	I^2	N_{fs}	Control
Seizure frequency	Goldstein (2010)	CBT	Seizure count	64	1.53*		0.00				Standard care
	Goldstein (2020)	CBT	Seizure count	368	0.38*		0.00				Standard care
	Senf-Beckenbach (2021)	CORDIS	DES-20	42	0.01		0.98				Self-help
			Total g_w		**0.65**		**0.11**	**0.66**	**87.76**	7	
Seizure severity	Goldstein (2020)	CBT	LSSS	368	0.90*		0.00				Standard care
	Senf-Beckenbach (2021)	CORDIS	SSS	42	0.54		0.17				Self-help
			Total g_w		**0.88***		**0.00**	**0.00**	**0.00**	10	
Anxiety	Goldstein (2010)	CBT	HADS	64	0.37		0.14				Standard care
	Goldstein (2020)	CBT	GAD-7	368	0.15		0.16				Standard care
			Total g_w		**0.18**		**0.06**	**0.00**	**0.00**	0	
Depression	Goldstein (2020)	CBT	PHQ-9	368	0.25*		0.02				Standard care
	Goldstein (2010)	CBT	HADS	64	0.14		0.58				Standard care
			Total g_w		**0.23***		**0.02**	**0.00**	**0.00**	0	
Quality of life	Goldstein (2020)	CBT	SF-12v2	368	**0.10**		**0.34**			0	Standard care

Abbreviations = .*N* = number of participants contributing to these data: *g* = Hedges' g effect size: g_w = weighted Hedges' g effect size: *p* = significance value associated with *g*: N_{fs} = fail-safe *N*: CBT Cognitive Behaviour Therapy: CORDIS: body-focused group therapy, DES-20: Dissociation Experience Scale, LSSS: Liverpool Seizure Severity Scale, SSS: Seizure Severity Scale, HADS: Hospital Anxiety and Depression Scale, GAD-7: Generalised Anxiety Disorder seven-item, PHQ-9: Patient Health Questionnaire nine-item, SF-12v2: Health-Related Quality of Life 12-item Short Form Survey version 2. *denotes statistically significant effect estimate.

3.5. Publication bias

As indicated in Tables 2 and 3, calculation of N_{fs} revealed mixed evidence of publication bias. In the domains of seizure frequency and quality of life, N_{fs} scores were consistently sufficient to indicate that the results were robust to publication bias. However, evidence of publication bias was evident for the remaining domains (anxiety, depression, seizure severity). The pooled findings may therefore be an overestimate due to the exclusion of unpublished studies with small or negligible effect sizes.

3.6. Effectiveness of psychosocial interventions

Of the five RCTs, only three reported significant improvements in one or more outcomes, some of which were maintained over time, once therapy had ceased. Individual effect sizes for each study, categorised according to outcome measure (seizure frequency, seizure severity, anxiety, depression, quality of life) and intervention modality (CBT or not CBT) are reported in Tables 2 to 4 and discussed in more detail below.

3.7.1. Seizure frequency

Three studies evaluated changes in seizure frequency pre- to immediately post-intervention (Table 2). Of these, one reported very large and significant improvement with CBT [36,49]– contributing to a pooled effect estimate that was a large effect. Senf-Beckenbach et al. [42] also reported a small to medium improvement in incidences of seizures, as assessed by the 20-item Dissociation Experience Scale (DES-20) although their small sample size likely contributed to the non-significant finding. The substantial variation in effect sizes among studies is highlighted by the large heterogeneity values ($I^2 > 85\%$, Tau = .66). In addition to the calculated effect sizes, La France et al. [52] reported a 51.4% reduction in seizure frequency following CBT ($p = 0.01$) and no significant changes in seizure frequency were reported in those who received standard medical care.

The two Goldstein et al. [49] studies reported continued medium to very large gains at follow-up (Table 3). CBT participants reported a marked reduction in median frequency of seizures: from 12 seizures per month at baseline to 1.5 per month at follow-up [49]. This finding was a significant contrast to the standard medical care control group, whereby participants reported an average reduction from 8 seizures per month to 5 seizures per month [49].

3.7.2. Seizure severity

Two studies evaluated seizure severity (Table 2). Of these, only the multi-centre CBT trial reported significant and immediate reductions in the severity of seizures [36]. In this study, participants' ratings of their seizure severity using a seven-point scale dropped from 4.8 out of 7 at baseline, to 3.9 out of 7 upon completion of CBT. The overall pooled effect of seizure severity, whilst positive, did not reach significance. Notably, this effect increased in magnitude to a large effect at approximately 6 months post- intervention (Table 3).

3.7.3. Anxiety

Of the four studies that evaluated changes in anxiety pre to immediately post-intervention, only the more recent Goldstein et al., [36] study reported a significant, medium reduction in anxiety symptoms with CBT – resulting in a pooled effect of similar magnitude (Table 2). Participants in this study presented with "moderate" anxiety at baseline and the group mean remained in the "moderate" range post intervention [36,67]. The remaining two CBT studies and one paradoxical therapy study did not reach significance [49,52,63]. In the longer-term, participants who received CBT were comparable to controls who received standard medical care resulting in a pooled effect that was small and non-significant (Table 3).

3.7.4. Depression

Four studies evaluated short-term changes in depressive symptoms with CBT [49,52] or CORDIS [42]. La France et al. [52] reported large and significant improvements in depressive symptoms when scored by the Hamilton Depression Scale, but not the Beck Depression Inventory- 2nd Edition. The recent and large CBT study conducted by Goldstein et al., [36] reported small to medium and significant improvements in depressive symptoms (PHQ-9; Table 2). In this study, group mean scores on the PHQ-9 fell from the “severe” range to the “moderate” range following CBT [68]. This same study reported continued small gains at follow up, contributing to an overall significant effect (Table 3).

3.7.5. Quality of life

Two studies, both evaluating CBT, included quality of life as an outcome measure [36,52]. Only Goldstein et al. [36] reported a very large and significant improvement in quality of life as assessed by the Health-Related Quality of life 12-item Short Form Survey (Version 2) – resulting in an equally large pooled effect estimate (Table 2). This measure included a physical component score which encompassed physical limitations, physical pain and general health perception. It also had a mental component summary which included questions relating to mental health, energy, fatigue, social functioning and emotional limitations. Whilst La France et al. [52] also reported improvements in quality of life with CBT, their small sample was underpowered, resulting in substantial variation in effect sizes between the two studies (I^2 > 85%, Tau = 1.35). Only Goldstein et al. [36] provided follow-up data, however gains diminished, as indicated by a small effect size, at 12 months post-randomisation (Table 3). Reasons for reduced quality of life at follow up were not provided.

Table 4.

Subgroup analyses examining therapy framework

	Framework	$N_{studies}$	$N_{participants}$	g_w	95% CI	p	Tau	I^2
Short-term	CBT	3	448	0.74*	0.54 – 0.94	0.00	0.13	51.61
(pre-post)	Non-CBT	2	72	0.32*	0.04 – 0.60	0.02	0.00	0.00
Longer-term	CBT	2	432	0.43*	0.16 – 0.70	0.00	0.16	23.34
(pre-follow up)	Non-CBT	1	42	0.27	-0.49 – 1.31	0.49	0.00	0.00

Abbreviations = $N_{studies}$ = number of studies contributing to these data, $N_{participants}$ = number of participants from studies contributing to these data: g_w = weighted Hedges’ g effect size: p = significance value associated with g: CBT = Cognitive Behaviour Therapy. *denotes statistically significant effect estimate.

3.8. Subgroup analysis

The relative effectiveness of CBT and non-CBT interventions was examined (Table 4). In the short- term, participants who received CBT [36,49,52] reported medium and significant improvements in seizure and mental health outcomes (i.e. anxiety and depression) although this finding was characterised by substantial between-study heterogeneity in effects ($I^2 = 51.61\%$, tau = 0.13). These improvements reduced to a small effect by follow up. Non-CBT interventions [42,63] were also associated with positive and significant, albeit consistently smaller gains across outcomes. In the longer-term, body-focused therapy produced a small and non-significant result at 6-month follow up. The small effect suggests that non-CBT treatment was comparable in the long term to controls who receive guided self-help.

4. Discussion

The current systematic review pooled the data from five high quality RCTs to investigate the effectiveness of psychosocial intervention in the management of PNES. The effectiveness of psychosocial interventions was measured by examining seizure frequency ($k = 3$), seizure severity ($k = 2$), anxiety ($k = 4$), depression ($k = 5$) and quality of life ($k = 2$). The most common intervention was CBT ($k = 3$), however studies also examined paradoxical therapy ($k = 1$) and CORDIS ($k = 1$). All but one of the calculated effect sizes were positive, suggesting psychosocial interventions are typically associated with improved outcomes for people with PNES.

The systematic review supports the implementation of psychosocial intervention for reducing seizures in people with PNES. CBT had a large to very large effect immediately, which was maintained at a small to medium effect after an average of 6-months post-intervention. These findings are in keeping with the reductions in seizure frequency found in a 2016 review [35]~~,~~however a direct comparison with this earlier study was not possible due to variations in how seizure frequency was measured (e.g., changes in percentiles verses effect sizes).

Alongside findings of reduced seizure frequency, this study was the first to collate evidence in support of improvements in the severity of seizures following psychosocial intervention. Notably, an immediate reduction in seizure severity was not observed, however medium effect size improvements were evident six months post- intervention. Therefore, mental health clinicians may be advised to inform patients with PNES who are undergoing psychosocial intervention that the severity of their seizures may not reduce instantly, but rather require persistent application of the strategies they have learnt in therapy. Overall, psychosocial interventions have the potential to reduce the frequency and severity of PNES which supports the recommendation by the ILAE that psychosocial intervention should be the first-line treatment for people with PNES.

Psychosocial interventions were less effective in improving mental health outcomes for people with PNES. Specifically, anxiety reduced immediately following a psychosocial intervention to a medium to large effect but diminished over time to a small effect approximately 6-months post- intervention. Depressive symptoms varied from not improving to improving by a large effect immediately post-intervention but diminished to only a small effect at follow-up. The effectiveness of psychosocial interventions on the mental health of people with PNES in this study was notably smaller than was reported in a recent meta-analysis [37], which may be attributed to RCTs typically reporting smaller effect sizes than non-RCTs. A more conservative approach to investigating psychosocial interventions on mental health outcomes was employed in this study by including only RCTs. Furthermore, the included studies excluded participants that had overt psychopathology. For example, Ataoglu et al. [63] explicitly excluded participants with anxiety or mood disorders, while La France et al. [52] and Goldstein et al. [49] excluded the use of certain psychiatric medications. Furthermore, exclusion criterion around suicidality was employed for the studies by La France et al. [52] and Senf-Beckenbach et al. [42]. Alternatively, these findings may indicate to clinicians the need for strategies targeted at reducing co-morbid anxious and depressive symptoms when implementing psychosocial intervention for people with PNES. In sum, more needs to be done to increase the effectiveness of psychosocial interventions in maintaining reduced mood and anxiety symptoms for people with PNES, in order to sustain better overall wellbeing.

The effect of psychosocial interventions on the quality of life of people with PNES was highly variable, with small to very large effects seen immediately and only small effects (and some people not experiencing any improvement) at follow-up. Although the effect size immediately post intervention was much larger than that found by Gaskell et al. [37] there was a large amount of variation between the effects for the two studies that investigated quality-of-life. This finding highlights the need for future studies to include quality of life measures to allow for a more comprehensive analysis of the impact of psychosocial intervention on the lives of people with PNES.

In this review, we compared the effectiveness of psychosocial interventions that employed a CBT framework and those that did not (referred to as non-CBT interventions). In the short term, CBT-based interventions exhibited more favourable outcomes compared to non-CBT interventions. This suggests that CBT, in its structured and goal-oriented approach, may provide individuals with more immediate relief and coping strategies for managing PNES. However, analysis of data collected at follow up demonstrated both CBT and non-CBT interventions were less effective in the longer-term. Although the effectiveness of psychosocial interventions was not maintained well overtime, the effect of the interventions was still positive, and given they are not associated with adverse effects, they should still be considered the first line of treatment for people with PNES.

4.1. Limitations

Several limitations were encountered that may have impacted the findings of this systematic review. First, two studies lacked essential information relevant to our analysis [69,70]. Despite efforts to obtain missing data, the absence of these studies may have impacted the comprehensiveness of this study. Second, a limited number of studies met eligibility for inclusion which constrained the ability to perform additional analyses (e.g., publication bias or a meta-regression looking at effects of age, gender and treatment length on intervention effectiveness). To mitigate the absence of publication bias analyses, the fail-safe N technique was employed to estimate the impact of potential missing studies on the results. A funnel plot would have been the preferred analysis of publication bias should there have been a larger number of included studies. Third, some of the effect size data differed from that published by the included studies because some studies commented on between-group differences at each time point and this study calculated change scores pre-post intervention. Fourth, the majority of outcomes in the included studies relied on self-reported data. Self-reported data is highly practical for researchers and clinicians as it is easy to administer and time efficient, however, it may enable under-reporting of undesirable symptoms, such as those related to depression and anxiety and the simultaneous over-reporting of more desirable social attributes such as quality of life [71,72].

4.2. Future Directions

The current systematic review provides valuable insights into short- and long-term effects of psychosocial intervention on seizure, mental health outcomes and the quality of life of people with PNES, and in doing so highlights potential areas for future research. More RCT studies are required to determine factors that make people with PNES more likely to respond well to a particular psychosocial intervention (e.g., characteristics of people, number of sessions, maintenance sessions). Other types of therapies should also be investigated, in particular, trauma-focused therapies (i.e., cognitive processing therapy [CPT], eye movement desensitisation and reprocessing [EDMR] and trauma focused CBT) given the strong association between PNES and underlying experiences of trauma [74–76]. There is some preliminary evidence in support of CPT and EDMR in reducing PNES for people who have comorbid post-traumatic stress disorder (PTSD), however these are case studies and need to be replicated on a wider scale within a RCT framework to consolidate findings [77,78].

Furthermore, studies included in this review reported high dropout rates, suggesting a barrier to treatment engagement and retention. The exploration of telehealth options for people with PNES may be useful in identifying whether it has the potential to reduce barriers often cited by those with PNES; namely physical illness, social problems or distance to treatment centres [36,49]. Telehealth may address these barriers with a recent study indicating that telehealth delivery of CBT to people with PNES [79] resulted in significant improvements across a wide range of seizure, mental health and quality of life outcomes. Additionally, assessing acceptability and feasibility of psychosocial treatment through measures of patient satisfaction may provide valuable insights into the suitability of different psychosocial interventions for people with PNES. The current systematic review exclusively focused on studies conducted within the adult population (18 years and over). Future research that tailors psychosocial intervention for children and adolescents may provide insights into the benefits and challenges associated with psychosocial intervention across the lifespan. Finally, this study did not calculate the number of people with PNES that need to be treated with a psychosocial intervention in order for one patient to have a beneficial outcome (otherwise referred to as the Number Needed to Treat) [73]. Calculating the number needed to treat may help healthcare services weight up the cost and benefits of providing psychosocial interventions to people with PNES.

4.3. Conclusion

In sum, this systematic review supports the effectiveness of psychosocial intervention for the management of PNES, with modest improvements observed in seizures outcomes in the long term. While there were some improvements in anxiety, depression and quality of life, these were not maintained over time. Overall, these findings are promising and may improve the confidence of health care professionals in implementing psychosocial intervention for people with PNES over the current lack of treatment options. The publication of more RCT studies is required to replicate these findings and investigate causes for the large variations in results (e.g., between treatment type). Exploration of other treatment modalities and barriers to the accessibility, acceptability and feasibility of psychosocial interventions for people with PNES across the lifespan is also required. Calculation of Number Needed to treat would also provide benefit for helping health care professionals weigh up the costs and benefits of psychosocial intervention for people with PNES.

Acknowledgments

First and foremost, I would like to extend my sincerest thanks to my two supervisors for their guidance and feedback during the year. You have shown me unconditional support and incredible patience in my research journey and have enhanced my learning process and writing immeasurably. Thank you for all of the hours you have spent helping me. I would also like to express gratitude to my fellow peers in the Master of Psychology cohort for making this journey brighter, and to the Bass family for their continued support.

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**denotes studies included in the systematic review.*

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Supplementary Material 1. Instructions to Authors for *Epilepsy & Behaviour*

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[1] Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. J Sci Commun 2010;163:51–9. https://doi.org/10.1016/j.Sc.2010.00372. Reference to a journal publication with an article number:
[2] Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. Heliyon. 2018;19:e00205. https://doi.org/10.1016/j.heliyon.2018.e00205 Reference to a book:
[3] Strunk Jr W, White EB. The elements of style. 4th ed. New York: Longman; 2000. Reference to a chapter in an edited book:
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[5] Cancer Research UK. Cancer statistics reports for the UK, http://www.cancerresearchuk.org/ aboutcancer/statistics/cancerstatsreport/; 2003 [accessed 13 March 2003]. Reference to a dataset: [dataset]
[6] Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. https://doi.org/10.17632/ xwj98nb39r.1.
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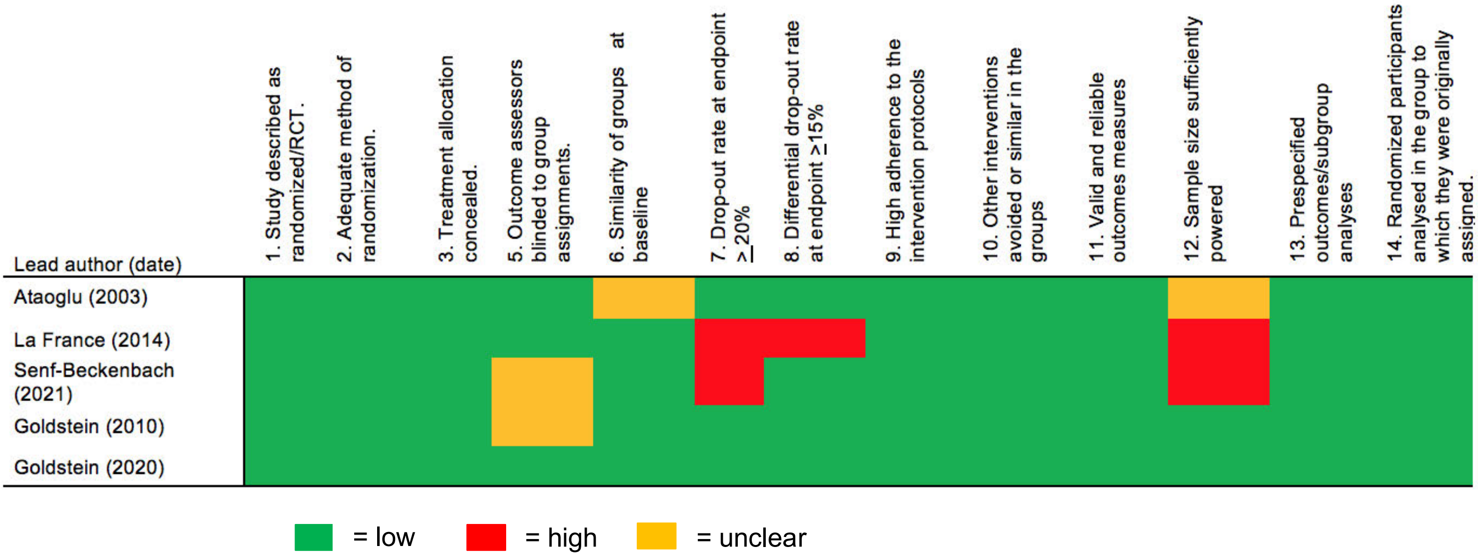
Supplementary Material 2. **Logic Grid**

Database	Search Terms
PubMed	"seizures"[mh:noexp] OR "psychogenic nonepileptic seizures"[mh] OR psychogenic seizure*[tiab] OR psychogenic nonepileptic[tiab] OR PNES[tiab] OR non epileptic attack disorder*[tiab] OR NEAD[tiab] OR psychogenic attack*[tiab] OR psychogenic spell*[tiab] OR psychogenic episode*[tiab] AND "psychotherapy"[mh] OR "mindfulness"[mh] OR psychotherap*[tiab] OR cognitive behavioural therap*[tiab] OR cognitive behavioral therap*[tiab] OR CBT[tiab] OR mindful*[tiab] OR therapy[tiab] OR therapies[tiab] OR psychosocial[tiab] OR intervention*[tiab] OR management[tiab] OR hypnosis[tiab] OR ACT[tiab], acceptance and commitment therap*[tiab]
PsycINFO	psychogenic nonepileptic seizure*.ti,ab OR nonepileptic seizure*.ti,ab OR psychogenic.ti,ab OR psychogenic pseudoseizure.ti,ab OR pseudoseizure.ti,ab OR psychogenic seizure*.ti,ab OR psychogenic nonepileptic.ti,ab OR PNES.ti,ab OR non-epileptic attack disorder*.ti,ab OR non-epileptic attack*.ti,ab OR NEAD.ti,ab OR psychogenic attack*.ti,ab OR psychogenic spell*.ti,ab OR psychogenic episode*.ti,ab OR non-epileptic seizure*.ti,ab OR pseudoseizure*.ti,ab OR conversion disorder*.ti,ab OR functional epilepsy.ti,ab OR hysterical seizure*.ti,ab OR non-organic epilepsy.ti,ab OR hysterical seizure*.ti,ab OR conversion seizure*.ti,ab AND psychotherapy.ti,ab OR mindfulness.ti,ab OR psychotherap*.ti,ab OR cognitive behavioural therap*.ti,ab OR cognitive behavioral therap*.ti,ab OR CBT.ti,ab OR mindful*.ti,ab OR therap*.ti,ab OR intervention*.ti,ab OR management.ti,ab OR hypnosis.ti,ab OR ACT.ti,ab OR "Acceptance and Commitment Therap*".ti,ab
Medline	psychogenic nonepileptic seizure.ti,ab OR nonepileptic seizure*.ti,ab OR psychogenic.ti,ab OR psychogenic pseudoseizure*.ti,ab OR pseudoseizure*.ti,ab OR non-epileptic attack disorder*.ti,ab OR non-epileptic attack*.ti,ab OR NEAD.ti,ab OR psychogenic attack*.ti,ab OR psychogenic spell*.ti,ab OR psychogenic episode*.ti,ab OR non-epileptic seizure*.ti,ab OR conversion disorder*.ti,ab OR functional epilepsy.ti,ab OR non-organic epilepsy.ti,ab OR hysterical seizure*.ti,ab OR conversion seizure*.ti,ab AND Exp*psychotherapy.ti,ab OR mindfulness.ti,ab OR cognitive behavioural therap*.ti,ab OR cognitive behavioral therap*.ti,ab OR CBT.ti,ab OR therap*.ti,ab OR intervention*.ti,ab OR management.ti,ab OR hypnosis.ti,ab OR ACT.ti,ab OR "Acceptance and Commitment Therap*".ti,ab

Supplementary Material 3. **Evaluation of study quality; individual studies.**



Lead author (date)	1. Study described as randomized/RCT.	2. Adequate method of randomization.	3. Treatment allocation concealed.	5. Outcome assessors blinded to group assignments.	6. Similarity of groups at baseline	7. Drop-out rate at endpoint ≥ 20%	8. Differential drop-out rate at endpoint ≥15%	9. High adherence to the intervention protocols	10. Other interventions avoided or similar in the groups	11. Valid and reliable outcomes measures	12. Sample size sufficiently powered	13. Prespecified outcomes/subgroup analyses	14. Randomized participants analysed in the group to which they were originally assigned.
Ataoglu (2003)	🟩	🟩	🟩	🟩	🟨	🟩	🟩	🟩	🟩	🟩	🟨	🟩	🟩
La France (2014)	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟩	🟩	🟩	🟥	🟩	🟩
Senf-Beckenbach (2021)	🟩	🟩	🟩	🟨	🟩	🟥	🟩	🟩	🟩	🟩	🟥	🟩	🟩
Goldstein (2010)	🟩	🟩	🟩	🟨	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Goldstein (2020)	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩

🟩 = low 🟥 = high 🟨 = unclear