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Review

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

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ABSTRACT

Background: Psychological interventions are the most recommended treatment for functional/dissociative seizures (FDS); however, there is ongoing uncertainty about their effectiveness on seizure outcomes.
Methods: This systematic review and meta-analysis synthesises the available data. In February 2023, we completed a systematic search of four electronic databases. We described the range of seizure-related outcomes captured, used meta-analytic methods to analyse data collected during treatment and follow-up; and explored sources of heterogeneity between outcomes.
Results: Overall, 44 relevant studies were identified involving 1,300 patients. Most were categorised as being at 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 at the end of treatment was 40 %, while for follow-up it was 36 %. Pooled rates for ≥50 % improvement in seizure frequency were 66 % and 75 %. None of the included moderator variables for seizure freedom were significant. At the group level, seizure frequency improved during the treatment phase with a moderate pooled effect size ($d = 0.53$). FDS frequency reduced by a median of 6.5 seizures per month. There was also evidence of improvement of the other (non-frequency) seizure-related measures with psychological therapy, but data were insufficient for meta-analysis.
Conclusions: The findings of this study complement a previous meta-analysis describing psychological treatment-associated improvements in non-seizure-related outcomes. Further research on the most appropriate FDS-severity measure is needed.

1. Introduction

Functional / dissociative seizures (FDS), also known as psychogenic non-epileptic seizures (PNES) and non-epileptic attack disorder (NEAD), are one of the most prevalent types of functional neurological disorder (FND) [1]. FDS are episodes that behaviourally resemble epileptic seizures or syncope [2,3]. They can be conceptualised as an involuntary response to internal or external triggers associated with dysfunctional emotion regulation [4]. FDS are a common condition and account for approximately 15 % of patients referred to neurology clinics with seizure-like events [5].

A range of interventions for FND have been investigated, including psychological treatments [6,7], neuromodulation [8], anti-depressant medication [9] and physiotherapy [10]. Of these, psychological treatments have been studied most intensively, and surveys have shown that healthcare professionals around the world consider psychological

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interventions as the treatment of first choice for patients with this disorder [6,7].

A recent meta-analysis of psychotherapy in FDS has synthesised the evidence concerning non-seizure outcomes [11]. Across 32 studies (171 outcomes, 889 patients) covering a range of outcomes a pooled effect size of $d = 0.51$ (medium strength) was observed. The review revealed the great 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 [12,13], especially as measures of well-being have been found to be better predictors of health-related quality of life (HR-QoL) than seizure-related outcomes [2,14] and as such, may be more sensitive to psychological treatment-associated change [15].

However, given that patients with FDS typically present with seizures as their primary problem, and that the cessation or reduced frequency, intensity, severity, and bothersomeness of seizures are common treatment goals, 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. While no frequency or severity measure has currently been shown to provide a valid and reliable reflection of the direct impact of FDS, studies have indexed a broad range of measures of seizure -frequency, -freedom, -severity and -duration. Likewise, there has been heterogeneity in how authors have defined when treatment-associated change in FDS-related measures is clinically significant. Many have used measures and cut-off points originally employed for epileptic seizure disorders although it cannot be assumed that these perform in the same way in patients with FDS [15].

Two previous meta-analyses of seizure-specific outcomes of psychological interventions for adults with FDS have been attempted. In 2014, the authors of a Cochrane review of treatments for FDS (12 studies, 343 patients) stated that they were unable to carry out a meaningful meta-analysis due to the heterogeneity of study designs and interventions [16]. In 2017, Carlson and Perry performed a pair of proportional meta-analyses for psychological intervention studies in FDS (13 studies, 227 patients) [17]. Aggregated results demonstrated that 47 % of individuals were seizure-free by the end of treatment, whilst 82 % reported a $\geq$ 50 % improvement in seizure frequency.

There are several reasons why an update of the this previous meta-analysis is warranted: Since 2017, many further psychological treatment studies have reported outcomes in adults with FDS, the most important being the CODES study, a multi-centre randomised control trial (RCT) examining the addition of Cognitive Behavioural Therapy (CBT) to standardised neurological and psychiatric management of 386 patients with FDS [15]. In addition to improving the statistical power of the previous analysis through the inclusion of additional studies, we intended to provide greater analytic detail by including (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, this new review was inspired by developments in research synthesis methods allowing for more advanced quantitative procedures, including the synthesis of medians [18], and exploration of moderator variables.

More specifically, our investigation of the effectiveness of psychological interventions on seizure-related outcomes in adults with FDS 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 changes associated with treatment are maintained or increased at follow-up.

2. Method

2.1. Search strategy

The protocol was pre-registered (https://osf.io/2hmc3). Reporting follows the PRISMA guidelines [19]. 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 [11] (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 removal of duplicates, titles and abstracts were screened, followed by screening of full-text manuscripts. Forward and backward searches were performed using the R package *citation chaser* [20].

Inclusion and exclusion criteria are consistent with our previous review [11] (Supplementary Table 1). Studies were excluded when the sample was not adult-focused (average age $\leq$ 16 years), when most patients ($\geq$ 50 %) had comorbid epilepsy, or when the entire population did not receive psychological treatment. Any form of psychological intervention was accepted. Studies were required to identify patients as having FDS. The current review excluded studies that did not measure change in a seizure-related outcome. We sought to establish effectiveness in the acute stage of treatment *and* consolidation of treatment effects at follow-up. 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 (i.e., not at highly variable follow-up points).

2.2. Data collection

Full details of the data extraction are reported elsewhere [11]. Relevant data were extracted from manuscripts by CG while effect-size data were extracted in duplicate by CG & NP. Coding disagreements were handled through consultation and majority vote rules (GHR as the deciding vote). When manuscripts reported overlapping samples, preference was given using a decision hierarchy favouring robustness (i.e., intention-to-treat), sample size, and recency. Treatment and patient variables included in the moderator analysis (see Supplementary Table 2) included treatment *format* (individual, group), *setting* (outpatient, inpatient, and tele-therapy), *modality* (behavioural, cognitive-behavioural, relational [i.e., psychodynamic/psychoanalytic], body-focused, psychoeducation, or other), *duration/dosage* (short, medium, long), risk of bias, age and gender. Treatment duration/dose was coded[1] as short ($\leq$ six sessions), medium (7–13 sessions) and long ($\geq$14 sessions). In situations when the treatment modality was ambiguous, decisions were made in research meetings.

2.3. Risk of bias

The Cochrane Collaboration's tool for assessing risk of bias was used (ROB-2) [21]. The tool covers seven items focusing on bias related to (i) random sequence generation and (ii) allocation; performance bias examining (iii) blinding of participants and personal; detection bias exploring (iv) blinding of outcome assessment; attrition bias investigating (v) incomplete outcome data; reporting bias via (vi) selective reporting; and (vii) other sources of bias. 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. [11] 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

[1] See previous study for rationale behind duration/dosage coding.

indirectness of treatment estimate effects was further assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [22]. The GRADE assessments were completed by SK & MSB during a consensus review meeting (rated as high, moderate, low, or very low quality, Supplementary Table 3).

2.4. 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 differentiated 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*[2] (proportion), *-clusters*, *-intensity, -severity*, *-burden*, and *-bothersomness*. For metrics sufficiently represented ($\geq$ 10 study outcomes), meta-analyses were used to aggregate effect-sizes.

Outcome variability (e.g., mean, median, proportion) was expected and is a challenge for research synthesis as different summary statistics cannot easily be synthesised [23,24]. Our approach to this was: (i) data were 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 were available in multiple forms (e.g., both means and medians are reported) then multiple metrics were calculated; (iii) when raw data were provided, all forms were manually calculated; (iv) meta-analyses were domain-specific; (v) where enough data were 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 [25]. Standardised mean change (i.e., Cohen's *d*) was calculated using the *metafor* package. 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 [26]. 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 [24] with the *metamedian* package [18], and finally proportions were handled using the *metaprop* package [27]. Freeman-Tukey transformations of very low or high proportions were made [28].

For the primary meta-analysis (seizure freedom), we sought to explore under what conditions study outcomes vary significantly 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). Holm-Bonferroni corrections were applied to moderator p-values (within and between moderators) to account for multiple comparisons.

Forest plots were generated using the *ggplot2* [29] package. The Q statistic [30] and the proportion of variance not attributable to sample error (I^2) [31] were reported to assess heterogeneity. τ^2 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.

3. Results

3.1. Systematic search

One additional eligible study was identified in our 2023 search [32] and added to those from our 2022 search. This means the current review is based on 43 studies and 49 individual samples (Fig. 1) .[3] See Table 1 for a full list of included studies.

3.2. Study characteristics

Data were collected from 1300 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 %).

3.3. Risk of bias

Most studies were categorised as being at high ($c = 17$, 39.5 %) or medium ($c = 18$, 41.9%) overall risk of bias (Fig. 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., I^2), imprecise effects based on wide confidence interval boundaries, and small sample sizes.

3.4. 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.

3.4.1. Seizure frequency

Seizure frequency was examined in 42 out of 43 studies (the study excluded was [36]). 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 were collected via self-report either from the perspective of the patient, a carer or healthcare professional, there was great variation in how data were 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; 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.

3.4.2. Seizure intensity, severity and bothersomeness

Ten studies employed outcomes pertaining to intensity, severity or bothersomeness of seizures [15,32,40,43,45,51,64–66,71] (Supplemental Table 5 & 6). While all measures were self-reported, one study used the full PNES (psychogenic non-epileptic seizure) scale [72] which considers FDS motor manifestations as an indicator of severity [32]. Measures ranged from asking participants a single-item to the use of

[2] Seizure improvement is commonly considered to represent the rate of patients who make a $\geq$ 50% improvement in rate of seizures.

[3] Note, we use *c* to denote the number of studies (or clusters) and *k* to denote the number of samples.

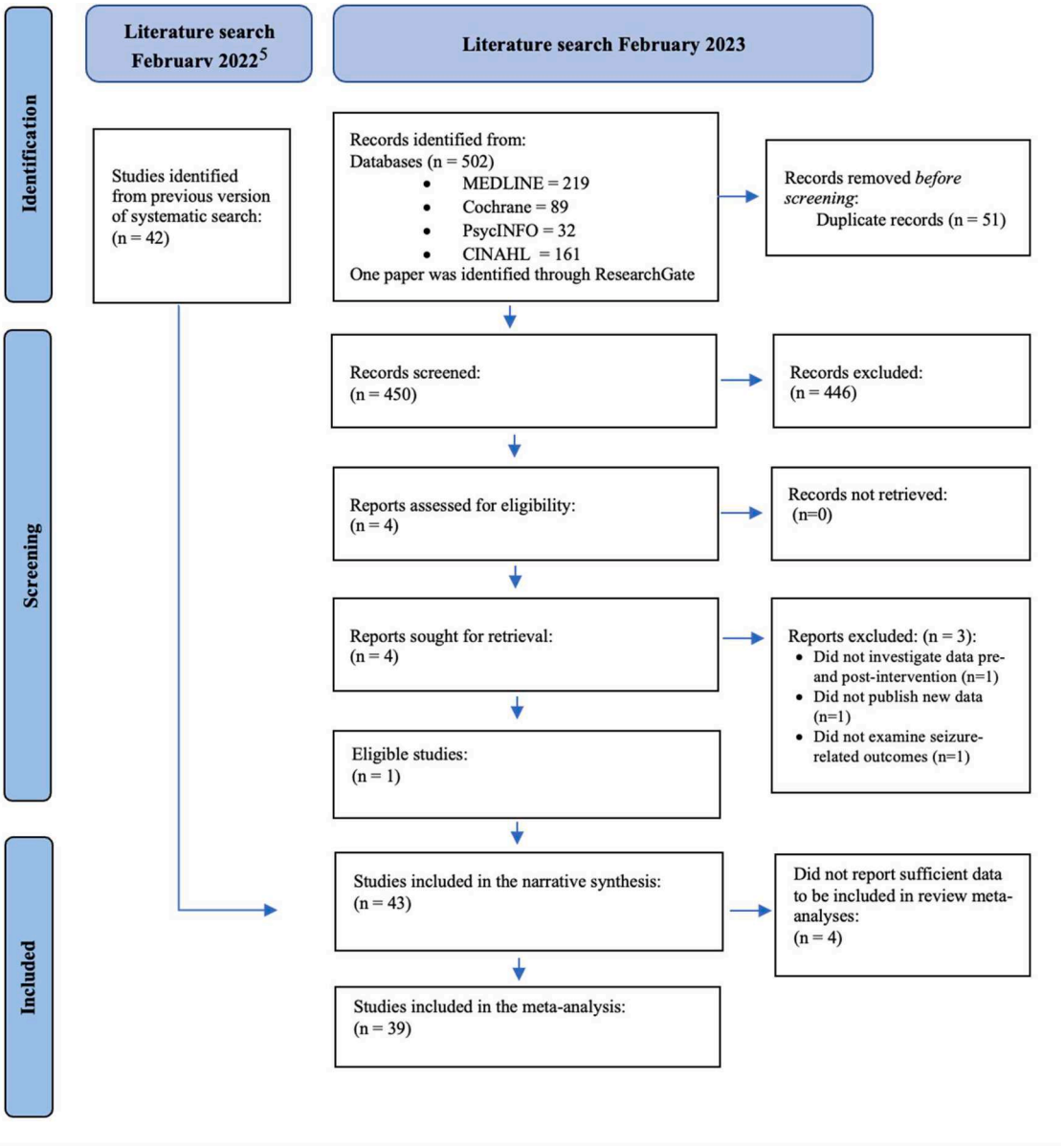

Fig. 1. PRISMA flow diagram of studies throughout the review.

20-items as part of the Liverpool Seizure Severity Scale [73].

Five of the studies reported a significant improvement in scores [15,32,40,64,71], and three also described an improvement which was either not statistically significant [15] or for which the significance level was not reported [51,65]. Two studies reported no significant change and did not report absolute values [43,66]. One study did not discuss the results relating to intensity of FDS [45]. Although the number of studies reporting seizure severity, intensity, and bothersomeness met our minimum threshold, the variation in reporting of outcomes precluded meta-analysis.

3.4.3. Seizure duration

This was examined in one study [40]. 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 ($p = 0.1$).

3.4.4. 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.

3.5. Meta analyses

Of the 43 studies, 39 reported quantitative outcomes with sufficient detail for inclusion in a meta-analysis (studies excluded were [43,50,66,74]). 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.

3.5.1. Seizure freedom

Overall, 28 studies ($k = 44$) assessed seizure freedom with 42

Table 1
Studies included in the meta-analysis († = same sample investigated: ‡, §, ϕ, ˆ, §, 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	32×90 min group Sessions	Individual + Group	Outpatient	High
Baslet [39]	USA	6 (6)	NR	Case series	C-B	12 sessions	Individual	Outpatient	High
Baslet [40]†	USA	26 (23)	46.4 (16.2)	Prospective uncontrolled trial	C-B	12 sessions	Individual	Outpatient	Medium
Baslet [40]†	USA	26 (23)	46.4 (16.2)	Prospective uncontrolled trial	C-B	12 sessions	Individual	Outpatient	Medium
Ben—Naim [41]	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 [32]	India	16 (12)	37.9 (18–58)	Case series	Brief online psychotherapy	10 sessions	Individual	Outpatient	High
Bullock [42]	USA	19 (18)	44.5 (NR)	Prospective naturalistic design	Dialectical Behavioural Therapy	Flexible (mean = 20.5 weeks)	Group	Outpatient	High
Chen [43]*	USA	20 (NR)	50.8 (12.3)	Pilot RCT	Psycho-education	3 × 1.5 hour sessions	Group	Outpatient	Medium
Conwill [44]	UK	10 (7)	33.1 (11.6)	Pilot study / service evaluation	C-B	4 group sessions	Group	Outpatient	Medium
Cope [45]	UK	25 (21)	NR	Evaluation	C-B	3 sessions	Group	Outpatient	Medium
DeLeuran [46]	Denmark	42 (36)	36 (18)	Retrospective study	C-B	10–15 sessions (mean = 12; SD = 5.7)	Individual	Outpatient	High
Duncan [47]	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 [48]	UK	16 (14)	34.9 (13.4)	Open, prospective trial	C-B	12 sessions	Individual	Outpatient	Medium
Goldstein [49]	UK	31 (24)	37.4 (12.6)	RCT	C-B	12 sessions	Individual	Outpatient	Low
Goldstein [15]	UK	185 (140)	37.3 (14.2)	Pragmatic, parallel-arm, multicentre RCT	C-B	12+1 (median = 13)	Individual	Outpatient	Low
Khattak [50]*	Pakistan	50 (NR)	24.3 (8.8)	RCT	Behavioural	NR	Individual	Inpatient	High
Korman [51]	Argentina	23 (20)	NR	Evaluation	Psychoeducation	1 psychoeducation session	Individual	Outpatient	High
Kuyk [52]	Netherlands	22 (NR)	30.6 (10.8)	Uncontrolled, prospective inpatient treatment program	C-B	Mean = 4.8 months	Individual + Group	Inpatient	High
Labudda [53]	Germany	80 (60)	33.8 (13.6)	Prospective, naturalistic evaluation	C-B	mean = 64.5 days	Individual + Group	Inpatient	High
LaFrance [54]	USA	20 (17)	36 (10.4)	Prospective non-randomised clinical trial	C-B	12 sessions	Individual	Outpatient	Medium
LaFrance [9]ϕ	USA	9 (7)	37.9 (11.5)	Pilot RCT at 3 sites	C-B	12 sessions	Individual	Outpatient	Low
LaFrance [9]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

(*continued on next page*)

Table 1 (*continued*)

Study	Country	N (female)	Age M (SD/ range)	Design	Modality	Dosage	Delivery	Setting	RoB
Mayor [57]	UK	29 (NR)	37 (23–38)	Prospective, multicentre, feasibility study	Psycho-education	4 × 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 min 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]ˆ	Mexico	9 (NR)	NR	RCT	C-B	36 weekly sessions	Individual	Outpatient	Medium
Santiago-Trevino [62]ˆ	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 [27]*	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 h long	Group	Outpatient	Medium
Senf-Beckenbach [64]§	Germany	22 (18)	36.6 (12.1)	Pilot RCT	Body focused	10×90-minute sessions	Group	Outpatient	Low
Senf-Beckenbach [64]§	Germany	20 (12)	32.8 (13.2)	Pilot RCT	Guided self-help	10×90-minute sessions	Group	Outpatient	Low
Streltzov [65]	USA	6 (6)	36.2 (9)	Non-randomised pilot study	C-B	8 sessions	Group	Outpatient	Medium
Thompson [66]*	USA	19 (11)	33 (NR)	Pilot RCT	Psychoeducation	1 session	Individual	Inpatient	Low
Tilahaun [67]	USA	64 (47)	36.3 (11.3)	Retrospective evaluation	C-B	7–12 sessions	Individual	Outpatient	Medium
Tolchin [68]σ	USA	31 (26)	40.7 (14.3)	RCT	C-B	12 sessions	Individual	Outpatient	Low
Tolchin [68]σ	USA	29 (23)	39.6 (16.8)	RCT	C-*B* + motivational interviewing	13 sessions	Individual	Outpatient	Low
Wiseman [69]	UK	25 (13)	41.8 (18.1)	Multicentre evaluation / service evaluation	Psychoeducation	4 × 1-hour sessions	Group	Outpatient	Medium
Zaroff [70]	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.

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 in the random-effects meta-analysis was 40 % (95 %CI=32–48 %, GRADE=low) across 28 studies ($N = 673$) (Fig. 3a). 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 (τ^2) was 0.03. The proportion of variation in effect-sizes that could not be attributed to sampling error (I^2) 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).

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). None of the included moderators produced a significant finding following application of Holm-Bonferroni.

Follow-up effect: Across the 12 studies ($k = 14, n = 486$) included in the meta-analysis that measured seizure freedom at follow-up (mean=11.2 months post-treatment end [range=1 week to 42 months]), the pooled freedom rate was 36 % (95 %CI=26–46 %) (Fig. 3b). Heterogeneity was significant (Q(df=13),=51.3, p=<0.001), the variance component was $\tau^2 = 0.02$, and the I^2 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.

3.5.2. 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*

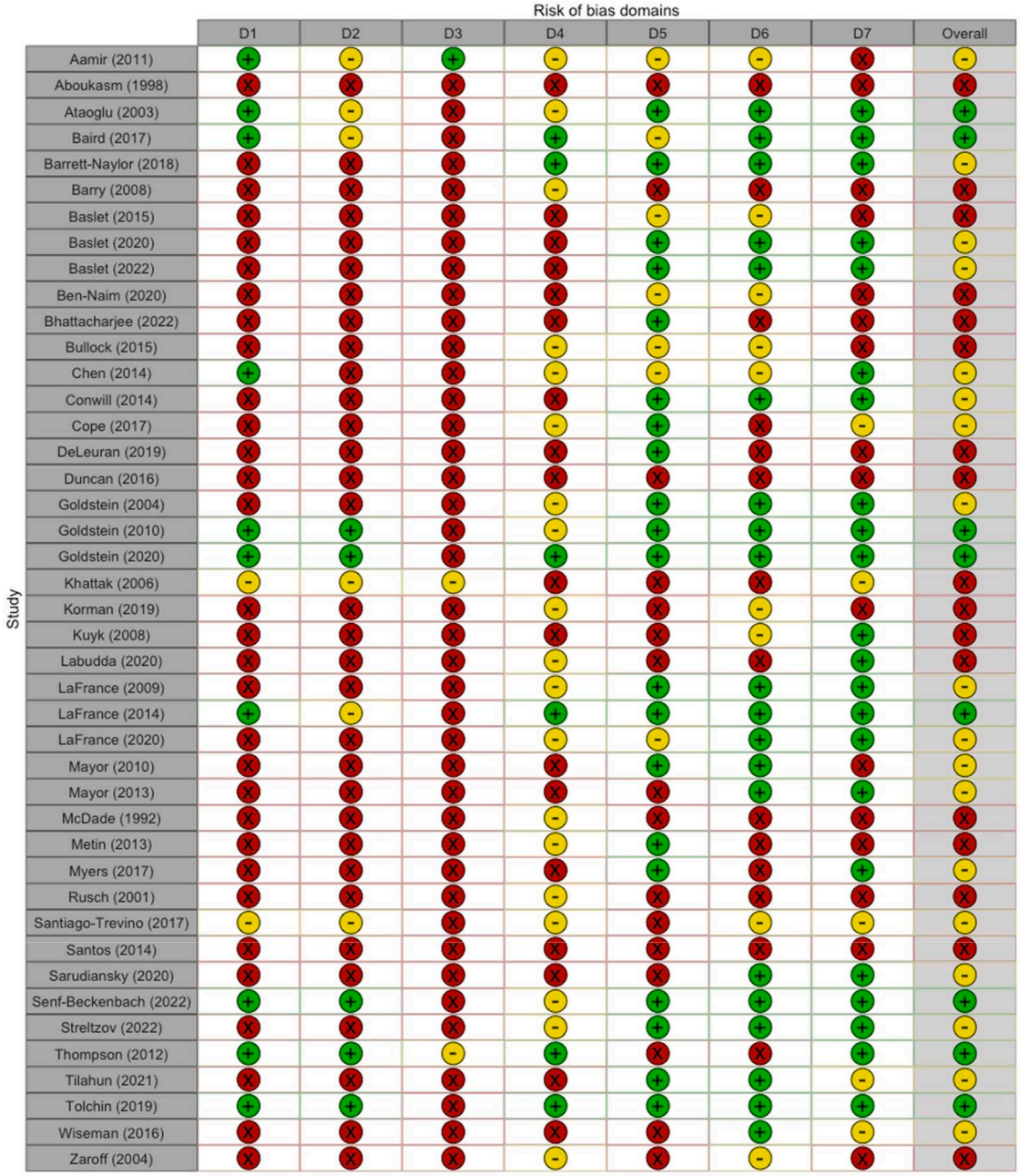

Fig. 2. *Risk of bias ratings for the studies included in the systematic review, as measured using the ROB-2.0* – red cross = high risk, yellow dash = unclear risk, green plus = low risk, *D1= Random sequence generation, D2= Allocation concealment, D3 = blinding of participants, D4 = Blinding of outcome assessment, D5 = Incomplete data, D6 = Selective reporting, D7 = Other sources of bias.*

= 23, *N* = 568), was 66 % (95 % CI=54–77 %, GRADE=low) (Fig. 4a). Heterogeneity was significant (Q[df = 22]=141.5, *p*=<0.001), the variance component was τ^2 = 0.06, and the I^2 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.

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) (Fig. 4b). The mean duration of follow-up was 9.4 months post-treatment (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 I^2 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.

Group level change (mean and median): Group level seizure frequency data were 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 [0.31,1.2], GRADE= very low). The degree of variability not due to sampling error (I^2) 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

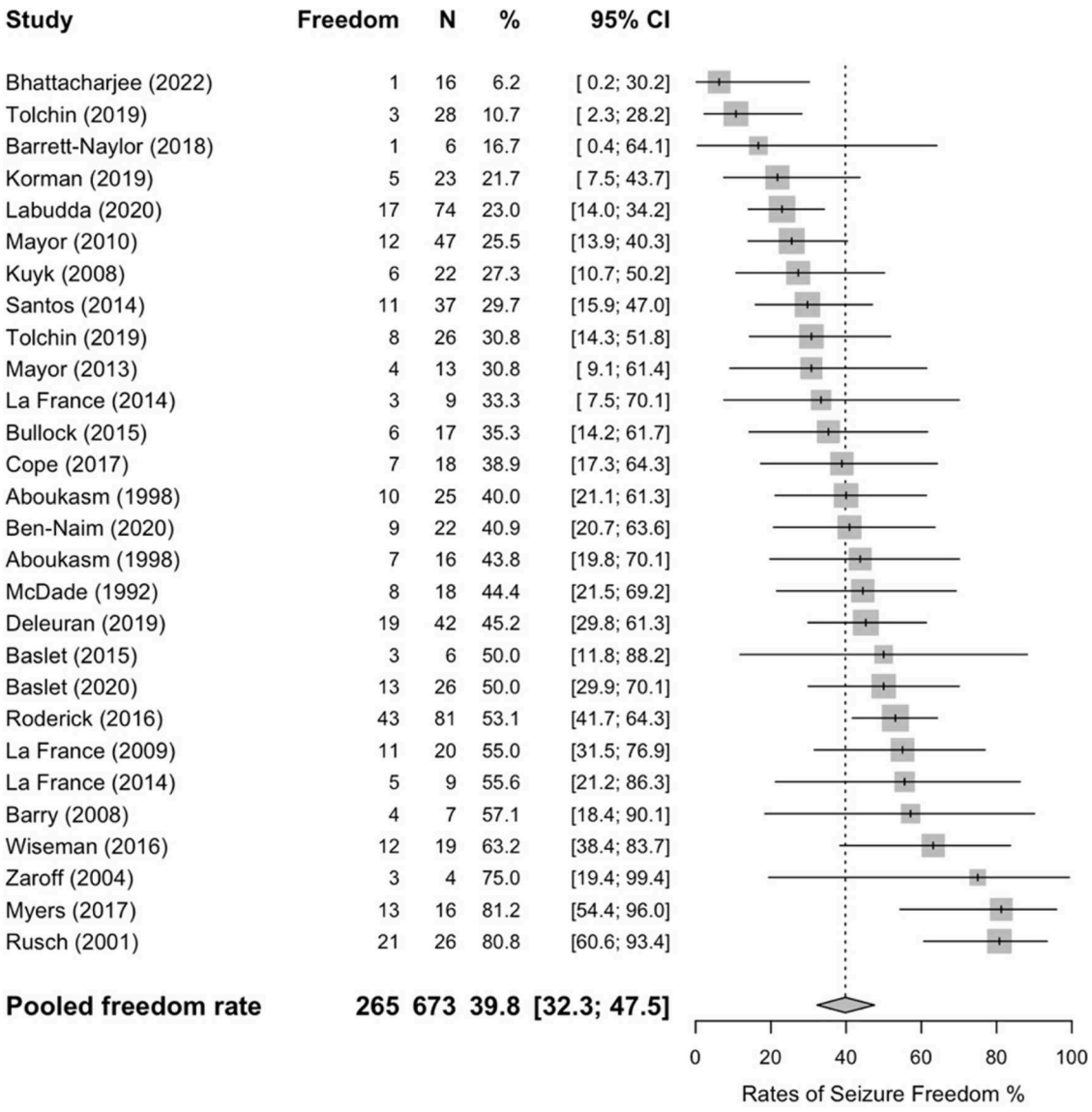

Fig. 3a. *Forest plot of seizure freedom rates at the end of treatment (pre-* versus *post-treatment). Error bars and the width of the diamond reflect the 95 % Confidence Interval (95 % CI) within each study and for the meta-analysis, respectively.* CI = Confidence intervals (95 %): *N*=number of participants.

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], I^2=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=8–12.5) seizures per month. The seizure frequency (weighted median of the difference of medians) improved by 6.5 seizures per month during psychological treatment (CI=5–6.8).

4. 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%) [17], the stability of the psychological-treatment associated improvements 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 the commonest 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. In real terms, approximately two in three patients 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.

There was no evidence that treatment -delivery, -duration, -modality, study risk of bias, setting, patient age or patient gender were moderators of treatment effect. Before Holm-Bonferroni corrections were applied, the treatment setting had been the only significant moderator.

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 6.5 per

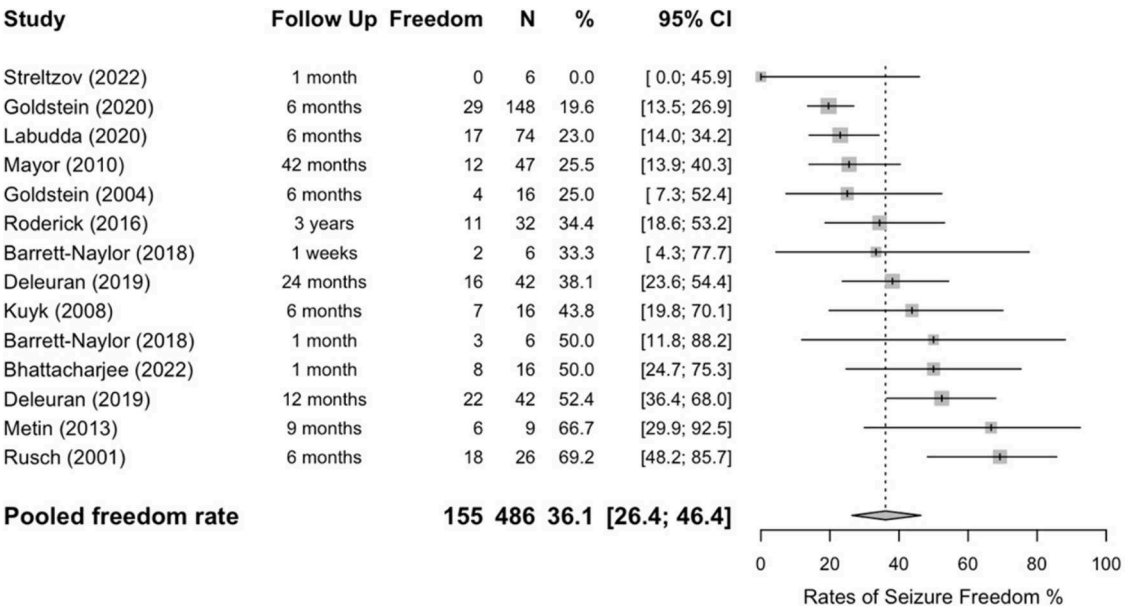

Fig. 3b. *Forest plot of seizure freedom rates at the end of treatment (follow-up),* CI = Confidence intervals (95 %): *N*=number of participants.

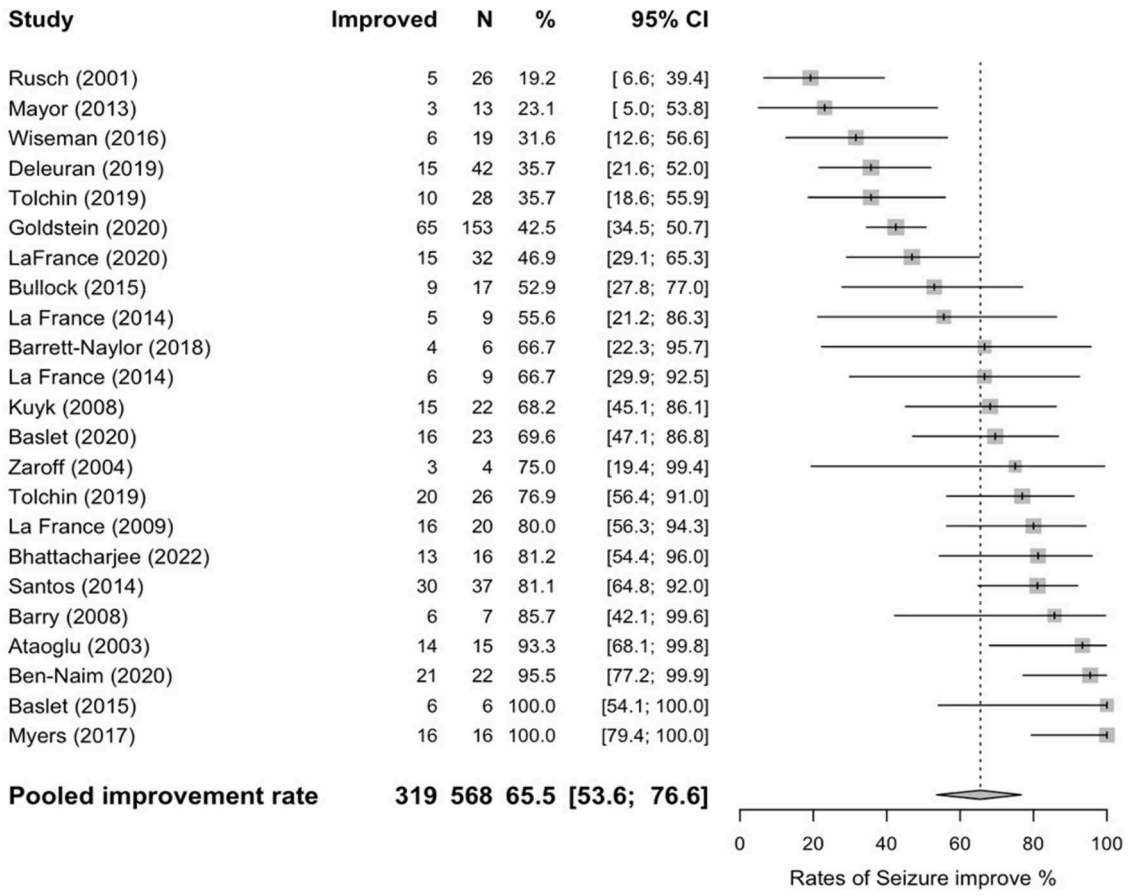

Fig. 4a. *Forest plot of seizure improvement rates at the end of treatment (acute treatment phase),* CI = Confidence intervals (95 %): *N*=number of participants.

month (CI=5–6.8), 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) and assessed in our previous meta-analysis [11].

Although non-seizure outcomes have often been utilised and advocated in FDS treatment research [13], 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 patients arrive at treatment seeking relief for. However, we agree

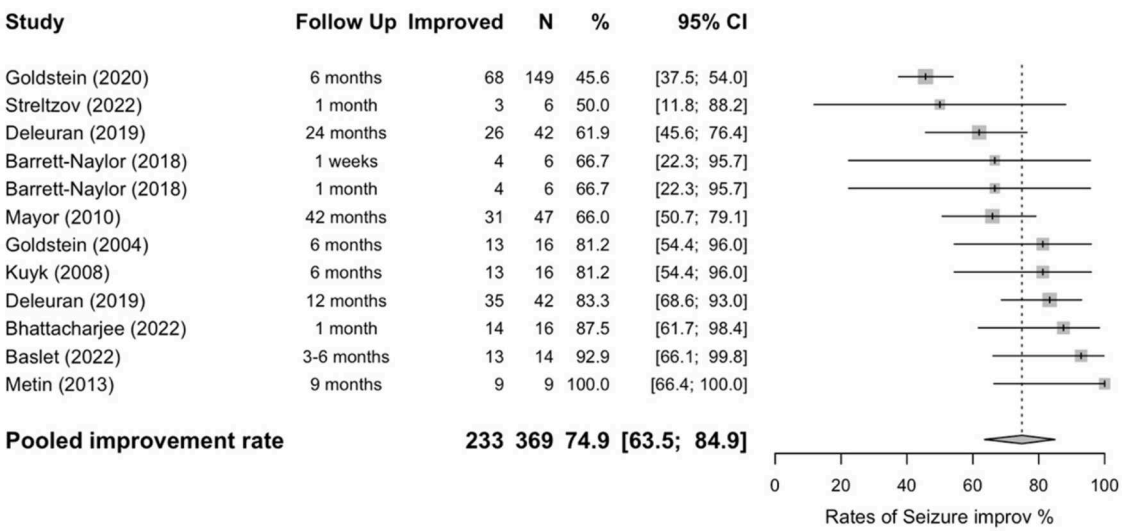

Fig. 4b. *Forest plot of seizure improvement rates at follow up.* CI = Confidence intervals (95 %): *N*=number of participants.

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 [13].

Our narrative review of measures of seizure related outcomes not directly related to frequency (severity/ intensity/ bothersomeness, duration and cluster) suggested that such measures are capable of capturing therapy associated changes. However, due to the limited amount of data and the varying ways in which outcomes were measured we were unable to perform a meta-analysis. Nevertheless, 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 collected from qualitative accounts revealing how distressing, frightening, and alarming FDS can be [75], this may be an important goal in itself for many patients with FDS seeking care. An important first step is to examine how best to standardise the measurement of this construct.

Unsurprisingly, all included studies relied upon self-report measures of seizures, as opposed to objective measurement technologies (e.g., wearable devices - we use the term objective measures to mean methods that are quantifiable, impartial, and measured using a scientific instrument [76]. This is despite limitations which have been reported in classifying and counting FDS. Indeed, in epilepsy studies, self-reported seizure frequency has been proven to be highly unreliable with a mean of 30 % of seizures remaining unreported [77]. In the current review, even when studies focused on the same seizure-related construct to examine (e.g., seizure frequency), there remained variation in how it was measured (e.g., temporal unit, diary method) and reported (proportion, median, mean). This may indicate that researchers are uncertain how best to assess, monitor, and report FDS treatment outcomes. This is particularly likely as no formal measures that have been validated for this purpose in this patient group. This notion is further supported by the finding that many studies used more than one measure or metric. As previously discussed, this poses methodological challenges in research synthesis as the different approaches to describing change (proportion, median, mean) prevents inclusion of all studies in a single meta-analysis. 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. Although FDS are a clinically heterogenous population, it was not possible to differentiate between sub-groups. It is conceivable that psychological treatments are more effective for some sub-populations than for others. Finally, while our analysis includes multiple treatment modalities, there was insufficient overlapping data to compare the effectiveness of each treatment modality.

The findings reported here suggest psychological interventions are associated with improvements in seizure-related outcomes, namely measures of seizure frequency, intensity, severity, bothersomeness, duration and clusters. Due to the heterogeneity of research methods, the type of analyses we were able to perform were limited. Further research is required to identify how to best standardise the measurement and reporting of seizure-related outcomes in FDS.

Declaration of competing 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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2024.05.016.

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