A proportional meta-analytic evaluation of the effectiveness and durability of psychotherapy for adults presenting with functional dissociative seizures.

Chris Gaskell1\*

Niall Power2

Barbora Novakova3

Melanie Simmonds-Buckley1,4

Wesley T. Kerr5,6

Markus Reuber6

Stephen Kellett4

Gregg H. Rawlings1

**Affiliations:**

1 Clinical and Applied Psychology Unit, University of Sheffield, UK

2 South West Yorkshire Partnership NHS Foundation Trust

3 Health and Wellbeing Service, NHS Sheffield Talking Therapies, Sheffield Health and Social Care NHS Foundation Trust, UK

4 Rotherham Doncaster and South Humber NHS Foundation Trust, UK

5 Departments of Neurology & Biomedical Informatics, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

6Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA

6 Academic Neurology Unit, University of Sheffield, Royal Hallamshire Hospital, Glossop Road, S10 2JF, Sheffield, UK

**Corresponding Author:**Dr Chris Gaskell - c.gaskell@sheffield.ac.uk

**Co-Author email addresses:**

Niall Power – niall.power@swyt.nhs.uk

Barbora Novakova – barbora.novakova@nhs.net

Melanie Simmonds-Buckley – [m.simmonds-buckley@sheffield.ac.uk](mailto:m.simmonds-buckley@sheffield.ac.uk)

Wesley Kerr – kerrw@pitt.edu

Markus Reuber – m.reuber@sheffield.ac.uk

Stephen Kellett - stephen.kellett@nhs.net

Gregg Rawlings – Gregg.Rawlings@sheffield.ac.uk

**ORCID ID:**

Chris Gaskell - 0000-0002-7589-5246

Niall Power - 0000-0002-7788-7418

Barbora Novakova – 0000-0001-9638-7032

Mel Simmonds-Buckley - 0000-0003-3808-4134

Wesley Kerr – 0000-0002-5546-5951

Markus Reuber – 0000-0002-4104-6705

Stephen Kellett - [0000-0001-6034-4495](https://orcid.org/0000-0001-6034-4495)

Gregg Rawlings – 0000-0003-4962-3551

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**Abstract**

**Background**: Psychological interventions are the most recommended treatment for functional / dissociative seizures (FDS). We synthesise the evidence involving psychological interventions for FDS that have examined a seizure-related outcome; use meta-analytic methods to analyse data collected during treatment and follow-up phases; and explore sources of heterogeneity between outcomes using moderator analyses.

**Methods:** In February 2023, we updated a systematic search from February 2022 of four electronic databases. We included data collected from randomised control trials and observational cohort studies.

**Results:** Overall, 44 relevant studies were identified involving 1300 patients. Most were categorised as high (39.5%) or medium (41.9%) risk of bias. Seizure frequency was examined in all but one study; seizure intensity, severity or bothersomeness in ten; and seizure duration and cluster in one study each. Meta-analyses could be performed on seizure freedom and seizure reduction. A pooled estimate for seizure freedom post-treatment was 40% reducing to 36% at follow-up. Treatment setting was the only significant moderator. Pooled rates for seizure improvement (indicated by patients reporting ≥50% improvement in seizure frequency) were higher at 66% and 75%. Examining group level seizure frequency data, a moderate pooled effect size (*d*=0.53) was observed during the treatment phase. Analysis of median change revealed a reduction of five seizures per month.

**Conclusion:** Combined with the results from a complementary previous meta-analysis performed by the current authors on non-seizure-related outcomes in the treatment of FDS, psychological interventions are associated with a significant reduction in seizure frequency and cessation, and improvements across a range of non-seizure related measures.

**What is already known on the topic**?

* A range of interventions have been investigated for functional / dissociative seizures (FDS), including neuromodulation, anti-depressant medication, and physiotherapy; although psychological treatments remain the most explored and have the largest evidence base.
* FDS cessation and / or a reduction in intensity, severity or bothersomeness are common shared goals of patients and services, and typically, seizure-related outcomes are the primary aim of intervention trials.
* While a recent meta-analysis was performed on non-seizure-related outcomes in effectiveness studies of psychotherapy for FDS demonstrating a medium effect size (*d*=0.53), there is no up-to-date analysis of seizure-related outcomes.

**What this study adds**

* Although there is evidence to suggest non-seizure related outcomes in FDS are sensitive to treatment-associated change, seizure-specific outcomes are most commonly used in intervention trials.
* Findings suggest approximately two in three patients with FDS maintain improvement in their seizures at follow-up, while two in five continue to demonstrate seizure freedom. Inherently, this demonstrates that a proportion of patients who initially seem to respond to psychological therapy go on to relapse following termination of treatment.

**How this study might affect research, practice, and policy**

* Analyses revealed that a reduction rather than cessation of FDS frequency is more likely following psychological therapy; these seem important goals to differentiate when counselling patients about the expected response to treatment.
* Although there is a relatively large amount of data in this area, the heterogeneity of outcomes and reporting detail limits the type of analyses we were able to perform. Research is required to identify how best to standardise methods, in particular the examination and reporting of seizure measurements.
* The narrative review found evidence suggesting the possible benefits of psychological therapy on seizure-related outcomes other than frequency (intensity, severity, bothersomeness, duration and clusters of seizures), however, further research is required for a meta-analysis.

# Introduction

Functional / dissociative seizures (FDS) can be conceptualised as an involuntary response to internal or external triggers associated with dysfunctional emotion regulation [1]. FDS account for approximately 15% of patients referred to neurology clinics for seizure-like events [2].

Psychological interventions are the most recommended treatment for FDS [3, 4] and subsequently, the most researched [5]. A recent meta-analysis of psychotherapy in FDS has synthesised the body of evidence concerning non-seizure outcomes [5]. Across 32 studies (171 outcomes, 889 patients) covering a range of outcomes, a pooled effect size of *d*=0.51 was observed. The review also revealed variation in the type and number of outcomes that have been used in FDS treatment studies. Indeed, there is ongoing debate about how treatment outcomes should be measured in this patient population [6, 7], especially as measures of psychological well-being have been found to be greater predictors of health-related quality of life (HR-QoL) than seizure-related outcomes in people with FDS [8, 9] and may be more sensitive to treatment-associated change [10].

Given patients with FDS primarily present with seizures as the ‘presenting problem’, and that the cessation or reduced frequency of seizures are common treatment goals (i.e., similar to the goals of treating epileptic seizures [11, 12]), the ability of an intervention to change the characteristics of seizures must be a crucial aspect of outcome. In view of this, many studies evaluating psychotherapies with people with FDS have utilised measures of seizure frequency or severity as their primary outcome.

Two previous meta-analyses of seizure-specific outcomes of psychological interventions for adults with FDS have been attempted. In 2014, a Cochrane review of treatments for FDS (12 studies, 343 patients) reported being unable to carry out a meaningful meta-analysis due to the heterogeneity of study designs and interventions [13]. Carlson and Perry in 2017 performed a pair of proportional meta-analyses for psychological intervention studies in FDS (13 studies, 227 patients) [14]. Aggregated results demonstrated that 47% of individuals were seizure-free by the end of treatment whilst 82% reported a ≥50% improvement in seizure frequency.

Interval completion of multiple trials prompted the current authors to re-visit these analyses, especially considering the seminal CODES study, a multi-centre randomised control trial (RCT) examining Cognitive Behavioural Therapy (CBT) in 386 patients with FDS [10]. In addition to evaluating these common metrics of seizure freedom and 50% responder rate, we also evaluate other metrics that potentially provide further detail and improved statistical power, including [15] (i) alternative frequency metrics (e.g., mean or median change), (ii) outcomes for treatment follow-up, and (iii) alternative seizure constructs (e.g., severity, duration etc.). Furthermore, developments in research synthesis methods allow for more advanced quantitative procedures, including the synthesis of medians [16], and exploration of moderator variables, which may explain the variation in outcomes across FDS studies.

We investigate the effectiveness of psychological interventions on seizure-related outcomes in adults with FDS. We aimed to: (i) narratively synthesise study characteristics; (ii) use meta-analytic methods to synthesise evidence for different seizure domains and reporting statistics; (iii) explore potential sources of heterogeneity using moderator analysis for seizure freedom rates; and (iv) investigate whether change associated with treatment are maintained or improved at follow-up.

**Method**

## Search strategy

The protocol was pre-registered (<https://osf.io/2hmc3>). In February 2023, we updated our previous systematic search of studies describing non-seizure outcomes of psychological treatments in adults with FDS from February 2022 [5] (see <https://osf.io/sk6xm> for original review).

Four electronic databases (CINAHL, PsycINFO, MEDLINE, Cochrane Reviews) were searched by GHR & BN using a combination of a *condition* and a *treatment* term (Supplementary Table 1). After duplicates were removed, the titles and abstracts were screened, followed by screening of full-text manuscripts. Forward and backward searches were performed using the R package *citation chaser* [17].

Inclusion and exclusion criteria are consistent with our previous review [5] (Supplementary Table 1). Studies were excluded when the sample was not adult-focused (average age ≤ 16 years), when most patients (≥ 50%) had comorbid epilepsy, or when the entire population did not receive psychological treatment. No exclusions were made based on the time elapsed since intervention to follow-up; however, we required that long-term follow-up outcomes were collected systematically.

**Data collection**

Relevant data were extracted from manuscripts (CG) while effect-size data were extracted in duplicate (CG & NP). When manuscripts reported overlapping samples, preference was given using a decision hierarchy favouring robustness. Treatment and patient variables included in the moderator analysis (see Supplementary Table 2) included treatment -format, -delivery, -modality, -duration, risk of bias, age, and gender.

## Risk of Bias

Cochrane Collaboration’s tool for assessing risk of bias was used (ROB-2) – see Figure 2 [18]. Studies were given a score of “high”, “low” or “unclear” risk for each of the seven items. All studies were given an overall risk of bias score of “high”, “medium” or “low”. See Gaskell et al., [5] for more information. All risk of bias ratings were performed in duplicate by GHR & BN.

The quality of the evidence base included in the meta-analyses in terms risk of bias, publication bias, inconsistency, imprecision, and indirectness of treatment estimate effects was further assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [19]. The GRADE assessments were completed (SK & MSB) during a consensus review meeting (rated as high, moderate, low, or very low quality, Supplementary Table 3).

## Analysis

For the narrative synthesis, no restrictions were made on how outcomes were reported; however, for meta-analyses, only outcomes reporting sufficient data to permit synthesis were included (see below). For the purposes of the meta-analysis, outcomes were distinguished as either relating to the acute treatment phase (pre-vs. post-treatment) *or* follow-up (pre-treatment vs. follow-up). Quantitative outcomes were delineated by construct and metric. This included seizure *-frequency* (mean change, median change), -*freedom* (proportion), -*improvement[[1]](#footnote-1)* (proportion), -*clusters*, -*intensity, -severity*, -*burden*, and -*bothersomness*. For metrics sufficiently represented (≥ 10 study outcomes), meta-analyses were used to aggregate effect-sizes.

Outcomes variability (e.g., mean, median, proportion) was expected and is a challenge for research synthesis as different summary statistics cannot easily be synthesised [20, 21]. Our approach to this was: (i) data was converted to effect-size metrics based on the type of data reported (i.e., mean and standard deviations expressed as Cohen’s *d,* medians expressed as median change); (ii) when data was available in multiple forms (e.g., both means and medians are reported) then multiple metrics were calculated; (iii) when raw data was provided then all forms were manually calculated; (iv) meta-analyses were domain-specific; (v) where enough data was reported then meta-analyses were conducted for both the acute treatment phase and follow-up.

All analyses were conducted using the R statistical analysis environment [22]. Standardised mean change (i.e., Cohen’s *d*) was calculated using the *metafor* package [23]. Random effects models were selected as effects were anticipated to show heterogeneity and results were intended to be generalisable beyond the current pool of studies [24]. Standardised mean change outcomes were aggregated using restricted maximum likelihood (*metafor* package), median change outcomes were aggregated using the weighted median of the difference of medians [20] with the *metamedian* package [16], and finally proportions were handled using the *metaprop* package (ref). Freeman-Tukey transformations of very low or high proportions were made [25].

For the primary meta-analysis (seizure freedom), we sought to explore under what conditions study outcomes significantly vary using categorical and continuous moderator variables. For subgroup moderators, the QM test (Wald-type test of the model coefficients) was used to examine differences between moderator levels and a designated reference level. A significant QM test indicates significant differences between moderator levels. Moderator output was reported in absolute terms (i.e., not relevant to an intercept). Correction for multiple moderators (i.e., Bonferroni) was not employed due to high risk for false negative results [26].

Forest plots were generated using the *ggplot2* [27] package. The Q statistic [28] and the proportion of variance not attributable to sample error (I2) [29] were reported to assess heterogeneity. τ2 was reported to quantify variance in true effect sizes. The impact of publication bias on treatment estimates was visualised using funnel plots and assessed statistically using Egger’s regression test for funnel plot asymmetry.

# Results

## Systematic Search

One additional eligible study was identified [30] from the original search, thus resulting in the current review consisting of 43 studies and 49 individual samples (Figure 1)[[2]](#footnote-2). See Table 3 for a full list of the included studies.

**Study characteristics**

Data was collected from 1,300 patients. Information on the sex of 42 samples (87.5%) were reported, with females comprising 68.2% of patients (*N*=886). The mean age of participants was 36.5 years (*k*=41, 85.4%). Most samples were recruited from the United States (*k*=21; 43.8%), followed by the United Kingdom (*k*=11; 22.9%). The median number of participants per trial was 20, with a range of 6 to 185.

**Figure 1:**

*PRISMA flow diagram of studies throughout the review.*

**A diagram of a flowchart

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**Table 3:**

*Studies included in the meta-analysis (*† = same sample investigated: ‡, §, φ, ^, §, σ = same study but different sample, \* = not included in meta-analyses)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Country | N (female) | Age M (SD/ range) | Design | Modality | Dosage | Delivery | Setting | RoB |
| Aamir [33] | Pakistan | 18  (15) | 22.22  (2.7) | RCT | Behavioural | 15 sessions | Individual | Outpatient | Medium |
| Aboukasm [34] ‡ | USA | 16  (13) | 42.7 (13) | Retrospective study | Psychotherapy – non-specified | At least 5 sessions | Individual | Outpatient | High |
| Aboukasm [34] ‡ | USA | 25 (22) | 38.4 (10.8) | Retrospective study | Psychotherapy – non-specified | - | Individual | Outpatient | High |
| Ataoglu [35] | Korea | 15  (15) | 23  (16-3) | RCT | Behavioural | 3 weeks inpatient treatment. 2 x sessions per day | Individual | Inpatient | Low |
| Baird [36]§ | USA | 9 (7) | 37.9 (11.5) | Pilot RCT at 3 academic medical centres | C-B informed psychotherapy | 12 sessions | Individual | Outpatient | Low |
| Baird [36]§ | USA | 9 (9) | 39.1 (13.2) | Pilot RCT at 3 academic medical centres | C-B informed psychotherapy plus sertraline | 12 sessions | Individual | Outpatient | Low |
| Barrett-Naylor [37] | UK | 6  (5) | NR | Non-concurrent case series | C-B - guided self-help | 6 weeks | Individual | Outpatient | Medium |
| Barry [38] | USA | 7  (7) | 45.4  (7.9) | Pilot study | Relational | 32 x 90 minute group Sessions | Individual + Group | Outpatient | High |
| Baslet [39] | USA | 6  (6) | NR | Case series | C-B | 12 sessions | Individual | Outpatient | High |
| Baslet [31]† | USA | 26  (23) | 46.4  (16.2) | Prospective uncontrolled trial | C-B | 12 sessions | Individual | Outpatient | Medium |
| Baslet [31]† | USA | 26 (23) | 46.4 (16.2) | Prospective uncontrolled trial | C-B | 12 sessions | Individual | Outpatient | Medium |
| Ben-Naim [40] | Israel | 22  (15) | 31.3  (13.8) | Within-group post-treatment vs pre-treatment study | Eclectic-  various | Months = (M = 15.77, SD = 10.96, range = 2 and 48 | Individual | Outpatient | High |
| Bhattacharjee [30] | India | 16 (12) | 37.9 (18-58) | Case series | Brief online psychotherapy | 10 sessions | Individual | Outpatient | High |
| Bullock [41] | USA | 19 (18) | 44.5 (NR) | Prospective naturalistic design | Dialectical Behavioural Therapy | Flexible (mean = 20.5 weeks) | Group | Outpatient | High |
| Chen [42]\* | USA | 20  (NR) | 50.8  (12.3) | Pilot RCT | Psycho-  education | 3 x 1.5 hour sessions | Group | Outpatient | Medium |
| Conwill [43] | UK | 10  (7) | 33.1  (11.6) | Pilot study / service evaluation | C-B | 4 group sessions | Group | Outpatient | Medium |
| Cope [44] | UK | 25  (21) | NR | Evaluation | C-B | 3 sessions | Group | Outpatient | Medium |
| DeLeuran [45] | Denmark | 42  (36) | 36  (18) | Retrospective study | C-B | 10-15 sessions (mean = 12; SD = 5.7) | Individual | Outpatient | High |
| Duncan [46] | UK | 89 (72) | 38.7 (15.6) | Prospective audit | C-B | Up to 10 sessions (mean = 4.9, range 1–10) | Individual | Outpatient | High |
| Goldstein [47] | UK | 16  (14) | 34.9  (13.4) | Open, prospective trial | C-B | 12 sessions | Individual | Outpatient | Medium |
| Goldstein [48] | UK | 31  (24) | 37.4  (12.6) | RCT | C-B | 12 sessions | Individual | Outpatient | Low |
| Goldstein [10] | UK | 185  (140) | 37.3  (14.2) | Pragmatic, parallel-arm, multicentre RCT | C-B | 12+1 (median = 13) | Individual | Outpatient | Low |
| Khattak [49]\* | Pakistan | 50  (NR) | 24.3  (8.8) | RCT | Behavioural | NR | Individual | Inpatient | High |
| Korman [50] | Argentina | 23 (20) | NR | Evaluation | Psychoeducation | 1 psychoeducation session | Individual | Outpatient | High |
| Kuyk [51] | Netherlands | 22  (NR) | 30.6  (10.8) | Uncontrolled, prospective inpatient treatment program | C-B | Mean = 4.8 months | Individual + Group | Inpatient | High |
| Labudda [52] | Germany | 80  (60) | 33.8  (13.6) | Prospective, naturalistic evaluation | C-B | mean = 64.5 days | Individual + Group | Inpatient | High |
| LaFrance [53] | USA | 20  (17) | 36  (10.4) | Prospective non-randomised clinical trial | C-B | 12 sessions | Individual | Outpatient | Medium |
| LaFrance [54]φ | USA | 9  (7) | 37.9  (11.5) | Pilot RCT at 3 sites | C-B | 12 sessions | Individual | Outpatient | Low |
| LaFrance [54]φ | USA | 9  (9) | 39.1  (13.2) | Pilot RCT at 3 sites | C-B with sertraline | 12 sessions | Individual | Outpatient | Low |
| LaFrance [55] | USA | 32  (5) | 49.1  (NR) | Single-arm, prospective, observational, cohort, consecutive outpatient study | C-B | 12 sessions | Individual | Outpatient | Medium |
| Mayor [56] | UK | 47 (33) | 47 (45) | Service evaluation | Brief augmented psychodynamic -psychotherapy | Maximum of 20 sessions (median = 5) | Individual | Outpatient | Medium |
| Mayor [57] | UK | 29  (NR) | 37  (23-38) | Prospective, multicentre, feasibility study | Psycho-  education | 4 x 1-hour sessions | Individual | Outpatient | Medium |
| McDade [58] | UK | 18 (7) | 34.1 (NR) | Prospective series | Multi-disciplinary treatment including supportive psychotherapy | Treatment lasted between 12 weeks and 6 months | Individual | Inpatient | High |
| Metin [59] | Turkey | 9  (8) | 22.5  (NR) | Pre- and post-evaluation | Eclectic-  various | Weekly 90 minute sessions for 12 weeks | Group | Outpatient | High |
| Myers [60] | USA | 16  (13) | 42.8  (NR) | Case series/uncontrolled intervention study | C-B | 12-15 sessions | Individual | Outpatient | Medium |
| Rusch [61] | USA | 33 (25) | 33.8 (11.7) | Case series uncontrolled | Eclectic-various | Flexible (mean = 9.5 sessions, range = 2–30) | Individual | Outpatient | High |
| Santiago-Trevino [62]^ | Mexico | 9  (NR) | NR | RCT | C-B | 36 weekly sessions | Individual | Outpatient | Medium |
| Santiago-Trevino [62]^ | Mexico | 7  (NR) | NR | RCT | Relational | 36 weekly sessions | Individual | Outpatient | Medium |
| Santos [63] | Brazil | 37 (29) | 32 (22-43) | Prospective longitudinal study | Psychoanalysis | 48 sessions | Individual | Outpatient | High |
| Sarudiansky [64]\* | Argentina | 12  (10) | 30.8  (14.1) | Longitudinal non-randomised study that included the administration of pre and post assessment measures | Psycho-  education | 3 bi-monthly sessions each 2 hours long | Group | Outpatient | Medium |
| Senf‐Beckenbach [65]§ | Germany | 22  (18) | 36.6  (12.1) | Pilot RCT | Body focused | 10 x 90-minute sessions | Group | Outpatient | Low |
| Senf‐Beckenbach [65]§ | Germany | 20  (12) | 32.8  (13.2) | Pilot RCT | Guided self-help | 10 x 90-minute sessions | Group | Outpatient | Low |
| Streltzov [66] | USA | 6  (6) | 36.2  (9) | Non-randomised pilot study | C-B | 8 sessions | Group | Outpatient | Medium |
| Thompson [67]\* | USA | 19 (11) | 33 (NR) | Pilot RCT | Psychoeducation | 1 session | Individual | Inpatient | Low |
| Tilahaun [68] | USA | 64  (47) | 36.3  (11.3) | Retrospective evaluation | C-B | 7-12 sessions | Individual | Outpatient | Medium |
| Tolchin [69]σ | USA | 31  (26) | 40.7  (14.3) | RCT | C-B | 12 sessions | Individual | Outpatient | Low |
| Tolchin ([69]σ | USA | 29  (23) | 39.6  (16.8) | RCT | C-B + motivational interviewing | 13 sessions | Individual | Outpatient | Low |
| Wiseman [70] | UK | 25  (13) | 41.8  (18.1) | Multicentre evaluation / service evaluation | Psychoeducation | 4 x 1-hour sessions | Group | Outpatient | Medium |
| Zaroff [71] | USA | 10  (6) | 35.7  (12.9) | Pre-post evaluation | Psychoeducation | 10 group sessions | Group | Outpatient | High |

C-B = Cognitive-Behavioural: N = Number of participants: NR = Not-reported: M =Mean: RCT = Randomised control trial: RoB = Risk of bias: SD = standard deviation: UK = United Kingdom: USA = United States of America

**Risk of bias**

Most studies were categorised as high (*c*=17, 39.5%) or medium (*c*=18, 41.9 %) overall risk of bias (see Figure 2). The inclusion of observational / cohort studies meant the starting GRADE of evidence was determined to be “low.” Assessment across the five GRADE domains highlighted general issues with inconsistency of results and imprecision, but there were minimal concerns regarding publication bias and the directness of the evidence. Across the meta-analyses, quality was commonly downgraded due to the significant variation not attributable to sampling error (i.e., I2), imprecise effects based on wide confidence interval boundaries, and small sample sizes.

## Seizure Outcomes

While 43 studies examined at least one seizure-related outcome, quantitative data could only be extracted from 39 studies (see below). The 39 studies included 135 seizure-related outcomes, 82 represented the acute treatment phase and 53 a post-treatment follow-up time point.

**Figure 2:**

Table

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Description automatically generatedRisk of bias ratings for the studies included in the systematic review, as measured using the ROB-2.0.

***Seizure frequency***

The frequency of seizures was examined in 42 out of 43 studies [excluding 65]. Seizure freedom rates were available for re-analysis in 28 studies (65.2%, *k*=44), seizure improvement rates in 24 studies (61.5%, *k*=35) and group-level change (i.e., mean/median) in 22 studies (51.2%, *k*=42). Group-level seizure frequency change was reported as mean change (*c*=12), median change (*c*=17), or both (*c*=7, Supplementary Table 4).

While all data relating to seizure frequency was collected subjectively, either from the perspective of patients, their carers or healthcare professionals, there was great variation in how it was measured and reported (Supplementary Table 5). Some researchers asked participants prospectively to keep a log or diary of their seizures over a specific period, such as daily or weekly - this log could include information such as the number of seizures, severity, duration, and triggers; other researchers asked participants retrospectively how many seizures they experienced over a certain period; and some researchers did not report how they captured this information.

***Seizure intensity, severity*** ***and bothersomeness***

Ten studies employed outcomes pertaining to intensity, severity or bothersomeness of seizures [10, 30-32, 42, 44, 50, 65-67]. (Supplemental Table 5 & 6). While all measures were subjectively rated, one study used the full PNES scale [72] which considers FDS motor manifestations as an indicator of severity [30]. Measures ranged from asking participants a single-item to 20-items as part of the Liverpool Seizure Severity Scale [73], which was originally developed for people with epileptic seizures.

Four of the studies reported a significant improvement in scores [30-32, 65], three described a difference that was not statistically significant [10, 50, 66]. Two studies reported no significant change and did not report absolute values [42, 67]. One study did not discuss the results relating to intensity of FDS [44]. Although the number of studies reporting seizure severity, intensity, and bothersomeness met our minimum threshold, the variation in reporting of outcomes precluded meta-analysis.

***Seizure duration***

This was examined in one study [31]. Information was captured using patient’s weekly seizure log. The authors reported a reduction in seizure duration following a 12-session mindfulness-based therapy but it was not statistically significant (*p*=0.1).

***Seizure clusters***

This was investigated in one study [36]. Researchers examined the number of seizures experienced by a patient over a specific time interval that exceeded what would have been expected. Participants randomised to receive either CBT- informed psychotherapy or CBT-informed psychotherapy plus sertraline reported a reduction of daily and weekly clusters.

## Meta Analyses

Of the 43 studies, 39 reported quantitative outcomes with sufficient detail for inclusion in a meta-analysis [excluding 42, 49, 64, 67]. From the different seizure constructs/outcomes described above, only seizure frequency-related outcomes met our threshold of ten contributing studies.

Meta-analyses were subsequently conducted for (i) seizure freedom post-treatment, (ii) seizure freedom at follow-up, (iii) seizure frequency improvement post-treatment (iv), seizure frequency improvement at follow-up, (v) seizure frequency mean change post-treatment and (vi) seizure frequency median change post-treatment

**Seizure Freedom**

Overall, 28 studies (*k*=44) assessed seizure freedom with 42 outcomes reported in forms that could be included in the meta-analysis.

***Treatment effect****:* The pooled estimate for the seizure-freedom rate at the end of psychological treatment was 40% (95%CI=32-48%, GRADE=low) across the 28 studies (*N*=673) in the random-effects meta-analysis (Figure 3). A leave-one-out analysis to account for highly influential studies, provided estimates of pooled seizure frequency between 38% and 41%. Heterogeneity was significant (Q[df=27],=91.9, *p*=<0.001). The variability in true effect sizes across studies (τ2) was 0.03. The proportion of variation in effect-sizes that could not be attributed to sampling error (I2) was 71% (95%CI=51-84%). In terms of potential publication bias, the Egger’s test was not statistically significant (𝛽=0.58 [CI=0.35-0.81], *p*=0.33) indicating an absence of evidence for small study null effects, and the funnel plot shows a symmetrical distribution of studies (Supplementary Figure 2).

**Figure 3a:**

*Forest plot of seizure freedom rates at the end of treatment (pre- versus post-treatment). Error bars and the width of the diamond reflect the 95% Confidence Interval (95% CI) within each study and for the meta-analysis, respectively.*

A graph of a number of individuals

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CI = Confidence intervals (95%): N=number of participants

#### **Moderators of the seizure treatment effect:** Supplementary Table 7 shows the model statistics for each moderator included in the meta-analysis for the acute treatment phase and outlines the pooled effect-sizes by moderator level (for moderator forest plot see Supplementary Figure 1). The only moderator model that produced a significant finding was treatment setting, with outpatient therapy samples showing larger rates of seizure freedom (44%) as compared to tele-therapy (10%, p=0.019).

**Follow-up effect:** Across the 12 studies (*k*=14, n=486) included in the meta-analysis for pre-treatment versus follow-up seizure freedom (mean=11.2 months post-treatment end [range=1 week to 42 months]) the pooled freedom rate was 36% (95%CI=26-46%) (Figure 3b). Heterogeneity was significant (Q(df=13),=51.3, *p*=<0.001), the variance component was τ*2*=0.02, and the I2 was 74.3% (CI=47.5-91.9). Leave-one-out analysis provided estimates between 33% and 38%. The accompanying funnel plot is in Supplementary Figure 3. The Egger’s regression test was not statistically significant (𝛽=0.58 [CI=0.35-0.82], *p*=0.55) indicating an absence of evidence of small study null effects.

**Figure 3b:**

*Forest plot of seizure freedom rates at the end of treatment (follow-up)*

**A graph of a study

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CI = Confidence intervals (95%): N=number of participants

**Seizure Improvement*.***

Twenty-four studies (*k*=35) assessed seizure improvement as measured by 50% responder rate, which included participants who were seizure free (100% seizure frequency reduction). Twenty-three studies (*k*=23) assessed outcomes from the acute treatment phase, and 11 studies (*k*=12) captured outcomes from the follow-up phase.

***Treatment effect:***The pooled rate of patients experiencing ≥50% improvement in seizures at the end of treatment across the 23 studies (*k*=23, N=568), was 66% (95% CI=54-77%, GRADE=low) (Figure 4a). Heterogeneity was significant (Q[df = 22]=141.5, *p*=<0.001), the variance component was τ*2*=0.06, and the I2 was 85.2% (95% CI=73.9-92.6). The Egger’s test was not statistically significant (𝛽=0.69 [CI=0.35-1.02], *p*=0.14). The funnel plot is located at Supplementary Figure 4.

**Figure 4a**

*Forest plot of seizure improvement rates at the end of treatment (acute treatment phase)*

**A graph of a study

Description automatically generated with medium confidence**

CI = Confidence intervals (95%): N=number of participants

***Follow-up effect:*** The pooled rate of patients with ≥50% improvement in seizure frequency at follow-up was 75% (95% CI=64-85%) across the 11 studies (*k*=12, N=369) (Figure 4b). The mean duration of follow-up was 9.4 months post-treatment end (range =1 week – 42 months). Heterogeneity was significant (Q[df=11]=52.1, *p*=<0.001). The variance component was τ*2*=0.03, and the I2 was 73.12% (95%CI=41.9-90.9). The Egger’s test was not statistically significant (𝛽=0.69 [CI=0.62-1.14], *p*=0.23). Funnel plot is located at Supplementary Figure 5.

**Figure 4b:**

*Forest plot of seizure improvement rates at follow up.*

A graph of a study

Description automatically generated with medium confidence

CI = Confidence intervals (95%): N=number of participants

**Group level change (mean and median):**Group level seizure frequency data was available for 42 samples (mean=11, median=18, both=13). Outcomes were evenly split (*k*=21 each) across pre-versus post-treatment, and pre-treatment and follow-up. The analyses below are based on the treatment effect.

Standardised mean change was calculated for the 13 samples with available data for the acute treatment phase (across pre-versus post-treatment). The pooled effect size *(N*=169) identified in the random effects meta-analysis was *d*=0.75 (95% CI [0.31,1.20], GRADE= very low). The degree of variability not due to sampling error (I2) was 81%. Leave-one-out analysis provided estimates between *d*=0.38 and *d*=0.95. Due to the potential influence of outliers, an adjusted analysis was run while discarding two irregularly high effect sizes. For the remaining 11 outcomes *(****N***=153)**,** the pooled effect size identified in the random effects meta-analysis was *d*=0.53 (95% CI [0.23,0.83], I2=62%). The Egger’s test was statistically significant (𝛽= -0.52 [CI=1.05-0.00], *p*=<0.01). The funnel plot is located at Supplementary Figure 6.

The meta-analysis of median change was based on 15 outcomes (*N*=428). Pre-treatment, the weighted median of medians indicated that patients experienced (on average) 12.50 (CI=8.00-12.50) seizures per month. The change in seizure frequency (weighted median of the difference of medians) showed a reduction of 6.50 seizures per month (CI=5.00-6.80).

## Discussion

The pooled rate of patients achieving seizure freedom was 40% post-treatment and 36% at follow-up. For the less stringent outcome of seizure improvement, the pooled rate was 66% at the end of treatment and 75% at follow-up. While we observed lower rates of improvement at the end of treatment than reported in the previous meta-analysis of psychotherapy outcomes in this patient group (FDS freedom=40% vs. 47%; (≥50% frequency reduction = 66% vs. 82 %) [14], the stability of these outcomes after a period of several months of follow-up demonstrated by the present meta-analysis provides some assurance of a sustained effect. Both meta-analyses demonstrate that a reduction rather than cessation of FDS frequency is a common outcome after psychological treatment. FDS reduction and cessation may be important goals to differentiate between, as patients may experience a reduction of seizures as an indication of treatment failure if they (understandably) wanted seizure freedom.

A range of moderator variables were performed to explain the high observed heterogeneity across FDS treatment outcomes. The only significant moderator was treatment setting, which indicated that outpatient treatments are more effective than teletherapy; however, caution is warranted due to the limited sample size for teletherapy (*k*=2).

In terms of group level change, the current review identified that treatment studies vary markedly in how outcomes are reported. This poses a challenge for research synthesis as uniform metrics are required for meta-analysis. When assessing studies that provide data for median level change, we observed that seizure frequency reduced by 6.50 per month (CI=5.00-6.80), which represents >50% reduction. In assessing studies that provided data available for mean level change, we observed a pooled treatment effect size of *d*=0.53 for seizure frequency. This is a moderate effect size, and comparable to that observed in relation to a range of non-seizure outcome domains of psychological treatment of patients with FDS (*d*= 0.36-0.75) [5].

Although non-seizure outcomes have often been utilised and advocated in FDS treatment research [7], the current study found that seizure-specific outcomes have been reported more commonly. This is unsurprising given that seizures are the core presenting symptom for which patient arrive at treatment seeking relief for. However, we agree with previously formulated arguments that a multi-dimensional approach to outcome assessment in FDS treatment research is required, including measures assessing core neurological symptoms in addition to relevant non-seizure outcome measures [7]. It does not seem appropriate to base the assessment of the effectiveness of treatments for FDS on measures used and validated in patients with a different disorder (typically epilepsy).

Our narrative review of measures of seizure-related outcomes not directly related to frequency suggested that such measures are capable of capturing therapy associated changes.

Although unable to perform a meta-analysis, there is evidence to suggest that therapy may be helpful in changing the subjective experience of seizures, such as making them less intense or severe, or reducing their impact on other areas of life. Given the wealth of evidence from qualitative accounts revealing how distressing, frightening, and alarming FDS can be [74], this may be an important goal in itself for many patients with FDS. An important first step is to examine how best to standardise the measurement of this construct.

Compared to other neurological conditions, a relatively large amount of data has been collected documenting the use of psychological therapy in patients with FDS, however much of the data cannot be uniformly synthesised due to variation in how summary statistics are reported. The scope of meaningful synthesis is further impacted by the limited methodological quality of many studies conducted to date, with only a minority of samples investigated via an RCT design. While randomisation did not seem to emerge as a moderator of outcome in our analysis, the variability of research designs and treatments delivered reduced our ability to group data. Use of the GRADE highlighted issues with inconsistency across results, treatment comparisons and some imprecision resulting in low quality meta-analytic comparisons.

It is a limitation that we did not systematically contact authors and request additional data. This could have helped to reduce bias associated with selective reporting and incomplete datasets. Although inclusion of observational evidence is likely to provide strong representation of clinical practice, it also precludes inferences about experimental effects due to the inability to exclude other potential explanations for improvement.

**Conclusion:**

This article complements our previous meta-analysis demonstrating the likely positive effect of psychological therapy on non-seizure-related outcomes in adults with FDS [5]. The findings reported here suggest psychological interventions are associated with improvements in seizure-related outcomes.

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**Conflicts of Interest:**

Dr. Kerr writes paid review articles on this topic for Medlink Neurology; is a paid consultant for SK Life Sciences, Biohaven Pharmaceuticals (Data Management Committee), Cerebral Therapeutics (Scientific Advisory Board), EpiTel; and has collaborative or data use agreements with Eisai, Janssen, Johnson & Johnson, Radius Health, UCB, GlaxoSmithKline, and Jazz Pharmaceuticals. These companies had no part in the current work. We affirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with these guidelines.

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1. Seizure improvement is commonly considered to represent the rate of patients who make a ≥50% improvement in rate of seizures. [↑](#footnote-ref-1)
2. Note, we use *c* to denote the number of studies (or clusters) and *k* to denote the number of samples. [↑](#footnote-ref-2)