Cognitive–behavioural therapy compared with standardised medical care for adults with dissociative non-epileptic seizures: the CODES RCT

Laura H Goldstein,[1*] Emily J Robinson,[2,3] Izabela Pilecka,[1] Iain Perdue,[1] Iris Mosweu,[4] Julie Read,[1] Harriet Jordan,[1] Matthew Wilkinson,[5,6] Gregg Rawlings,[7] Sarah J Feehan,[1] Hannah Callaghan,[8] Elana Day,[1] James Purnell,[1] Maria Baldellou Lopez,[1] Alice Brockington,[9] Christine Burness,[10] Norman A Poole,[11] Carole Eastwood,[1] Michele Moore,[12] John DC Mellers,[6] Jon Stone,[8] Alan Carson,[8] Nick Medford,[6] Markus Reuber,[13] Paul McCrone,[4] Joanna Murray,[14] Mark P Richardson,[15] Sabine Landau[2†] and Trudie Chalder[16†]

[1]Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[2]Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[3]School of Population Health and Environmental Sciences, King's College London, London, UK
[4]King's Health Economics, King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, UK
[5]Canterbury Christ Church University, Salamons Institute for Applied Psychology, Tunbridge Wells, UK
[6]South London and Maudsley NHS Foundation Trust, London, UK
[7]School of Clinical Psychology, University of Sheffield, Sheffield, UK
[8]Department of Clinical Neuroscience, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK
[9]Department of Neurology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
[10]The Walton Centre NHS Trust, Liverpool, UK
[11]Department of Neuropsychiatry, St George's Hospital, South West London and St George's NHS Mental Health NHS Trust, London, UK
[12]Centre for Social Justice and Global Responsibility, School of Law and Social Sciences, London South Bank University, London, UK

[13]Academic Neurology Unit, Royal Hallamshire Hospital, University of Sheffield, Sheffield, UK
[14]Department of Health Services & Population Research, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[15]Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[16]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

*Corresponding author laura.goldstein@kcl.ac.uk
†Joint last author

Declared competing interests of authors: Alan Carson reports being a paid editor of the *Journal of Neurology, Neurosurgery and Psychiatry*, and is the director of a research programme on functional neurological disorders; he gives independent testimony in court on a range of neuropsychiatric topics (50% pursuer, 50% defender). Sabine Landau is a paid editor of the *Journal of Child Psychology and Psychiatry*. Markus Reuber is the paid editor-in-chief of *Seizure – European Journal of Epilepsy* and receives authorship fees from Oxford University Press (Oxford, UK) in relation to a number of books about dissociative seizures. Markus Reuber benefited from the support of the National Institute for Health Research (NIHR) Sheffield Biomedical Research Centre (Translational Neuroscience). Mark P Richardson reports funding from Xenon Pharma (Burnaby, BC, Canada). Jon Stone reports independent expert testimony work for personal injury and medical negligence claims, royalties from UpToDate for articles on functional neurological disorders and runs a free non-profit self-help website, www.neurosymptoms.org. Jon Stone is also supported by an NHS Scotland NHS Research Scotland (NRS) Career Fellowship. Jon Stone and Alan Carson also acknowledge the financial support of NHS Research Scotland through the Edinburgh Clinical Research Facility. Laura Goldstein, Trudie Chalder and Sabine Landau report support from the NIHR Maudsley Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and King's College London. Emily J Robinson received salary support from the NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. Gregg Rawlings is entitled to authorship fees from Oxford University Press for several books on dissociative seizures.

Published June 2021
DOI: 10.3310/hta25430

Scientific summary

The CODES RCT

Health Technology Assessment 2021; Vol. 25: No. 43
DOI: 10.3310/hta25430

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Dissociative seizures are paroxysmal events superficially resembling epileptic seizures or syncope, but with typical diagnostic characteristics that distinguish them from these or other medical disorders. Dissociative seizures represent the most common functional neurological disorder and may co-occur with epilepsy. In the *International Classification of Diseases*, Eleventh Edition, they are currently classified as dissociative neurological symptom disorder, and in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, they are currently classified as conversion (functional neurological symptom) disorder. They are also referred to as psychogenic non-epileptic seizures, among other terms.

It has been estimated that between 12% and 20% of adults presenting at epilepsy clinics have dissociative seizures, posing diagnostic and management challenges. Incidence in the UK is approximately 4.9 per 100,000 people per year. People with dissociative seizures frequently present with comorbid psychiatric disorders, may have a low quality of life and often have poor outcomes. Although the UK National Institute for Health and Care Excellence recommends that when dissociative seizures are identified or suspected in epilepsy services patients should be referred to psychiatric and psychological services for further assessment and management, there is no consistent care pathway in the UK for these patients. Nonetheless, psychological interventions are generally accepted to be the treatment of choice for dissociative seizures. A UK-based pilot randomised controlled trial provided preliminary evidence of efficacy of dissociative seizure-specific cognitive–behavioural therapy; however, there is little robust evidence, and adequately powered multicentre randomised controlled trials have been lacking.

Objectives

In response to the National Institute for Health Research Health Technology Assessment programme's commissioned call, we set out to determine the clinical effectiveness and cost-effectiveness of dissociative seizure-specific cognitive–behavioural therapy by evaluating, at 12 months post randomisation:

- the effectiveness of cognitive–behavioural therapy (plus standardised medical care) compared with standardised medical care alone in reducing monthly dissociative seizure frequency (primary outcome)
- the effectiveness of cognitive–behavioural therapy plus standardised medical care compared with standardised medical care alone in relation to reducing dissociative seizure severity and improving seizure freedom, psychosocial and psychological well-being, and health-related quality of life (secondary outcomes)
- participants' global clinical improvement and satisfaction with treatment (secondary outcomes)
- differences in resource use and cost-effectiveness of cognitive–behavioural therapy plus standardised medical care compared with standardised medical care alone (secondary outcomes).

We also planned a process evaluation, involving either nested qualitative studies or an online survey, investigating patients' and healthcare professionals' (neurologists, psychiatrists and cognitive–behavioural therapists) experiences of receiving and delivering treatment, respectively, in the trial. Finally, we sought to evaluate the treatment fidelity of the dissociative seizure-specific cognitive–behavioural treatment and to measure any adverse events occurring during the study.

Methods

Design

We undertook a pragmatic, multicentre, parallel-arm, mixed-methods randomised controlled trial with clinical and health economic evaluation. Patients were randomised to receive standardised medical care alone or to receive 12 sessions of dissociative seizure-specific cognitive–behavioural therapy (plus one booster session) with standardised medical care. The primary outcome was monthly dissociative seizure frequency at 12 months post randomisation. The researchers collecting outcomes and the statistician were blind to treatment allocation. The trial manager, chief investigator, patients and treating clinicians were unblinded.

Settings

Secondary and tertiary care neurology, liaison psychiatry/neuropsychiatry and cognitive–behavioural therapy services in England, Scotland and Wales participated.

Participants

Inclusion criteria for the screening phase

Adults were included who were aged ≥ 18 years who had experienced dissociative seizures within the previous 8 weeks with a diagnosis supported by either video electroencephalography or clinical consensus; had no recorded intellectual disability; were able and willing to complete seizure diaries and questionnaires, and attend a psychiatric assessment 3 months after receiving their dissociative seizure diagnosis in the study; and were able to provide informed consent.

Exclusion criteria for the screening phase

People were excluded if they had experienced epileptic seizures in the previous year as well as dissociative seizures; were unable to independently complete seizure records or questionnaires; met criteria for current alcohol or drug dependence according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; had insufficient fluency in the English language to complete questionnaires or receive cognitive–behavioural therapy without an interpreter; were attending cognitive–behavioural therapy sessions for another disorder, if this would be continuing at the time of the psychiatric assessment; or had previously received cognitive–behavioural therapy for dissociative seizures at one of the centres participating in the randomised controlled trial.

Inclusion criteria for the randomised controlled trial

Adults were included who were aged ≥ 18 years recruited into the study in the screening stage and willing to continue completing seizure diaries and questionnaires; had provided data about their seizure occurrence on a regular basis in the screening phase; were willing to attend weekly or fortnightly cognitive–behavioural therapy sessions if randomised to cognitive–behavioural therapy; the patient and their clinician considered randomisation to be acceptable in this case; and were able to provide written informed consent.

Exclusion criteria for the randomised controlled trial

People were excluded if they were experiencing epileptic seizures plus dissociative seizures; had no dissociative seizure occurrence in the 8 weeks preceding the psychiatry assessment; had previously received cognitive–behavioural therapy for dissociative seizures at one of the centres participating in the randomised controlled trial; were currently receiving cognitive–behavioural therapy for another disorder; had active psychosis; met the criteria for current alcohol or drug dependence according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; were currently using benzodiazepines exceeding the equivalent daily dose of 10 mg of diazepam; were thought to be at high risk of imminent self-harm following the psychiatry assessment or following the structured psychiatric assessment administered by the research worker, followed up by a discussion with the patient's psychiatrist; and already had a diagnosis of factitious disorder.

Recruitment

There was a two-stage, written, informed consent process. Patients were initially consented to a screening phase from 27 neurology/specialist epilepsy services in England, Scotland and Wales. The patients were asked by research workers for seizure diary data every 2 weeks for about 3 months. They then underwent an assessment by a liaison or neuropsychiatrist in one of 17 services. The screening phase allowed confirmation that dissociative seizures persisted beyond diagnosis and permitted appointments with psychiatrists to be arranged. Eligible and willing patients were subsequently consented to the randomised controlled trial, and the baseline assessment was undertaken prior to randomisation. Seizure diary data were again collected every 2 weeks.

Randomisation

Participants were randomised via an online system hosted by the King's Clinical Trials Unit. Randomisation used a 1 : 1 ratio, was stratified by neuro/liaison psychiatry sites and used randomly varying block sizes within sites.

Interventions

Standardised medical care was delivered by the diagnosing neurologist and subsequently by the assessing/treating psychiatrist. The neurologist and psychiatrist were provided with guidelines for delivering the diagnosis and explaining the disorder, as well as study-specific information booklets about dissociative seizures to give to patients. They were given other guidelines for providing patients with further information. Psychiatrists were asked to provide general support and review, but not to use cognitive–behavioural therapy techniques. Although not prescribed, we anticipated that, following the initial neurology assessment and the psychiatric assessment, patients might receive up to two neurology standardised medical care sessions and three to four psychiatry sessions of standardised medical care.

Dissociative seizure-specific cognitive–behavioural therapy was delivered by therapists already trained in cognitive–behavioural therapy who were working in one of 18 cognitive–behavioural therapy services and were drawn from a range of health professions and levels of experience; they received specific training (a 3-day workshop or individual training) to deliver our model of dissociative seizure-specific cognitive–behavioural therapy. Therapists had a therapy manual outlining the content of 12 sessions of cognitive–behavioural therapy plus one booster session that was due to occur 9 months post randomisation. Patients were provided with a handbook describing various interventions. Therapists were allocated to telephone supervision groups that met 4- to 6-weekly. With patients' consent, therapy sessions were audio-recorded.

Compliance with cognitive–behavioural therapy was defined as patients attending at least nine sessions. Treatment fidelity was assessed by two independent raters who blindly rated a random selection of recorded therapy sessions from 36 out of the 39 therapists delivering therapy.

Outcome measures

The effectiveness of our interventions was evaluated at 12 months post randomisation. In addition to baseline recording, measures were collected at 6 months post randomisation to assist with data modelling and participant retention. Our primary outcome was self-reported monthly dissociative seizure frequency. Secondary outcomes included self-reported measures of how severe and bothersome seizures were; the longest number of seizure-free days in the last 6 months of the study; the proportion of participants showing seizure freedom during the last 3 months of the study; the proportion showing > 50% reduction in dissociative seizure frequency; carers'/informants' ratings of patients' dissociative seizures (not analysable owing to insufficient data); health-related quality of life (assessed using the Physical and Mental Component Summary scores from the Short Form questionnaire-12 items, version 2 and the visual analogue scale from the EuroQol-5 Dimensions, five-level version); psychosocial functioning (assessed using the Work and Social Adjustment Scale); anxiety (assessed using the Generalised Anxiety Disorder-7), depression (assessed using the Patient Health Questionnaire-9) and general psychological

distress (assessed using the Clinical Outcome Routine Evaluation-10), as well as somatic symptoms (assessed using the modified Patient Health Questionnaire-15); self-rated and clinician-rated measures of clinical global improvement; and patient-rated treatment satisfaction. We obtained measures of quality-adjusted-life-years using the EuroQol-5 Dimensions, five-level version, and the utility score derived from the Short Form questionnaire-12 items, version 2. Service use was measured with the Client Service Receipt Inventory. Hospital service use was also estimated using objective data sets obtained from NHS Digital, NHS National Services Scotland Information Services Division and NHS Wales Informatics Service. Adverse events were reviewed by three independent clinicians.

Sample size

Our initial power calculation indicated a randomisation target of 298 participants to detect an effect size of $d = 0.42$ in terms of dissociative seizure frequency. This required a target of 501 people from whom to recruit those to be randomised. These targets were increased to 356 for the randomised controlled trial and 698 for the screening phase after initial assumptions were reviewed during recruitment; slightly fewer participants were entering the randomised controlled trial from the screening phase and fewer randomised participants were then completing follow-up data than expected.

Statistical analysis

The analyses followed a statistical analysis plan that was agreed with the Trial Steering Committee and later published. Multiple imputation, specifically multivariate imputation by chained equations, was used to produce inferences that are valid under a realistic missing-at-random data-generating process. This was necessary because non-compliance with therapy was found to be predictive of missing values in the primary outcome variable (dissociative seizure frequency at 12 months). For overdispersed count variables (dissociative seizure frequency and the secondary outcome seizure freedom), negative binomial distributions were assumed. For continuous and discrete secondary outcome variables, for example seizure severity or bothersomeness, modelling was based on normal distributions. Finally, logistic regression models were employed for binary secondary outcomes.

Economic evaluation

A health and social care perspective was used. Intervention costs were calculated and combined with costs derived from self-report service use data and standard unit costs. Cost-effectiveness was assessed by combining cost with quality-adjusted life-years derived from the EuroQol-5 Dimensions, five-level version. Uncertainty was addressed using cost-effectiveness planes and acceptability curves. Secondary analyses used societal costs (i.e. including lost work and informal care), hospital costs derived from routine sources and combined costs with reductions in seizures. Sensitivity analyses estimated cost-effectiveness using the Short Form questionnaire-6 Dimensions (i.e. utility score).

Results

In the screening phase, 698 adults with dissociative seizures were recruited across 27 neurology/specialist epilepsy services between October 2014 and February 2017. A total of 368 adults were then randomised from 17 psychiatry services between January 2015 and May 2017. Of these, 182 were allocated to standardised medical care alone and 186 to cognitive–behavioural therapy plus standardised medical care. Data were analysed on an intention-to-treat basis. Overall, 85% of the sample provided primary outcome data [standardised medical care, $n = 157/182$ (86%); cognitive–behavioural therapy plus standardised medical care, $n = 156/186$ (84%)]. Compliance with therapy was met by 140 out of 186 (75.3%) patients who were randomised to cognitive–behavioural therapy plus standardised medical care.

Of the 368 randomised patients, 72.3% were female, the median age was 35 years (interquartile range 25–48 years), the median age at onset of dissociative seizures was 29 years (interquartile range 19–42 years) and the median duration of the disorder was 3 years (interquartile range 1–8 years). Fifty-three per cent of patients received this diagnosis via video electroencephalography. Sixty-seven per cent of patients

had predominantly hyperkinetic rather than predominantly hypokinetic seizures. One-third of patients were in employment or education, 65.5% had previously sought help for a mental health problem and 27.4% self-reported a previous epilepsy diagnosis. In addition, 69.3% of patients had at least one comorbid psychiatric diagnosis, as measured using the Mini-International Neuropsychiatric Interview.

Evaluations of cognitive–behavioural therapy treatment fidelity indicated good levels of adherence to the CODES (COgnitive behavioural therapy vs. standardised medical care for adults with Dissociative non-Epileptic Seizures: a multicentre randomised controlled trial) therapy manual, the therapeutic alliance and whether or not the therapy being delivered was cognitive–behavioural therapy. Median scores all fell in the upper end of the respective scales. For dissociative seizure-specific techniques, scores were more in the mid-range for the ratings.

At 12 months post randomisation, the between-group difference in monthly dissociative seizure frequency was not statistically significant at the 5% level (estimated incidence rate ratio 0.78, 95% confidence interval 0.56 to 1.09; $p = 0.144$). All clinical secondary outcomes were in the direction of greater benefit from cognitive–behavioural therapy plus standardised medical care than from standardised medical care alone. Nine out of 16 treatment effects reached statistical significance at the unadjusted 5% level, including five that attained p-values ≤ 0.001, namely the longest number of consecutive dissociative seizure-free days in the final 6 months of the study (incidence rate ratio 1.64, 95% confidence interval 1.22 to 2.20; $p = 0.001$), better psychosocial functioning (Work and Social Adjustment Scale: standardised treatment effect −0.39, 95% confidence interval −0.61 to −0.18; $p < 0.001$) and greater self-rated and clinician-rated clinical improvement (self-rated: standardised treatment effect 0.39, 95% confidence interval 0.16 to 0.62; $p = 0.001$; clinician rated: standardised treatment effect 0.37, 95% confidence interval 0.17 to 0.57; $p < 0.001$). In addition, greater satisfaction with treatment was reported by the cognitive–behavioural therapy plus standardised medical care arm (standardised treatment effect 0.50, 95% confidence interval 0.27 to 0.73; $p < 0.001$). No outcomes were better in the standardised medical care-alone arm. There was no difference between arms in reported harms.

Adjusting for baseline, the difference in health and social care costs between the arms was £1834 (95% confidence interval £478 to £3475). The cognitive–behavioural therapy plus standardised medical care arm was found to demonstrate 0.0152 more quality-adjusted life-years (95% CI −0.0106 to 0.0392 quality-adjusted life-years) than the standardised medical care-alone arm. The incremental cost-effectiveness ratio for cognitive–behavioural therapy plus standardised medical care compared with standardised medical care alone was £120,658. The cost-effectiveness ratio was £116,815 when the Short Form questionnaire-6 Dimensions (i.e. utility score) was used. Hospital Episode Statistics data indicated fewer inpatient days than the self-report data for the cognitive–behavioural therapy plus standardised medical care arm. However, the cost-effectiveness ratio still exceeded £90,000 when this was taken into account.

Nested qualitative studies of 30 trial participants, 10 psychiatrists and 12 cognitive–behavioural therapists and an online survey of 43 participating neurologists highlighted the usefulness of the study information materials. Healthcare professionals had confidence in the intervention at all stages of the care pathway devised for the study. Patients and therapists identified useful intervention components and therapists identified the need for clinical experience of dealing with complexity in delivering the treatment.

Conclusions

To the best of our knowledge, the UK-based CODES trial is the largest psychotherapy trial for dissociative seizures worldwide. Although we were not able to demonstrate an additional benefit of dissociative seizure-specific cognitive–behavioural therapy in the reduction of dissociative seizure

frequency, this large trial indicated that there were additional benefits of dissociative seizure-specific cognitive–behavioural therapy across several secondary seizure-related and other clinical outcomes. There was no evidence of greater harms brought about by the cognitive–behavioural therapy intervention. Although we could not demonstrate a high cost-effectiveness ratio over standardised medical care, there are potentially clinically relevant advantages to patients with dissociative seizures receiving what we conceptualise as specialist and standardised medical care with adjunctive dissociative seizure-specific cognitive–behavioural therapy.

Trial registration

This trial is registered as ISRCTN05681227 and ClinicalTrials.gov NCT02325544.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 43. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 12/26/01. The contractual start date was in June 2014. The draft report began editorial review in April 2020 and was accepted for publication in August 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

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