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Cognitive behavioural therapy vs standardised medical care for dissociative non-epileptic seizures

Submission date
02/03/2014

Recruitment status
No longer recruiting

Registration date
05/03/2014

Overall study status
Completed

Last Edited
07/06/2023

Condition category
Nervous System Diseases

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
About 12-20% of patients who attend neurology or specialist epilepsy clinics because of seizures do not in fact have epilepsy. Most of these people have what are referred to as dissociative (non-epileptic) seizures (DS). This means that they have episodes that resemble epileptic seizures but which have no medical reason for their occurrence and instead are due to psychological factors. In younger adults DS are about four times more common in women than men. A high percentage of these people have other psychological or psychiatric problems and may have other medically unexplained symptoms. It is generally thought that people with DS benefit from psychological treatments. However, studies on this have been small or have not compared the psychological therapy with the treatment people normally receive (standardised medical care). There is some evidence that cognitive behavioural therapy (CBT), which is a widely accepted talking therapy that focuses on the person's thoughts, emotions and behaviour, as well as considering the physical reactions and sensations that may occur in people's bodies, may lead to a reduction in how often people have DS. A CBT package has been developed for people with DS. In a relatively small study, people receiving CBT overall showed greater reduction in how often they had their DS. This is a larger study across several different hospitals to obtain more definite results about the effectiveness of the CBT approach for DS.

Who can participate?
Adult patients with DS (but without current epilepsy), who have been given their diagnosis by a neurologist or specialist in epilepsy

What does the study involve?
Initial information is collected about these people and ask them to keep a record of how often they have their DS following diagnosis. Three months after the diagnosis, those who have agreed to take part in the study are seen by a psychiatrist, who undertakes a psychiatric assessment and asks them about factors which may have led to the development of their DS. Those people who have continued to have DS in the previous 8 weeks are randomly allocated to standardised medical care or CBT (plus standardised medical care) as further treatment for their seizures. These people continue to complete seizure diaries and questionnaires, provide regular

seizure frequency data following receipt of DS diagnosis and are willing to attend weekly /fortnightly sessions if allocated to CBT.

What are the possible benefits and risks of participating?
By taking part in the study, people receive information leaflets about their condition as a minimum before they receive any further assessment and treatment. This gives them access to information to which they can refer at a later date. By taking part in the comparison between treatments they will help to find out about treatments that are effective in helping people with DS as it is not known at this stage which of the two treatments will help the most. If the CBT plus standardised medical care is found to be more effective, this may affect what treatments are offered to people in the future by the NHS. In terms of risks, when people are seen by a psychiatrist, attend CBT sessions (if they are allocated to that part of the study) and fill in some of the questionnaires, they may end up thinking and talking more about their feelings and about things that have happened to them as well as about their seizures. For some people, this may be upsetting. However, psychiatrists and CBT therapists are used to helping people in distress and may be able to help patients manage these feelings. Patients are not entered into the comparison study if they and their doctor do not feel this is suitable for them. In addition, completing questionnaires, attending CBT and research interviews all take people's time.

Where is the study run from?
Institute of Psychiatry, King's College London (UK)

When is the study starting and how long is it expected to run for?
June 2014 to March 2020

Who is funding the study?
National Institute of Health Research (NIHR) (UK)

Who is the main contact?
Prof. Laura H. Goldstein
laura.goldstein@kcl.ac.uk

Study website
http://www.codestrial.org

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT02325544

Secondary identifying numbers
5.0; HTA 12/26/01

Study information

Scientific Title
COgnitive behavioural therapy vs standardised medical care for adults with Dissociative non-Epileptic Seizures: a multicentre randomised controlled trial (CODES)

Acronym
CODES

Study objectives
The study sets out to test the hypothesis that Cognitive Behavioural Therapy plus Standardised Medical Care (SMC) will have greater clinical and cost effectiveness than SMC alone in treating adult patients with dissociative seizures which had not initially ceased following diagnosis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee London - Camberwell St Giles, 18/12/2013, ref. 13/LO/1595

Study design
Initial observational phase followed by a parallel group two-arm multi-centre pragmatic randomised controlled trial (interventional phase)

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Dissociative seizures (also referred to as psychogenic nonepileptic seizures)

Interventions
How the CBT will be delivered:
CBT will be delivered over 12 sessions (each approximately one hour in length) over a 4-5 month period with one booster session at 9 months post randomisation. The model has been developed from a single case study, trialled in an open label study and then in a Pilot RCT. Thus, based on the Pilot RCT a 12-session (plus one booster session) package of CBT specifically modified for treating DS will be assessed. The model is based on the two-process fear escape-avoidance model and conceptualises DS as dissociative responses to cues (cognitive/emotional /physiological or environmental) that may (but not in all cases) have been associated with profoundly distressing or life-threatening experiences, such as abuse or trauma, at an earlier stage in the persons life and which have previously produced intolerable feelings of fear and distress. There are essentially five stages to the treatment; engagement and rationale giving; teaching and use of seizure control techniques; reducing avoidance exposure technique; dealing with seizure-related cognitions and emotions; and relapse prevention. The treatment is manualised, which is important for subsequent rollout, but the structure allows treatment to be formulation-based so that particular issues raised in therapy that might be maintaining seizure occurrence (e.g. trauma-related issues) can be addressed. Written handouts supplement the content of face-to face therapy sessions. We will record therapy sessions and undertake treatment fidelity ratings. Therapists will receive training prior to treating study patients.

SMC will be provided to study patients by neurologists and psychiatrists. Neurologists will have a key role in delivering the initial diagnosis of DS, when they will:
1. Explain the disorder: i) what patients do not have (epilepsy) and why (explanation of diagnosis, i.e. a restatement of why tests have not shown organic basis, drawing attention to positive aspects of the diagnosis); ii) what they do have (describing dissociation/switching off)
2. Reassure the patient: i) they are not suspected of 'putting on' the attacks - DS are real events; ii) the disorder is common
3. Explain causes of DS: i) relation to 'stress' may not be immediately apparent; ii) the best understanding of the disorder is that there is an underlying psychological mechanism; this is a complex matter and does not simply reflect a reaction to immediate stresses
4. Regarding treatment: i) explain that AED withdrawal should be gradual; ii) many people may lose their DS following diagnosis alone; iii) cognitive behavioural therapy may be helpful for some people but not yet clear for whom
5. Provide the patient with an information sheet including direction to self-help information.

Psychiatrists' provision of SMC of patients begins post diagnosis. The initial pre-randomisation clinical psychiatric assessment will include the following components and partly have a psychoeducational function:
1. Explanation of any psychiatric comorbidity and its psychopharmacological treatment
2. Reiteration of the points covered by the neurologist at diagnosis
3. Discussion of factors emerging from the clinical history that seem to have aetiological significance: relevance of predisposing, precipitating and perpetuating factors in their case if apparent
4. Acknowledge fears about a psychiatric label
5. Provision of an information sheet including direction to self-help information (as above)
6. General information provision about distraction but not specific techniques and not discussed repeatedly so that this does not become therapy.

Further SMC by psychiatrists will include support, consideration of psychiatric comorbidities and any associated drug treatment and general review but no CBT techniques.

The trialists will allow for some local variation in the number of neurology and psychiatry SMC sessions after randomisation.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
Monthly DS frequency at 12 months post-randomisation. This is a continuous variable that comprises a count of seizures over a four-week exposure period and therefore will reflect all participants' outcomes, whether they improve or not during the study. Seizure frequency has been used as an outcome measure in other studies of psychological interventions for DS.

Added 31/03/2020:
Frequency will also be measured at baseline and 6 months post-randomisation but the outcome will be assessed at 12 months post-randomisation.

Secondary outcome measures

Added 31/03/2020: The following secondary outcome measures are collected at baseline, 6- and 12-month follow up (unless otherwise specified). The assessment of the outcomes is at 12 months only.

1. A rating by an informant as to whether, compared to study entry (i.e. time of diagnosis) the patient's seizure frequency is worse, the same, better or whether they are seizure free
2. Self-rated seizure severity and bothersomeness, measured using two items from the Seizure Severity Scale (Cramer et al., 2002), asking how severe and bothersome DS were in the past month
3. Seizure freedom: patients' self-reported longest period of seizure freedom in days, measured between the 6- and 12-month follow-up (and previous 6 months at baseline); and whether or not the patient is seizure free in the last 3 months of the trial
4. The number of patients in each group who at the 6- and 12-month follow-up show >50% reduction in seizure frequency, compared to baseline
5. Quality of life (QoL): a generic measure of health-related QoL, the SF-12v2 (Ware et al.,1996) to allow more direct comparison to be made with other disorders. This will also allow the calculation of QALYs, although the principal measure for doing that in this study is the EQ-5D-5L (EuroQol group, 1990), a 5-domain, 5-level, multi-attribute scale which will also be used. Added 31/03/2020: Relevant summary measures will be: SF-12v2 Physical Composite Scale (PCS), SF-12v2 Mental Health Composite Scale (MCS), and EQ-5D-5L visual analogue scale (VAS) of health today
6. Psychosocial functioning: the 5-item Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002) to measure patients' own perceptions of the impact of DS on their functioning in terms of work, home management, social leisure and private leisure activities, family and other relationships
7. Psychiatric symptoms and psychological distress: anxiety, depression and somatisation measured with the GAD7 (Spitzer et al., 2006), PHQ9 (Kroenke et al., 2001) and an extended PHQ15 (Kroenke et al., 2002; Sharpe et al., 2010), derived from the Patient Health Questionnaire which reflects DSM-IV diagnoses. The GAD7 is a 7-item anxiety scale with good internal consistency (Cronbach's alpha = 0.92), test-retest reliability (intraclass correlation = 0.83), sensitivity (89%), specificity (82%) criterion, construct and factorial validity. The PHQ9 is a 9-item depression scale that can be used to diagnose major depression (DSM-IV). It has good internal consistency (Cronbach's alpha = 0.86-0.89) and test-retest reliability (r=0.84); sensitivity and specificity and construct validity are good. The PHQ15 has been shown to have high internal validity (Cronbach's alpha = 0.8) and strong convergent and discriminant validity. A general measure of psychological distress, the CORE-10 (Connell & Barkham, 2007), is also used to assess self-reported global psychological distress
8. Patients' self-rated global outcome and satisfaction with treatment. The Clinical Global Impression (CGI) (Guy 1976) change score yields a self-rated global measure of change and has been used in previous trials of CBT interventions (baseline N/A)
9. The CGI change scale rated by CBT therapists at the end of session 12 and by the SMC doctor at the 12-month follow-up (baseline N/A)
10. Health service use (including hospital attendances and admissions, GP contacts), informal care, lost work time and financial benefits (which will be used as predictors of outcome in our analysis) measured via the self-report Client Service Receipt Inventory (Beecham & Knapp, 2001)
11. Objective measure of health service use; linkage data sets from NHS Health and Social Care Information Centre (Hospital Episode Statistics) eDRIS (NHS National Services Scotland Information Services Division (ISD) and Wales (NHS Wales Informatics Service) to allow quantification of objective measures of hospital attendances and admissions pre-randomisation and during follow-up using ICD-10 codes

Overall study start date

01/06/2014

Completion date
31/03/2020

Eligibility

Key inclusion criteria
Current inclusion criteria as of 14/05/2015:

Inclusion criteria applied at the initial recruitment stage:
1. Adults (≥18 years) with DS that have continued to occur within the previous 8 weeks and have been confirmed by video EEG telemetry or, where not achievable, clinical consensus; patients who have chronic DS can be included if they have been seen by the relevant Study Neurologist who has reviewed their diagnosis and communicated this to them according to the study protocol
2. Ability to complete seizure diaries and questionnaires
3. Willingness to complete seizure diaries regularly and undergo psychiatric assessment 3 months after DS diagnosis
4. No documented history of intellectual disabilities
5. Ability to give written informed consent

Inclusion criteria evaluated at the randomisation stage:
1. Adults (≥18 years) with DS initially recruited at point of diagnosis;
2. Willingness to continue to complete seizure diaries and questionnaires;
3. Having provided regular seizure frequency data to research team following receipt of DS diagnosis;
4. Willingness to attend weekly/fortnightly sessions if randomised to CBT
5. Both clinician and patient agree that randomisation is acceptable
6. Ability to give written informed consent;

Previous inclusion criteria:

Inclusion criteria applied at the initial recruitment phase:
1. Adults (≥18 years) with DS confirmed by video EEG telemetry or, where not achievable, clinical consensus
2. Patients who have chronic DS can be included if they have been seen by the relevant study neurologist who has reviewed their diagnosis and communicated this to them according to the study protocol
3. Ability to complete seizure diaries and questionnaires
4. Willingness to complete seizure diaries regularly and undergo psychiatric assessment 3 months after DS diagnosis
5. No documented history of intellectual disabilities
6. Ability to give written informed consent

Inclusion criteria evaluated at the randomisation phase:
1. Adults (≥18 years) with DS initially recruited at point of diagnosis
2. Willingness to continue to complete seizure diaries and questionnaires
3. Provision of regular seizure frequency data following receipt of DS diagnosis

4. Willingness to attend weekly/fortnightly sessions if randomised to CBT
5. Both clinician and patient think that randomisation is acceptable
6. Ability to give written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Target: observational phase 501; interventional phase 298; Final: observational phase 698; interventional phase 368; please note that 368 is a subset of the 698 not an additional sample

Total final enrolment
368

Key exclusion criteria
Current exclusion criteria as of 14/05/2015:

Exclusion criteria applied at the initial recruitment stage:
1. Having a diagnosis of current epileptic seizures as well as DS
2. Inability to keep seizure records or complete questionnaires independently
3. Meeting DSM-IV criteria for current drug/alcohol dependence
4. Insufficient command of English to later undergo CBT without an interpreter or to complete questionnaires independently
5. Having previously undergone a CBT-based treatment for dissociative seizures at a trial participating centre
6. Currently having CBT for another disorder, if this will not have ended by the time that the psychiatric assessment takes place

Exclusion criteria evaluated at the randomisation stage:
1. Current epileptic seizures as well as DS, for reasons given above
2. Not having had any DS in the 8 weeks prior to the psychiatric assessment, 3 months post diagnosis
3. Having previously undergone a CBT-based treatment for dissociative seizures at a trial participating centre
4. Currently having CBT for another disorder
5. Active psychosis
6. Meeting DSM-IV criteria for current drug/alcohol dependence; this may exacerbate symptoms /alter psychiatric state and health service use and affect recording of seizures
7. Current benzodiazepine use exceeding the equivalent of 10mg diazepam/day
8. The patient is thought to be at imminent risk of self-harm, after psychiatric assessment or

structured psychiatric assessment by the Research Worker with the MINI, followed by consultation with the psychiatrist
9. Known diagnosis of Factitious Disorder

Previous exclusion criteria:

Exclusion criteria applied at the initial recruitment phase:
1. Having a diagnosis of current epileptic seizures as well as DS
2. Inability to keep seizure records or complete questionnaires independently
3. Meeting DSM-IV criteria for current drug/alcohol dependence
4. Insufficient command of English to later undergo CBT without an interpreter or to complete questionnaires independently

Exclusion criteria evaluated at the randomisation phase:
1. Current epileptic seizures as well as DS, for reasons given above
2. Not having had any DS in the 8 weeks prior to the psychiatric assessment, 3 months post diagnosis
3. Having previously undergone a CBT-based treatment for dissociative seizures at a trial participating centre
4. Currently having CBT for another disorder
5. Active psychosis
6. Meeting DSM-IV criteria for current drug/alcohol dependence; this may exacerbate symptoms /alter psychiatric state and health service use and affect recording of seizures
7. Current benzodiazepine use exceeding the equivalent of 10 mg diazepam/day
8. The patient is thought to be at imminent risk of self-harm, after (neuro)psychiatric assessment and structured psychiatric assessment by the Research Worker with the MINI
9. Known diagnosis of Factitious Disorder

Date of first enrolment
01/10/2014

Date of final enrolment
31/05/2017

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
United Kingdom
SE1 7EH

Study participating centre
Croydon Health Services NHS Trust
United Kingdom
CR7 7YE

Study participating centre
Lewisham and Greenwich NHS Trust
United Kingdom
SE13 6LH

Study participating centre
King's College Hospital NHS Foundation Trust
United Kingdom
SE5 9RS

Study participating centre
University College London Hospitals NHS Foundation Trust
United Kingdom
NW1 2BU

Study participating centre
St George's University Hospitals NHS Foundation Trust
United Kingdom
SW17 0QT

Study participating centre
Barts Health NHS Trust
United Kingdom
EC1A 7BE

Study participating centre
Imperial College Healthcare NHS Trust
United Kingdom
W2 1NY

Study participating centre
Royal Free London NHS Foundation Trust
United Kingdom
NW3 2QG

Study participating centre
Western Sussex Hospitals NHS Foundation Trust
United Kingdom
BN11 2DH

Study participating centre
East Sussex Healthcare NHS Trust
United Kingdom
BN21 2UD

Study participating centre
Brighton and Sussex University Hospitals NHS Trust
United Kingdom
BN1 6AG

Study participating centre
Dartford and Gravesham NHS Trust
United Kingdom
DA2 8DA

Study participating centre
Maidstone and Tunbridge Wells NHS Trust
United Kingdom
TN2 4QJ

Study participating centre
East Kent Hospitals University NHS Foundation Trust
United Kingdom
CT1 3NG

Study participating centre

Medway NHS Foundation Trust
United Kingdom
ME7 5NY

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
United Kingdom
CB2 0QQ

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
United Kingdom
S5 7AU

Study participating centre
Chesterfield Royal Hospital NHS Foundation Trust
United Kingdom
S44 5BL

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
United Kingdom
B15 2TH

Study participating centre
Birmingham & Solihull Mental Health NHS Foundation Trust
United Kingdom
B1 3RB

Study participating centre
The Leeds Teaching Hospitals NHS Trust
United Kingdom
LS1 3EX

Study participating centre

Cardiff & Vale University Health Board
United Kingdom
CF5 2LD

Study participating centre
The Royal Berkshire NHS Foundation Trust
United Kingdom
RG1 5AN

Study participating centre
NHS Lothian
United Kingdom
EH1 3EG

Study participating centre
South London and Maudsley NHS Foundation Trust
United Kingdom
SE5 8AZ

Study participating centre
South West London & St Georges Mental Health NHS Trust
United Kingdom
SW17 7DJ

Study participating centre
East London NHS Foundation Trust
United Kingdom
E1 8DE

Study participating centre
West London Mental Health Trust
United Kingdom
UB1 3EU

Study participating centre

Sussex Partnership NHS Foundation Trust
United Kingdom
RH1 5RH

Study participating centre
Kent and Medway NHS and Social Care Partnership Trust
United Kingdom
ME16 9PH

Study participating centre
Cambridgeshire and Peterborough NHS Foundation Trust
United Kingdom
CB21 5EF

Study participating centre
Sheffield Health and Social Care NHS Foundation Trust
United Kingdom
S10 3TH

Study participating centre
Derbyshire Healthcare NHS Foundation Trust
United Kingdom
DE22 3LZ

Study participating centre
Berkshire Healthcare NHS Foundation Trust
United Kingdom
RG12 1BQ

Study participating centre
Leeds and York Partnership NHS Foundation Trust
United Kingdom
LS15 8ZB

Study participating centre

Derbyshire Community Health Services NHS Trust
United Kingdom
DE45 1AD

Study participating centre
The Newcastle Upon Tyne Hospitals NHS Trust
Newcastle
United Kingdom
NE1 4LP

Study participating centre
Northumberland Tyne and Wear NHS Foundation Trust
Newcastle upon Tyne
United Kingdom
NE6 4QD

Study participating centre
University Hospital Southampton NHS Trust
Southampton
United Kingdom
SO16 6YD

Sponsor information

Organisation
King's College London

Sponsor details
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57 Waterloo Road
London
England
United Kingdom
SE1 8WA

Sponsor type
University/education

Website

http://www.kcl.ac.uk/index.aspx

ROR
https://ror.org/0220mzb33

Organisation
South London and Maudsley NHS Foundation Trust

Sponsor details
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Joint SLaM/IoP R&D Office
Institute of Psychiatry
De Crespigny Park
London
England
United Kingdom
SE5 8AF

Sponsor type
Hospital/treatment centre

Website
http://www.slam.nhs.uk/

ROR
https://ror.org/015803449

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

United Kingdom

Results and Publications

Publication and dissemination plan
The trialists intend to publish the main trial findings in a high-impact peer-reviewed journal around 1 year after the overall trial end date.

2020 video in https://www.youtube.com/watch?v=pUFKbYH7BcQ (added 29/09/2020)

Intention to publish date
31/12/2020

Individual participant data (IPD) sharing plan
At present anonymised data from the clinical dataset generated during and/or analysed during the RCT may be available from around 22/11/2021 until 21/05/2023 upon reasonable request. In the first instance at that point contact Prof. Laura Goldstein (laura. goldstein@kcl.ac.uk) when access criteria will be specified and further information will be available.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	27/06/2015		Yes	No
Other publications	statistical and economic analysis plan	06/06/2017		Yes	No
Other publications	qualitative study	09/05/2019	13/05/2019	Yes	No
Other publications	baseline characteristics	01/11/2019	28/10/2019	Yes	No
Results article	results	01/06/2020	22/05/2020	Yes	No
Other publications	participant characteristics	11/05/2020	08/10/2020	Yes	No
Other publications	participant experiences	01/10/2020	08/10/2020	Yes	No
Other publications	psychiatrists' perspectives	09/05/2019	08/10/2020	Yes	No
Results article		01/06/2021	05/07/2021	Yes	No
HRA research summary			28/06/2023	No	No