



Dissociations and Cognitive Distortions: True, True, and Possibly Related

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Cognitive Behavioural Therapy for Adults With Dissociative Seizures (CODES): A Pragmatic, Multicentre, Randomized Controlled Trial.

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Background: Dissociative seizures are paroxysmal events resembling epilepsy or syncope with characteristic features that allow them to be distinguished from other medical conditions. We aimed to compare the effectiveness of cognitive behavioral therapy (CBT) plus standardized medical care with standardized medical care alone for the reduction of dissociative seizure frequency. **Methods:** In this pragmatic, parallel-arm, multicenter, randomized controlled trial, we initially recruited participants at 27 neurology or epilepsy services in England, Scotland, and Wales. Adults (≥ 18 years) who had dissociative seizures in the previous 8 weeks and no epileptic seizures in the previous 12 months were subsequently randomly assigned (1:1) from 17 liaison or neuropsychiatry services following psychiatric assessment, to receive standardized medical care or CBT plus standardized medical care, using a web-based system. Randomization was stratified by neuropsychiatry or liaison psychiatry recruitment site. The trial manager, chief investigator, all treating clinicians, and patients were aware of treatment allocation, but outcome data collectors and trial statisticians were unaware of treatment allocation. Patients were followed up 6 months and 12 months after randomization. The primary outcome was monthly dissociative seizure frequency (ie, frequency in the previous 4 weeks) assessed at 12 months. Secondary outcomes assessed at 12 months were seizure severity (intensity) and bothersomeness; longest period of seizure freedom in the previous 6 months; complete seizure freedom in the previous 3 months; a greater than 50% reduction in seizure frequency relative to baseline; changes in dissociative seizures (rated by others); health-related quality of life; psychosocial functioning; psychiatric symptoms, psychological distress, and somatic symptom burden; and clinical impression of improvement and satisfaction. *P* values and statistical significance for outcomes were reported without correction for multiple comparisons as per our protocol. Primary and secondary outcomes were assessed in the intention-to-treat population with multiple imputation for missing observations. This trial is registered with the International Standard Randomised Controlled Trial registry, ISRCTN05681227, and ClinicalTrials.gov, NCT02325544. **Findings:** Between January 16, 2015, and May 31, 2017, we randomly assigned 368 patients to receive CBT plus standardized medical care ($n = 186$) or standardized medical care alone ($n = 182$); of whom 313 had primary outcome data at 12 months (156 [84%] of 186 patients in the CBT plus standardized medical care group and 157 [86%] of 182 patients in the standardized medical care group). At 12 months, no significant difference in monthly dissociative seizure frequency was identified between the groups (median: 4 seizures [interquartile range: 0–0] in the CBT plus standardized medical care group vs 7 seizures [1–35] in the standardized medical care group; estimated incidence rate ratio [IRR]: 0.78 [95% CI: 0.56–1.09]; $P = .144$). Dissociative seizures were rated as less bothersome in the CBT plus standardized medical care group than the standardized medical care group (estimated mean difference: -0.53 [95% CI: -0.97 to -0.08]; $P = .020$). The CBT plus standardized medical care group had a longer period of dissociative seizure freedom in the previous 6 months (estimated IRR: 1.64 [95% CI: 1.22–2.20]; $P = .001$), reported better health-related quality of life on the EuroQoL-5 Dimensions-5 Level Health Today visual analog scale (estimated mean difference: 6.16 [95% CI: 1.48–10.84]; $P = .010$), less impairment in psychosocial functioning on the Work and Social Adjustment Scale (estimated mean difference: -4.12 [95% CI: -6.35 to -1.89]; $P < .001$), less overall psychological distress than the standardized medical care group on the Clinical Outcomes in Routine Evaluation-10 scale (estimated mean difference: -1.65 [95% CI: -2.96 to -0.35]; $P = .013$), and fewer somatic symptoms on the modified Patient Health Questionnaire-15 scale (estimated mean difference: -1.67 [95% CI: -2.90 to -0.44]; $P = .008$). Clinical improvement at 12 months was greater in the CBT plus standardized medical care group than the standardized medical care alone group as reported by patients (estimated mean difference: 0.66 [95% CI: 0.26–1.04]; $P = .001$) and by clinicians (estimated mean difference: 0.47 [95% CI: 0.21–0.73]; $P < .001$), and the CBT plus standardized medical care group had greater satisfaction with treatment than did the standardized medical care group (estimated mean difference: 0.90 [95% CI: 0.48–1.31]; $P < .001$). No



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significant differences in patient-reported seizure severity (estimated mean difference: -0.11 [95% CI: -0.50 to 0.29]; $P = .593$) or seizure freedom in the last 3 months of the study (estimated odds ratio [OR]: 1.77 [95% CI: 0.93 - 3.37]; $P = .083$) were identified between the groups. Furthermore, there were no significant differences in dissociative seizure frequency reduction compared with baseline (OR: 1.27 [95% CI: 0.80 - 2.02]; $P = .313$). Additionally, the 12-item Short Form survey—version 2 scores (estimated mean difference for the Physical Component Summary score: 1.78 [95% CI: -0.37 to 3.92]; $P = .105$; estimated mean difference for the Mental Component Summary score: 2.22 [95% CI: -0.30 to 4.75]; $P = .084$), the Generalized Anxiety Disorder-7 Scale score (estimated mean difference: -1.09 [95% CI: -2.27 to 0.09]; $P = .069$), and the Patient Health Questionnaire-9 Scale depression score (estimated mean difference: -1.10 [95% CI: -2.41 to 0.21]; $P = .099$) did not differ significantly between groups. Changes in dissociative seizures (rated by others) could not be assessed due to insufficient data. During the 12-month period, the number of adverse events was similar between the groups: 57 (31%) of 186 participants in the CBT plus standardized medical care group reported 97 adverse events and 53 (29%) of 182 participants in the standardized medical care group reported 79 adverse events. Interpretation: Cognitive behavioral therapy plus standardized medical care had no statistically significant advantage compared with standardized medical care alone for the reduction of monthly seizures. However, improvements were observed in a number of clinically relevant secondary outcomes following CBT plus standardized medical care when compared with standardized medical care alone. Thus, adults with dissociative seizures might benefit from the addition of dissociative seizure-specific CBT to specialist care from neurologists and psychiatrists. Future work is needed to identify patients who would benefit most from a dissociative seizure-specific CBT approach.

Commentary

Although evidence is mixed, now may be an enlightened time for the treatment of dissociative seizures, otherwise known as psychogenic non-epileptic seizures (PNES). This is welcome news, since treatment options are in demand from patients and clinicians alike. Psychotherapy of varying sorts has been shown to reduce non-epileptic events in at least two recent studies,^{1,2} and two small clinical trials suggest that antidepressant medicine may have benefits.^{3,4} However, the results are not always robust, and given the heterogeneity of clinical presentations and treatment approaches, it is difficult to make conclusions that are stringently data-based. Sometimes the best information available only suggests trends toward improvement.

Precise treatments, such as a single medicine or a specific replicable procedure, are much easier to prospectively assess in a controlled manner. However, in the world of psychiatry, precise homogeneous treatments are nearly impossible to find. Even sophisticated studies of psychotropic medicines have a robust placebo response, which challenges confidence in the evidence. Psychotherapy is even more ambiguous, unavoidably dependent upon personal characteristics of the practitioner, overriding reliable and replicable methods of conducting the therapy. However, there is one possible exception.

Cognitive behavioral therapy (CBT) has the potential to be a homogeneous treatment approach. It is a very popular, well-established method with defined goals and techniques, standing in sharp contrast to other types of therapy, such as psychoanalysis, which have no defined end points. Instead, CBT emphasizes relatively clearly described and defined errors in thinking. Many people have a tendency to make “mountains out of molehills” or have “black and white thinking,” not appreciating nuances in interactions with others or with their own actions. People may overreact to perceived disapproval from others, and maladaptive patterns of thinking can become

ingrained and yield a negative self-image. People who are in a rut with such cognitive distortions have troubles finding a way to think differently. With CBT, there is a manual, a lesson plan, even homework, and people may be proactive in taking control of their own states of mind.

Cognitive behavioral therapy is popular in research because less is dependent upon nebulous virtues of affability or charismatic personality that may inconsistently influence therapeutic alliances or rapport. Although positive regard between therapists (and doctors) and patients is always important, with CBT, the agenda is the more important part. The programmatic approach is reassuring to those who find psychiatry murky and mysterious. It is also reassuring for neurologists who work with PNES since it has been studied.² Clinicians can refer people to CBT knowing that there is at least some evidence that it is an effective treatment . . . or is it?

Goldstein and colleagues seem to disagree, at least at first.⁵ The sample includes a carefully selected group of patients with dissociative seizures, as well defined and as homogeneous as possible. The study groups were large and participants randomized to receive either CBT or standard medical care. The details of the standard medical care are unknown, though CBT was apparently not involved. The outcome measures were broad, including psychiatric symptoms, quality of life, functionality, satisfaction ratings, and of course “seizure” counts. Additionally, the outcome measures were assessed a year after the treatment was completed, so the study was geared to assess lasting change. Participants were aware of their group assignments though raters were not. Unfortunately, after a long course of CBT, the primary outcome variable—the number of dissociative seizures—did not differ between the groups. However, nearly every secondary outcome variable, including quality of life, psychiatric symptoms, and disruption (bother) resulting from the events, improved in the CBT group.




This seems to be a conundrum, that although the seizure events are unchanged, the patient still gets better in measurable and meaningful ways. The result is a dissociation in its own right, fitting for the actual PNES episodes in the first place. However, the important lesson is that CBT nevertheless plays a significant and positive role. Empowering patients to take strides to control their lives has tangible benefits even if the defined illness is not significantly changed. An analogous dichotomy was also found in one of the most sophisticated treatment studies in child psychiatry done to date. The multimodal treatment study for attention-deficit/hyperactivity disorder (ADHD), completed over 20 years ago, compared 4 treatments: intensive psychotherapy, medicine, both, or a control group which included regular medical care.⁶ Medicine improved ADHD symptoms independent of psychotherapy; however, the arms that included psychotherapy yielded higher satisfaction and improvement in anxiety and disruptive behavior, regardless of the improvement in ADHD symptoms.


In this clinical trial, the real conundrum is that with the primary outcome variable of reducing dissociative seizures, even though it was a full year after the treatment intervention was completed, this is a negative study. Nevertheless, the investigators did identify some groundbreaking results, mainly that this primary aim may be irrelevant to the patient. It is much easier to focus on seizure counts, to keep diaries, and to be very compulsive about variances in presentations of events, but the reality is that none of it may matter. Psychotherapy benefitted people by helping them to reduce their anxiety about the events and improve their quality of life. The whole point is to make people better, and CBT did just that.

Analogies abound in medicine and psychiatry. If someone with Tourette syndrome has residual tics but is not bothered by them and functions well, then the treatment is a success. The same goes for chronic pain, headaches, irritable bowel syndrome, and any number of illnesses that are ambiguously defined or understood. Could it be that future treatment studies

in any field of medicine should have as primary outcomes, quality of life, and functionality? Maybe a psychologically minded, holistic approach to all treatment is the wave of the future. Or maybe, this is just an overgeneralizing cognitive distortion on my part. Either way, I feel better and I thank Goldstein et al for that.

By Jay A. Salpekar 

ORCID iD

Jay A. Salpekar  <https://orcid.org/0000-0002-6023-9430>

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