Differential effects of cranial electrotherapy stimulation on changes in anxiety and depression symptoms over time in patients with generalized anxiety disorder.

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Abstract

Background. Cranial electrotherapy stimulation (CES) is a safe and well-tolerated 6-12 week treatment that is clinically and cost effective on both anxiety and depression symptoms resulting in sustained remission of these symptoms at 12 and 24 weeks in generalized anxiety disorder (GAD) patients. The aim of the current report was to explore whether the effectiveness of CES was related to its effects on depression or anxiety over time

Methods. A consecutive sample of 161 eligible patients with GAD was recruited from two publicly funded services in England while they waited for individual cognitive behaviour therapy (CBT) after failing to achieve remission on the GAD-7 with computerised CBT. They received 60 minutes per day Alpha-Stim CES for 6-12 weeks. Outcomes were changes in PHQ-9, GAD-7 score from baseline to 4, 6, 8, 12 and 24 weeks. Latent variable cross-lagged panel analysis permitted an analysis of the differential effects of anxiety and depression with CES treatment over time.

Results. Anxiety at baseline significantly predicted depression at week 4 (standardized regression weight = .40, $p<0.001$). Depression at week 12 significantly predicted anxiety at week 24 (standardized regression weight = .28, $p<0.05$).

Limitations. Not a randomized controlled trial but further analysis of a prospective observational cohort. High rates of loss to follow up by 24 weeks.

Conclusion. Sustained effectiveness required a CES response to anxiety symptoms in first 4 weeks and improvement in depression symptoms by 12 weeks.

234 words

Background.

The majority of patients with generalised anxiety disorder (GAD) also have a current depression disorder (Lamers et al, 2011). Such patients with both anxiety and depression disorders have a longer duration of symptoms, higher symptoms severity, use more health care resources and respond more slowly to both pharmacological and psychological treatments than those with only anxiety or depression disorders (McLaughlin et al, 2006; van Balton et al, 2008; Fava et al, 2008; Savenu et al, 2015; Vittengl et al, 2019).

Meta-analysis found evidence from five randomised controlled trials (RCT) in 198 participants with anxiety disorders of the effectiveness of cranial electrical stimulation (CES) versus depression and anxiety symptoms, and that CES is safe (Shekelle et al, 2018). A recent prospective observational study in 161 participants with GAD reported that Alpha-Stim CES was associated with improved anxiety and depression symptoms, resulted in remission from generalised anxiety disorder at 12 and 24 weeks and was cost saving compared to individual cognitive behaviour therapy (iCBT) (Morriss et al, 2019). Clinical improvements in samples with primary anxiety disorders (Barclay and Barclay, 2014; Morriss et al, 2019) may be driven by an effect of CES on anxiety symptoms with secondary improvement in depression symptoms or a response to CES on both anxiety and depression symptoms. Therefore we report a further temporal analysis of previously reported data (Morriss et al, 2019) to explore the differential effects of 6-12 weeks CES treatment in anxiety and depression symptoms over 4, 6, 8, 12 and 24 weeks to address two objectives:

1. Is anxiety a reliable and significant predictor of depression longitudinally?
2. Is depression a reliable and significant predictor of anxiety longitudinally?

Methods

The design and methods have been outlined previously in detail (Morriss et al, 2019). An open consecutive patient cohort design with 24 week follow up in National Health Service (NHS) mental health treatment settings in England was employed where all participants were offered Alpha-Stim CES for 6-12 weeks if they had not reached remission with guided self-help and were waiting to receive individual cognitive behaviour therapy (iCBT) for generalized anxiety disorder. Consecutive participants meeting inclusion/exclusion criteria for the study were recruited from two NHS Improving Access to Psychological Treatment (IAPT) services in the same county in England covering a more affluent urban and rural area and a less affluent inner-city area. Possible participants who appeared to meet inclusion/exclusion criteria were identified from IAPT service records. Eligibility was checked over the telephone. The study team checked their eligibility over the phone, and then face to face sought written and oral informed consent to the study. If the participant consented,

study staff showed the participants how to use the Alpha-Stim CES device, outlined how to obtain support while using it, and negotiated the return of the CES device at the end of 6-12 weeks treatment. Ethical approval for the study was granted by the Nottingham 2 NRES committee (IRAS206555).

Inclusion criteria for the whole study were: a clinical diagnosis of generalized anxiety disorder made by IAPT clinically trained health professionals; a score of 8 or more on the self-rated Generalized Anxiety Disorder, seven-item scale (GAD-7; Spitzer et al, 2006); failure to reach remission (GAD-7 score $\geq$8) after course of computerised self-management or bibliotherapy for GAD facilitated by IAPT staff; on the waiting list for iCBT from IAPT staff; giving both oral and written informed consent to the study; agreement to return the CES equipment at the end of treatment. Exclusion criteria were: a clinical diagnosis of substance use disorder, eating disorder, bipolar disorder, non-affective psychosis or organic mental disorder; requiring urgent clinical care; pregnancy; implantation with a pace maker or an implantable cardioverter device. The presence of other anxiety and depression disorders, personality disorder or physical health problems were not exclusions. Women of child-bearing potential completed a urine pregnancy dipstick human chorionic gonadotropin test.

Clinical outcome measures were collected at baseline face to face, then at four, six, eight, 12 and 24 weeks by e-mail, telephone or post according to participant preference. In this report we examined changes in the self-rated depression symptoms on the Patient Health Questionnaire, nine-item (PHQ-9; Kroenke et al, 2001), and anxiety symptoms on the GAD-7.

Alpha-Stim AID is a CE marked and FDA cleared for direct sale to the public medical device to deliver CES which is a non-invasive treatment delivering tiny electric currents as adjunctive treatment to drug or psychological treatment or a treatment on its own for anxiety or depression disorders. All participants were offered 60 minutes per day of alpha-stim AID CES treatment at a current of 100 micro amps per day seven days per week for six consecutive weeks. Participants could increase the current incrementally to 500 micro amps if there was no response and no side-effects. The 60 minutes session starts when the ear clips with pads coated in electrolyte solution are attached to right and left earlobes and stops automatically after one hour. The device was not locked and did not automatically record adherence to treatment. Participants could choose to continue with the same CES treatment for a further six weeks, thereby completing 12 weeks CES treatment in total. They were asked about side-effects at the end of treatment. At the end of 12 weeks the participants could

not receive any further CES treatment. Decisions concerning delivery of iCBT were made by IAPT staff with the participants; the study team did not influence this decision.

Statistical analysis. Intention-to-treat (ITT) analysis avoids overoptimistic estimates of the efficiency of an intervention resulting from the removal of non-compliers by accepting that noncompliance and protocol deviations are likely to occur in clinical practice (Fisher et al 1990). To evaluate the type or pattern of missing scores for each outcome measure, the missing completely at random (MCAR) test was employed (Little and Rubin, 2002). Once the data was determined to adhere to MCAR (i.e. $p > .05$), replacement of scores proceeded using model-based Bayesian full information maximum likelihood (FIML) estimation.

Most observational studies must include potential confounding variables, which generates random variation due to the measurement of these variables. In order to address anxiety as a potential confounding variable related to depression, a latent variable cross-lagged panel analysis (LVCLPM) was conducted within a structural equation modelling (SEM) framework using all the 161 participants (Mackinnon, 1995; Krull and MacKinnon,1999; Shadish et al, 2002; Little, 2013). To evaluate the adequacy of our sample size relative to statistical power we conducted a power analysis using the Monte Carlo facility within the M*p*lus version 8.3 statistical software. We treated sample parameter estimates in the LVCLPM as population parameters in the Monte Carlo study. Following guidelines (Bandalos and Leite, 2013; Price, et al. 2019), we conducted 1000 replications to evaluate (a) parameter bias, (b) adequacy of mean square error of parameter estimates, (c) 95% coverage over replications (i.e., proportions of replications for which the null hypothesis that a parameter is equal to zero is rejected at the .05 level of significance), and (d) statistical power for each parameter in the model. Across 1000 replications, the model displayed excellent fit to the data (i.e., difference between observed versus expected Chi-square fit less than 1.2) with average root mean square error of approximation (RMSEA) of .02. The results of the power analysis revealed that (a) all parameters displayed bias less than 5%, (b) mean square error of less than .02 for all parameters, (c) 94% or greater coverage of parameter estimates, and (d) power estimates greater than .80 in 13 out of 20 parameters (65%). Power estimates lower than .80 were observed in 7 out of 20 parameter estimates. Given the low level of parameter estimation bias and adequacy of performance of the simulation study, observation of low statistical power in parameters with low standardized regression weights (i.e., .20 or smaller) was expected. The LVCLPM provided a way for us to examine the parallel, simultaneous effects of anxiety and depression in a unified modelling framework. For example, the LVCLPM analysis was used to quantify the amount of variance explained by anxiety if

anxiety was a significant predictor of depression in patients receiving CES treatment at each successive time point after baseline in the study. Concurrently, the analysis allowed us to quantify the amount of variance explained by depression and if depression was a significant predictor of anxiety in patients receiving CES treatment at each successive time point after baseline.

Results

The sample of 161 participants had a mean (sd) age of 38.0 (11.2) years, 118 (78%) were female, 153 (95.0%) were white British, 95 (59.0%) were married, 106 (65.8%) were employed, and 143 (89%) met case level depression (PHQ-9 >10) at baseline. One hundred and twelve (69%) patients completed the study protocol of at least 6 weeks of treatment. Forty-nine (30.4%) participants withdrew by week 12 but only four (2.5%) because of adverse effects of CES.

Table 1 shows that there were significant improvements of large effect size over all time points in GAD-7 and PHQ-9 scores with CES. The pattern of improvement was similar for the GAD-7 and PHQ-9 over all time points except there was a slight worsening of the PHQ-9 between 12 and 24 weeks.

Figure 1 shows the LVCLPM model. Anxiety at baseline significantly predicted ($p < 0.001$) depression at week 4 (standardized regression weight = .40). Anxiety explained 16% of the variation in depression at week 4. The severity of depression at baseline had a significant inverse effect on severity of depression at week 4. At weeks 6, 8, 12 and 24, anxiety non-significantly predicted < 7% of the variation in depression. Depression did not significantly predict anxiety at any time point up to week 12.. Only depression at week 12 significantly predicted ($p < .05$) anxiety at week 24 (standardized regression weight = .28) while anxiety at week 12 explained only 8% of the variation in anxiety at week 24.

Discussion.

The LVCLPM model indicates that improvement in anxiety symptoms with CES was a reliable and significant predictor of both anxiety and depression symptoms in the first 4 weeks in consecutive patients with moderate to severe GAD that had not responded to computerised CBT. The presence of depression at baseline led to a worsening of depression symptoms at 4 weeks. At 6, 8 and 12 weeks, improvements in anxiety with CES were predicted only by the preceding anxiety score, and improvements in depression with CES only by the preceding depression score. The effects of CES on depression scores at 12 weeks was a reliable predictor of both anxiety and depression scores at 24 weeks. Therefore sustained improvements on both anxiety and depression symptoms with CES

required effects on anxiety initially and then at 12 weeks on depression not just an effect of CES on anxiety symptoms alone. Taken together, the presence of both anxiety and depression symptoms suggest longer course of daily CES for up to 12 weeks are required. The findings are consistent with both the slower response to antidepressants and CBT if anxiety and depression are both present than either alone, and the need for improvement in both anxiety and depression symptoms with these treatments for sustained improvement (e.g. Fava et al, 2008; Savenu et al, 2015; Vittengl et al, 2019).

There are important limitations of the study. The study is naturalistic with no control group so observed effects cannot necessarily be attributed to CES. Approximately 50 percent of this sample also had iCBT and medication, neither of which was under the control of the study team so the effectiveness of CES may have been enhanced by other treatments. In this naturalistic study there was also a 30% dropout rate at 12 weeks. We did not measure adherence to CES and we cannot rule out that changes in the parameters of delivery of CES might enhance its effects on anxiety or depression symptoms. A limited amount of variance in outcome of anxiety and depression with CES was explained in the current analysis so further investigation on the mode of action of CES is merited.

1,994 words.

Abbreviations

Alpha-Stim AID cranial electrotherapy: stimulator for control of anxiety, insomnia and depression; CBT: cognitive behaviour therapy; CE: Conformité Européene, European Union regulatory marking; CES: cranial electrotherapy stimulation; CI: confidence interval; DSM-IV-Diagnostic and Statistical Manual of Mental Disorders 4th Edition; FDA: Food and Drugs Administration; FIML: full information maximum likelihood estimation; GAD: generalised anxiety disorder; GAD-7: self-rated measure of generalised anxiety disorder symptoms; GLM: general linear model; iCBT: individual cognitive behaviour therapy; IAPT: Improving Access to Psychological Treatment service; IRAS: Integrated Research Application Service; ITT: intention to treat; LVCLPM: latent variable cross-lagged panel analysis; MCAR: missing completely at random; NHS: National Health Service; NRES: National Research Ethics Service; PHQ-9: Personal Health Questionnaire 9 item; RCT: randomised controlled trial; RM ANOVA: repeat measures analysis of variance; RMSEA: root mean square error of approximation; SEM: structural equation modelling.

Conflict of interest

The chief investigator (RM) reports no financial or other conflicts of interest for their involvement in the study. Part of LP's funding is from Electromedical Products International as a statistical consultant.

Role of the funder

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CRediT authorship contribution statement

Richard Morriss: Writing - review & editing, Conceptualization, Funding acquisition, Supervision, Validation. **Larry Price:** Writing - review & editing, Conceptualization, Project administration.

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Table 1: Depression and anxiety symptoms of participants with generalized anxiety disorder receiving 6-12 weeks cranial electrical stimulation (n=161).

Clinical feature	Baseline	4 weeks	6 weeks	8 weeks	12 weeks	24 weeks
PHQ-9, mean (sd)[1]	16.07 (4.94)	11.22 (6.09)	10.38 (5.91)	10.04 (6.46)	8.91 (5.78)	10.42.(6.97)
GAD-7, mean (sd)[2]	15.77 (3.21)	10.44 (4.86)	9.73 (4.89)	9.34 (4.58)	8.92 (5.42)	8.99 (6.18)

PHQ-9 = Patient Health Questionnaire, nine-item; GAD-7 = Generalised Anxiety Disorder, seven-item

[1] $F=58.80$, $p<0.001$, partial eta $=0.29$, large effect

[2] $F=85.58$, $p<0.001$, partial eta $= 0.37$, large effect