**Supplementary Table S1:** Database searches

Date through 2021/07/21

Total: 3025 after removed of duplicated

Pubmed N=134

Keyword: (CES OR Cranial Electrotherapy Stimulation OR cranial electrotherapy stimulation OR noninvasive brain stimulation OR Alpha-Stim) AND (anxiety OR anxious OR panic OR phobia OR worrisome) with limitation on humans species and clinical trial

Medline N= 766

Keyword: (CES OR Cranial Electrotherapy Stimulation OR cranial electrotherapy stimulation OR noninvasive brain stimulation OR Alpha-Stim) AND (anxiety OR anxious OR panic OR phobia OR worrisome)with limitation on humans species

Embase N=1722

Keyword: (CES OR Cranial Electrotherapy Stimulation OR cranial electrotherapy stimulation OR noninvasive brain stimulation OR Alpha-Stim) AND (anxiety OR anxious OR panic OR phobia OR worrisome) ) with limitation on humans and clinical trial

Cochrane library N=403

Keyword: (CES OR Cranial Electrotherapy Stimulation OR cranial electrotherapy stimulation OR noninvasive brain stimulation OR Alpha-Stim) AND (anxiety OR anxious OR panic OR phobia OR worrisome)

**Supplementary Table S2 reasons of excluded trial**

Excluded references with reasons

**Inadequate data: n=31**

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**Supplementary Table S3 Jadad scores**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **First Author (year)** | **Randomisation** |  **Blinding** | **Withdrawl and drop out** | **Total scores** |
| **Barclay TH, 2014** | **2** | **2** | **1** | **5** |
| **Gong BY, 2016** | **2** | **0** | **0** | **2** |
| **Chen Y, 2007** | **1** | **0** | **0** | **1** |
| **Do JK, 2021** | **2** | **2** | **1** | **5** |
| **Cho S-Y, 2016** | **2** | **0** | **0** | **2** |
| **Cork RC , 2004** | **1** | **2** | **0** | **3** |
| **Lu L, 2014** | **1** | **1** | **0** | **2** |
| **Wu WJ, 2020** | **1** | **2** | **0** | **3** |
| **Tan G, 2011** | **2** | **2** | **0** | **4** |
| **Lyon D, 2015** | **2** | **2** | **0** | **4** |
| **NCT00723008** |  **1** | **2** | **1** | **4** |

**Supplementary Figure S4:** Risk of bias(Rob)



|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study ID | weight | domain1 | domain 2 | domain 3 | domain 4 | domain 5 | overall |
| Barclay TH, 2014 | 10.2 | low | Some concerns | low | low | Some concerns | Some concerns |
| Cho S-Y, 2016 | 1 | low | Some concerns | low | Some concerns | low | low |
| Cork RC, 2004 | 1 | low | low | low | low | low | low |
| Do JK, 2021 | 2.96 | low | low | low | low | low | low |
| Gong BY, 2016 | 9.25 | low | low | low | low | low | low |
| Lu L, 2014 | 13.88 | low | Some concerns | low | low | low | Some concerns |
| Lyon D, 2015 | 18.47 | low | low | low | low | low | low |
| NCT00723008 | 2.87 | low | Some concerns | low | low | low | Some concerns |
| Tan G, 2011 | 13.4 | low | low | low | low | low | low |
| Wu WJ, 2020 | 1 | low | low | low | low | low | low |
| Chen Y, 2007 | 1 | low | low | low | Some concerns | low | Some concerns |

Domain 1: Randomization process

Domain 2: Deviation from the intended intervention

Domain 3: Missing outcome data

Domain 4: Measurement of the outcome

Domain 5: Selection of the reported result

**Supplementary Table S5A:** Random-effects meta-regression analyses of potential moderators of the association of CES and anxiety symptoms

|  |  |  |  |
| --- | --- | --- | --- |
| **Clinical variables** | **Number of datasets** | **coefficient; 95% CI** | ***P*-value** |
| Female (%) | 11 | -0.7809;-2.9593 to 1.3975 | 0.4823 |
| Jadad score | 11 | -0.1012;-0.5454 to 0.3431 | 0.6553 |
| total sessions | 11 | 0.0056;-0.0120 to 0.0233 | 0.5316 |
| duration of each sessions | 11 | -0.0063;0.0356 to 0.0231 | 0.6758 |

\* *p*<0.05

**Supplementary Table S5B:** Random-effects meta-regression analyses of potential moderators of the association of CES and depression symptoms

|  |  |  |  |
| --- | --- | --- | --- |
| **Clinical variables** | **Number of datasets** | **coefficient; 95% CI** | ***P*-value** |
| Female (%) | 8 | 0.4252;-1.6720 to 2.5224 | 0.8486 |
| Jadad score | 8 | -0.2173;-0.7718 to 0.3373 | 0.7954 |
| total sessions | 8 | -0.0011;-0.0282 to 0.0381 | 0.7704 |
| duration of each sessions | 8 | 0.0025;-0.0727 to 0.0777 | 0.9478 |

\* *p*<0.05

**SupplementaryTable S6** Drop-out and adverse event

|  |  |  |
| --- | --- | --- |
| Author, year, study design | Drop-out (N/baseline sample, %)  | Adverse event (description: N) |
| Barclay TH, 2014, double blind RCTAnxiety disorder | Intervention group: 3/60=5%Control group: 4/55=7.2% | No adverse events reported: 0  |
| Gong BY, 2016, RCTFunctional constipation ‘ s anxiety symptoms | Intervention group: 14/38=36.8%Control group: 16/36=44.4% | Both grouppulsing, tickling, or tingling sensations of the ears : 3ear clips too tight : 2drowsiness : 1  |
| Chen Y, 2007,RCT, mixed anxiety and depressive disorder | Intervention group: 0/30=0%Control group: 0/30= 0% | Not mentioned  |
| Do JK, 2021,double blinded RCTHeadache ,anxiety symptoms | Intervention group: 1/12: 8.3%Control group: 1/12= 8.3% | Not mentioned |
| Cho S-Y, 2016,RCT,Obessity patient,anxiety symptoms | Both group: 0% | Not mentioned |
| Cork RC, 2004,double blinde RCTFibromyalgia,anxiety symptoms | Not mentioned | Not mentioned  |
| Lu L, 2014,RCT,anxiety disorder ,anxiety symptoms | Intervention group: 0/60=0%Control group: 0/60= 0%  | Not mentioned  |
| Wu WJ, 2020, double blinded RCT,Tic disorder ,anxiety symptoms | Intervention group: 3/32 = 9.4%Control group: 6/30= 20%  | Intervention group: 18Ear discomfort:5 ,headache: 2,dizzy: 5,sleepy: 2 ,nausea:1, Tinnitus:2Control group: 12Ear discomfort:6 ,headache:1,dizzy:1,sleepy: 0 ,nausea:1, Tinnitus:3  |
| Tan G, 2011,double blind RCTSpinal cord injury, anxiety symptoms  | Intervention group: 1/46 = 2.2%Control group: 4/59= 6.8%  | Intervention group:32Ear disconfort:12,legs and buttock discomfort:3,tinnutis:1,sleepy:7,dizzy:3, Nause:1,headache:2, unusual taste of mouth:1,increased pain:2Control group:25Ear disconfort:6,legs and buttock discomfort:3,tinnutis:1,sleepy:4,dizzy:1Nause:2,headache:4, unusual taste of mouth:1, palpitation and chest tightness:2,increased pain:1 |
| Lyon D, 2015, double blinded RCT,Breast cancer,anxiety symptoms | Intervention group: 14/84 = 16.7%Control group:16/83= 19.2%  | Intervention group: 1 has seizureControl group:0 |
| NCT00723008 | Intervention group: 5/10=50%Control group: 5/9=55.6% | Intervention group:9Nausea: 1, ear pain:3 , headache:1 , Increased Injury Site Pain:4 ,increased irritability : 1, night terrors:1 ,insomnia:2Control group:8stiffness: 1, ear pain:4 , headache:0 , Increased Injury Site Pain:3 , Lightheadedness: 1,increased irritability : 0, night terrors:1 ,insomnia:2 |

**Supplementary Figure S7:** Drop-out rate and adverse events rate

Drop-out rate

