European Journal of Integrative Medicine 54 (2022) 102157

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.sciencedirect.com/journal/european-journal-of-integrative-medicine

Systematic review

Is auriculotherapy effective and safe for the treatment of anxiety disorders? – A systematic review and meta-analysis

Andreia Vieira [a,b,*], António Moreira [c], Jorge Pereira Machado [a,b], Nicola Robinson [d], Xiao-Yang Hu [e]

[a] ICBAS - Institute of Biomedical Sciences, University of Porto, 4099-030 Porto, Portugal
[b] CBSin, Center of BioSciences in Integrative Health – Porto, Portugal
[c] Sport Sciences School of Rio Maior, 2040-413 Rio Maior, Portugal
[d] Institute of Health and Social Care, London South Bank University, UK
[e] Primary Care, Population Science, and Medical Education, University of Southampton, UK

ARTICLE INFO

Keywords:
Anxiety disorders
Auriculotherapy
Auricular acupuncture
Acupressure
Brain stimulation
Systematic review

ABSTRACT

Introduction: Auriculotherapy (AA) could support standard treatment for anxiety disorders (AD), but its effectiveness and safety remain undetermined. The aim of this systematic review was to determine whether AA was effective and safe for treating people with AD.

Methods: Searches were conducted on eight databases for randomized controlled trials (RCT) evaluating the effectiveness and safety of AA compared with placebo, waiting list treatment, routine care, or alternative treatment. Searches were run from inception until the 30th of June 2021. Methodological quality of included studies was assessed using the Cochrane risk of bias assessment tool and quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation tool. Meta-analyses were conducted using statistical software RevMan V5.4. The protocol was published and registered PROSPERO ID: CRD42021254503.

Results: Thirteen trials met the inclusion criteria for quality and of these nine were included in the meta-analysis. AA (n=386) reduced anxiety levels compared with placebo (n=382) standardized mean difference (SMD): -0.44 95% of Confidence Intervals (CI) [-0.60, -0.28], 9 studies, for AA compared with a waiting list (n=360), 8 studies SMD (-0.55; 95% CI [-0.70, -0.41]). Certainty was graded as moderate and with unlikely publication bias. There was moderate certainty of evidence for an AA (n=130) intervention for pre-operatory anxiety levels when compared with placebo (n=129) SMD -1.40 95% CI [-2.54, -0.26], 3 studies and when compared with a waiting list group (n=98) Mean difference (MD) -5.02 95% CI [-8.15, -1.90], 2 studies. Few studies reported adverse events and other important secondary outcomes such as salivary cortisol and vital signs.

Conclusion: AA may be effective as a complementary treatment for situational anxiety. There is still an evidence gap regarding its safety and efficacy. The type and frequency of AA used for anxiety treatment requires further exploration.

1. Introduction

Anxiety is one of the most natural body reactions in response to a given threat [1,2]. However, individual differences in physical and emotional health impairment can lead to hormonal changes, and anxiety can become pathological [3]. Although effective treatment approaches (e.g., pharmacotherapy, psychotherapy, and their combination) for anxiety are available, epidemiological studies have revealed that its prevalence has been increasing over time, particularly during the coronavirus pandemic[4]. In light of this, novel preventive and

Abbreviation: AA, Auriculotherapy; AD, Anxiety disorders; CI, Confidence intervals; CONSORT, Consolidated standards of reporting trials; DSM-V, Diagnostic and statistical manual of mental disorders; GRADE, Grading of recommendations assessment development and evaluation; MD, Mean difference; PRISMA, Preferred reporting items for systematic reviews and meta-analyze; RRs, Relative risks; RCT, Randomized controlled trials; STAI, State-trait anxiety inventory; SMD, Standardized mean difference; TCM, Traditional Chinese medicine; VAS, Visual analogue scale; WMD, Weighted mean differences.

* Corresponding author at: ICBAS, 4099-030 Porto, Portugal.
E-mail address: up201106326@icbas.up.pt (A. Vieira).

https://doi.org/10.1016/j.eujim.2022.102157
Received 8 May 2022; Received in revised form 26 June 2022; Accepted 7 July 2022
Available online 9 July 2022

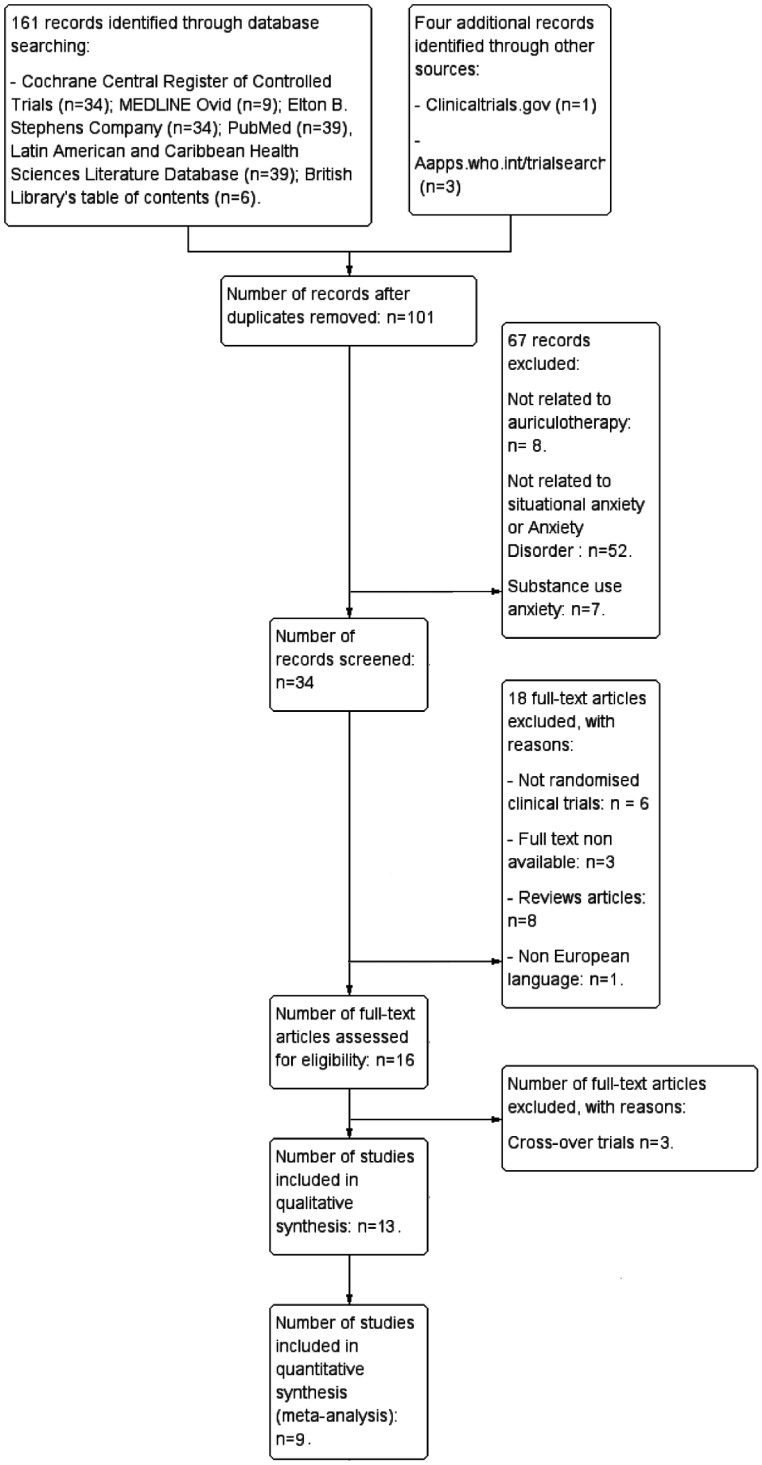

Fig. 1. - The systematic reviews and meta-analysis protocol flow chart.

treatment strategies need to be explored [5]. Some trials have shown encouraging findings using acupuncture for AD treatment, but there is insufficient research evidence to reach solid conclusions. [6–9].

AA is a technique derived from traditional acupuncture that developed into a distinct treatment system [10]. The stimulation of auricular areas appears to be associated with the reticular formation through the sympathetic and parasympathetic nervous systems [11,12]. Such information coming through the thermal, algic and proprioceptive stimuli are transmitted from the auricular pavilion by the trigeminal nerve fibres, auricular magnum, and minor occipital (sensitive branch of the cervical plexus). The vagus nerve[13] is responsible for the parasympathetic innervation of the lungs, heart, stomach, and small intestine, as well as the pharynx and larynx muscles, and it also sends information to essential brain regions in the regulation of anxiety (locus coeruleus, orbitofrontal cortex, hippocampus, and the amygdala) [14]. The trigeminal nerve mainly controls the muscles involved in mastication and facial sensitivity [15]. Finally, the cervical plexus innervates the neck, diaphragm, and thorax, where its rootlets diverge from the spinal accessory nerve after its exit from the jugular foramen and subsequently the course through the vagus fibres [16]. Recordings of vagus

Table 1
- Auriculotherapy compared to placebo group for anxiety treatment

Patient or population: anxiety disorders. **Intervention:** Auriculotherapy. **Comparison:** Placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Anticipated absolute effects Risk difference with Auriculotherapy
Auriculotherapy vs Placebo assessed with: State-Trait-Anxiety, Visual Analogic Scale for anxiety and Hamilton Anxiety Rating Scale	768 (8 RCTs)	⨁⨁⨁◯ Moderate[a]	SMD **0.44 lower** (0.6 lower to 0.28 lower)
Pre-operative anxiety assessed with: State-Trait-Anxiety, Visual Analogic Scale for anxiety and Hamilton Anxiety Rating Scale	259 (3 RCTs)	⨁⨁⨁◯ Moderate[a]	SMD **1.4 SD lower** (2.54 lower to 0.26 lower)
Exam anxiety in students assessed with: State-Trait-Anxiety Inventory	114 (2 RCTs)	⨁⨁◯◯ Low[c,d,e]	MD **2.44 lower** (5.67 lower to 0.79 higher)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **SMD:** standardized mean difference
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Different anxiety scales used
b. Some differences regarding the type of situational anxiety (students vs pre-operative).
c. small sample size.
d. Possible selective reporting bias.
e. Wide confidence intervals along on the included trials.

somatosensory have been shown to evoke potentials in the scalp [17] and have revealed the feasibility of AA as an effective therapeutic strategy for managing several clinical disorders, including pain [10,18], epilepsy [19], depression [20], migraine [21], and substance dependence [22, 23] and tinnitus [24]. Regarding anxiety, as per the protocol previously published, there is some limited evidence in favour of auricular acupuncture for perioperative anxiety [6,25], for AD disorders and major depressive disorders [26], for situational anxiety primary school examinations [27,28], and the reduction of state anxiety before dental treatments [29]. Although, there have been no systematic reviews to demonstrate AAś effectiveness for AD treatment [30]

Regarding the adverse events associated with AA, Correa et al., 2020 stated that AA used for the treatment of stress, anxiety and depression in adults and older adults could cause, headaches and bleeding at the needle application site [31] and local pain [32]. However, the authors [9] used the Jadad scale to determine the trials' quality, our systematic review aimed to appraise included studies using Cochrane's risk of bias tool and update the possible adverse events caused by AA in anxiety management.

Therefore, the primary aims were to:

I) Assess the effectiveness of AA on remission of AD.
II) Calculate the effectiveness of AA in anxiety symptoms evaluated through psychometrically robust and validated measures for anxiety symptoms.

Our secondary aims were to:

I) Evaluate the effectiveness of AA in reducing cortisol in saliva samples.
II) Describe changes in symptoms according to TCM (Traditional Chinese Medicine) diagnosis or general physical examination (e.g., temperature, heart rate, blood pressure or respiratory rate).
III) Determine the comparative efficacy of AA alone or plus usual care with other forms of AA (e.g., auricular acupuncture versus acupressure).
IV) Assess the safety of AA.
V) Describe frequent points used in AA for anxiety trials.

2. Methods

This is a systematic review of the literature based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyze (PRISMA) recommendations [33]. The PRISMA checklist is available in our protocol previously published [30] registered on PROSPERO, registration number/ ID: CRD42021254503.

2.1. Search strategy

Searches were run from inception until the 30th of June 2021 on the following databases: Cochrane Central Register of Controlled Trials; PubMed; MEDLINE Ovid; Elton B. Stephens Company; Latin American and Caribbean Health Sciences Literature Database; British Library's table of contents; Scopus, and ScienceDirect. We also searched the international trial registries (including US National Institutes of Health Ongoing Trials Register – ClinicalTrials.gov (clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/)) to identify additional ongoing and unpublished trials. The trial selection was independently performed by two reviewers (AV and AM) using the inclusion/exclusion criteria given below, followed by discussion and consensus with a third author (JM). The first stage of selection was conducted by identifying potentially relevant papers through the titles and abstracts and at the second stage the full text of the papers was appraised.

Full details of the search strategy, including Mesh terms, can be found in our protocol supplementary file [30].

3. Eligibility criteria

3.1. Included trials

The population consisted of all participants with AD following the Diagnostic and Statistical Manual of Mental Disorders, (DSM-V) diagnosis and situational anxiety: perioperative anxiety, anxiety before school examinations, anxiety post-abortion, postpartum-specific anxiety/ breastfeeding, or anxiety before dental treatment.

Regarding the intervention, we included trials that had used AA to treat AD as auricular acupuncture, auricular electroacupuncture, auricular acupressure, auricular moxibustion, auricular laser therapy, or auricular bloodletting therapy. AA was compared with waiting list control or with anxiety usual care (e.g., cognitive-behavioural therapies, music therapy, hypnosis, relaxation techniques). The primary outcomes were:

i) Remission/proportion of participants with the absence of all diagnoses for AD post-treatment, made by reliable and valid structured interviews as defined by DSM-V.

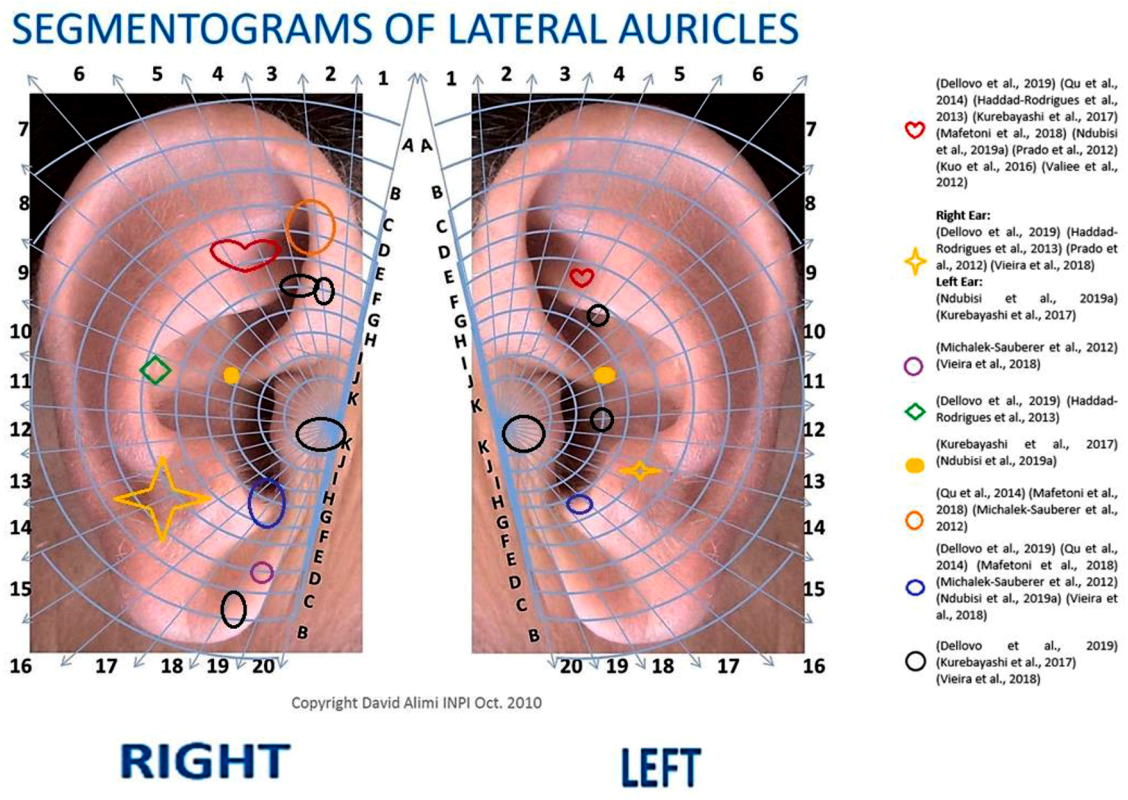

Fig. 2. – Points applied along the trials using Aimi D and Chelly J (2018) Cartography of French University scientific school of Paris (right and left medial auriculogram) from International AA Nomenclature. This cartography was used with permission [62].

ii) Reduction in anxiety symptoms post-treatment: measured using psychometrically robust measures of anxiety symptoms that yielded symptom scores on continuous scales [34], such as:
   a State-Trait Anxiety Inventory (STAI) [35,36].
   b Anxiety and Depression Scale [37].
   c Anxiety Visual Analogue Scale numerical rating scale (0-10/100) (VAS) [38].
   d Beck Anxiety Inventory [36,39].
   e Hamilton Rating Scale for Anxiety [36,40]).

The secondary outcomes were:

f) Reduction in cortisol in saliva samples [41].
g) Changes in symptoms according to TCM diagnosis or general physical examination (e.g., temperature, heart rate, blood pressure or respiratory rate).
h) Adverse events (AEs) reported by the number and type of reported adverse events during the trial, from randomization to post-treatment assessment. In this trial, an adverse event was "any untoward and unintended responses to the trial intervention, any dose administered, including all AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the trial intervention" [42].

This systematic review only included RCTs in English, French, Spanish, German, Portuguese, or Italian.

3.2. Excluded trials

The authors excluded all RCTs that, according to the diagnostic criteria of the Diagnostic Statistical Manual DSM-V; trial participants who were not assessed for AD diagnosis or those who did not report the situational anxiety as stated in our included standard criteria. Also, excluded were; guidelines for treatments, surveys, case series, case reports, quasi-RCTs, crossover trials, interrupted time-series trials, experimental and non-experimental trials, qualitative trials, trials with missing or incomplete data, cohort studies, reviews, conference abstracts/posters, expert opinion, duplicate publications, newspaper articles, book reviews, 'mass media publications', health publications, general comments, or letters, due to their potential high risk of bias. RCTs dated prior to January 2011 following the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines [43].

3.2.1. Data extraction and management

Two review authors (AV, AM) independently screened the titles and abstracts of all identified trials. The trials were coded as either "retrieve" (eligible or potentially eligible) or "do not retrieve". The trial characteristics and outcome data were extracted as follows:

- Methods: trial design, total duration of the trial, details of any 'run-in' period, withdrawals, and trial date).
- Participants: number, mean age, the severity of the condition, diagnostic criteria, comorbidities, inclusion criteria, and exclusion criteria.
- Setting: number of trial centres and location, trial setting.
- Interventions: type of intervention, length of the intervention, comparison group, excluded medications, delivery format, therapist contact time, person delivering the intervention and description of their qualification/years of experience.
- Outcomes: primary and secondary outcomes.

3.2.2. Risk of bias assessment

The risk of bias for each trial was assessed independently by two review authors (AV and AM), employing the criteria summarized in the Cochrane Handbook for Systematic Reviews of Interventions [44]. Any discrepancies were discussed with another review author (JM). The

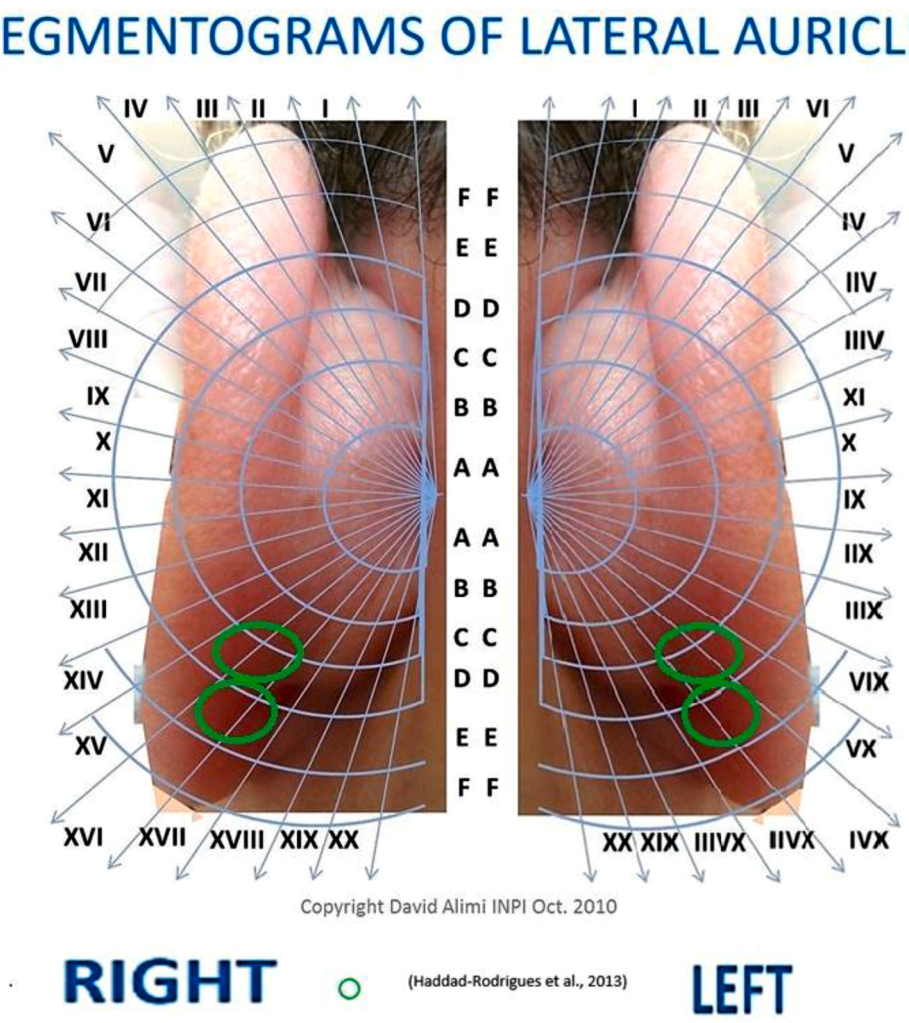

Fig. 3. - Points applied along the trials using Aimi D and Chelly J (2018) Cartography of French University scientific school of Paris (Medial auricular Segmentogram) from International AA Nomenclature. This cartography was used with permission [62].

same authors had judged each potential source of bias as low, high, or unclear risk of bias and had provided a supporting quotation from the trial to justify their judgment in the "Risk of bias" table. The risk of bias assessments were performed according to domains available in our protocol previously published [30]

3.2.3. Measures of treatment effect

Data from the assessment administered immediately after treatment (or the assessment closest to the end of therapy) was used to assess post-treatment outcomes. Dichotomous data (remission of primary anxiety diagnosis) and continuous data (anxiety scales, cortisol analyses, and general physical examination) were collected using standardized measures to assess post-treatment outcomes.

3.2.4. Effects of interventions

RevMan 5.4.1, the standard software provided by the Cochrane Collaboration, was employed to analyze the results of the RCTs. We performed a meta-analysis when the patients, interventions, controls, and outcomes were similar, and the corresponding data were sufficiently homogeneous. Continuous outcomes were expressed as weighted mean differences (WMDs) and dichotomous data as relative risks (RRs) with 95% confidence intervals (Cis). If there was significant heterogeneity, we explored the possible reasons by conducting a sensitivity analysis.

Heterogeneity was identified across the trials using both Chi-squared tests as well as I2.

To minimize bias in our findings and recommendations, we graded and assessed the available evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Profiler (pro), with four levels of evidence: high, moderate, low, and very low [45].

3.3. Dichotomous data

Odds Ratios (Ods) and 95% CI based on the random-effects model, with pooling of data via the inverse variance method of weighting, were employed and the estimate of significance was set at $P<0.05$. The authors calculated the number needed to treat an additional beneficial outcome with 95% CI, along with a summary statistic of all those responding to treatment reported as a percentage of the total number of participants for each comparison.

3.4. Continuous data

The continuous data was analyzed as MD or SMD and data was presented as a scale with a consistent direction of effect.

Skewed data was narratively described and reported as medians and interquartile ranges and analyses continuous data based on the random-effects model, with pooling of data via the inverse variance method of weighting. We use the SMD to pool continuous data measured in different ways across trials but conceptually the same (i.e. measuring

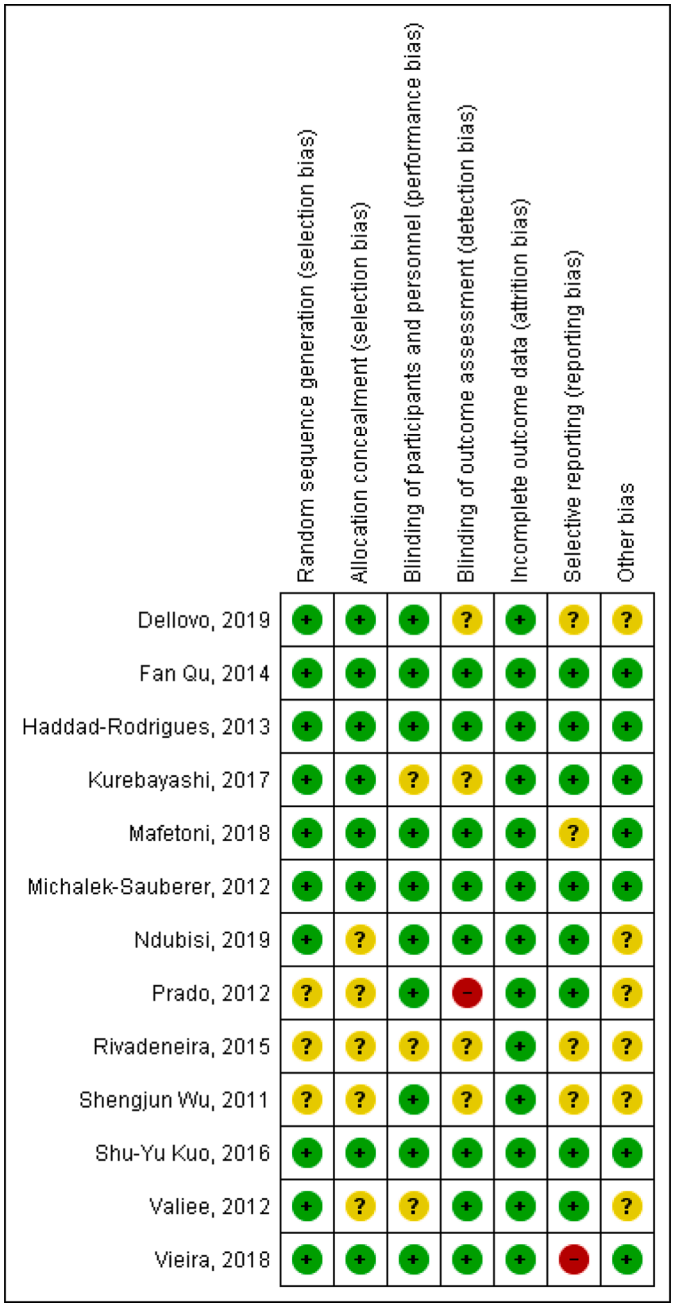

Fig. 4. - Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

anxiety or cortisol). We presented the endpoint data available for the same outcome with significance at $P < 0.05$.

3.5. Dealing with missing data

All investigators or trial sponsors were contacted via email to verify key trial characteristics and obtain missing numerical outcome data. All included trials that had not provided statistical data were suitable for estimating risk of bias, but not for meta-analyses.

3.6. Missing participants

The authors assumed all participants non-completers in the AA group were treatment failures, and non-completers in the control group were treatment successes. For dichotomous outcomes, we undertook completed analysis, using only data from participants who completed post-treatment assessments.

3.7. Publication bias assessment and sensitivity analysis

The authors conducted Publication bias by inspecting funnel plots and performing Egger's regression test [46] in the presence of more than 5 studies as recommended [44]. The funnel plot and the Eggers test was performed in the comparison of AA compared to placebo and waiting list controls.

The sensitivity analyses were also performed by examining each study to determine the source of any substantial heterogeneity[44]. To determine the existence of heterogeneity, we used the Chi^2 test and the I^2 statistic with a significance of $p < 0.1$. The Cochrane Handbook for Systematic Reviews of Interventions recommends sensitivity analyses if either moderate heterogeneity (I^2 around 30% to 60%) or substantial heterogeneity (I^2 in the range of 60% to 90%)[44] is found. Specifically, where it was meaningful to do so, we undertook subgroup analyses to investigate differences between:

i) Types of AA (e.g., auriculotherapy with needles, laser, electrotherapy, or seeds).
ii) AA interventions with a different number of sessions (1 session, ≥ 5 sessions and≥ 10 sessions).
iii) Studies specifying different healthcare practitioners (e.g., licensed acupuncturists, physicians, physiotherapists, nurses, or allied health professionals) with those studies without a description of who performed the auriculotherapy treatment.

4. Data synthesis

We conducted meta-analyses by carrying out separated analyses to identify whether AA was more effective post-treatment than waiting list, treatment as usual, or alternative therapies; and whether AA in combination with standard care was more effective than usual care alone or placebo.

Data was entered into Review Manager 5.4 [47] and presented graphically. The area to the left of the line of no effect indicates a favorable outcome for AA. Trials characteristics, and the excluded trials list can be found in supplementary file.

The five GRADE considerations (e.g., trial limitations, consistency of effect, imprecision, indirectness, and publication bias) were used to assess the quality of evidence following the Cochrane Handbook for Systematic Reviews of Interventions, employing GRADEpro GDT software [45].

5. Results

Our search identified 165 citations, and 34 full-text articles were reviewed, as shown in the flow diagram (Fig. 1). A total of 13 trials (1366 subjects) met our inclusion criteria (Table 1) and were included in the quality analysis. We attempted to contact the authors of three additional publications [48–50] that may have been eligible for inclusion. However, they did not reply. We also found some trials measuring one or more outcomes relevant to this review. But, those trials either did not report the outcomes in a format suitable for meta-analysis [51–54] or had a cross-over methodology [27,31] or had a non-randomized arm [55] and were therefore not included in the meta-analyses.

The 13 included trials included a wide variety of AA interventions (Table 1). Auricular acupuncture trials were more frequent (eight trials) than acupressure (five trials). Regarding auricular acupuncture, ASP needles were more commonly used [28,29,32,53,54] than steel needles [56,57]. Concerning acupressure, only two trials had used semen vaccariae seeds [52,58], while other trials used plastic beads [59]; crystal microspheres [60]; mustard seeds [51] or Mexican Argemona seeds [61]. We found only one trial [32] comparing AA using seeds versus

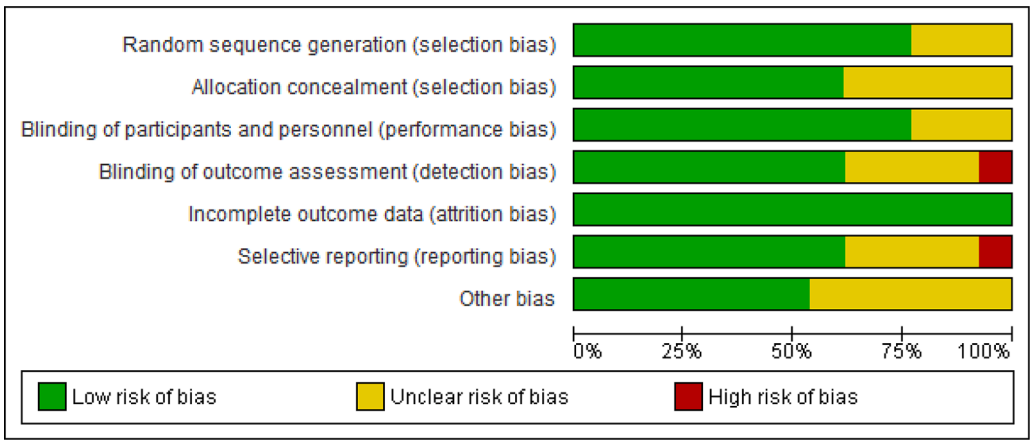

Fig. 5.-. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

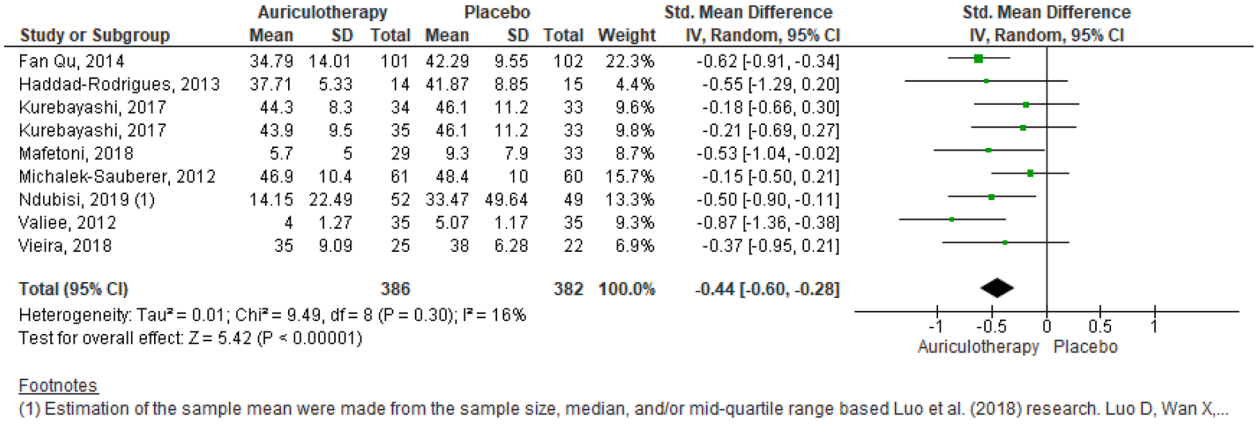

Fig. 6. - Forest plot of comparison: Auriculotherapy compared to placebo for all types of anxiety, outcome: Anxiety Scales.

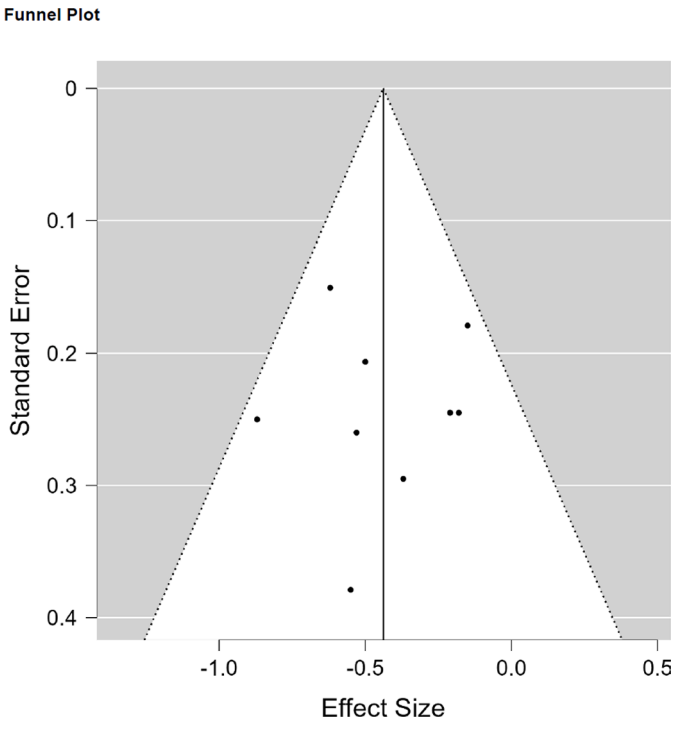

Fig. 7. - Funnel plot of comparison: Auriculotherapy compared with placebo for all types of situational anxiety using all anxiety scales.

semi-permanent needles for exam anxiety in students. Authors have cited that AA produced the best result for reducing state anxiety with needles compared with seeds [44].

Following the International AA Nomenclature, the area covered from E3-5 and F5 (Figs. 2 and 3) were the most frequent areas selected for treatment by the majority of the included trials (nine trials), followed by I17-16, H16-18, G18-17, F18 (6 trials) and F13-15, E14,15, D14-16 (4 trials). The most frequent areas chosen by most of the included trials (E3-5 and F5) referred to the "Shen-Men point" or "Cosmonaut point", followed by "Hypophysis" (H17), "Hippocampus" (F14)," and "Sympathetic master point" (E14). Only two trials [28, 57] reported using alternate ears bilaterally (e.g., right, or left ear) for selected points.

Regarding outcome measures (Table 1), most trials used the STAI [28,29,32,52,53,56,58,61], followed by VAS for anxiety [28,32,57,59], cortisol levels [52]. Other trials used vital signs [51,52,59] or SN-TCM [28] as a secondary outcome. However, it was not possible to conduct a meta-analyses for those secondary outcomes. While Kuo et al. [52] have reported the cortisol levels and vital signs for post-caesarean section women comparing AA with control group, Valie et al. [59] have reported vital signs comparing the AA with placebo group and Dellovo et al. [51] but did not provide enough data to allow comparisons.

The duration and intensity of treatment specified in the trial protocol varied between trials. Most trials (n=10) in this review assessed outcomes after one session [28,29,32,51,52,57–61], while one trial assessed after 2 treatments [56], only two trials assessed after 8 treatments [54,61], and one trial evaluated after 12 sessions of AA (one session per week) lasting 5 to 10 minutes per session [53]. For the majority of included trials (6 trials) acupuncturists delivered the intervention [28,29,53,61] specifically, nurses who were also practicing

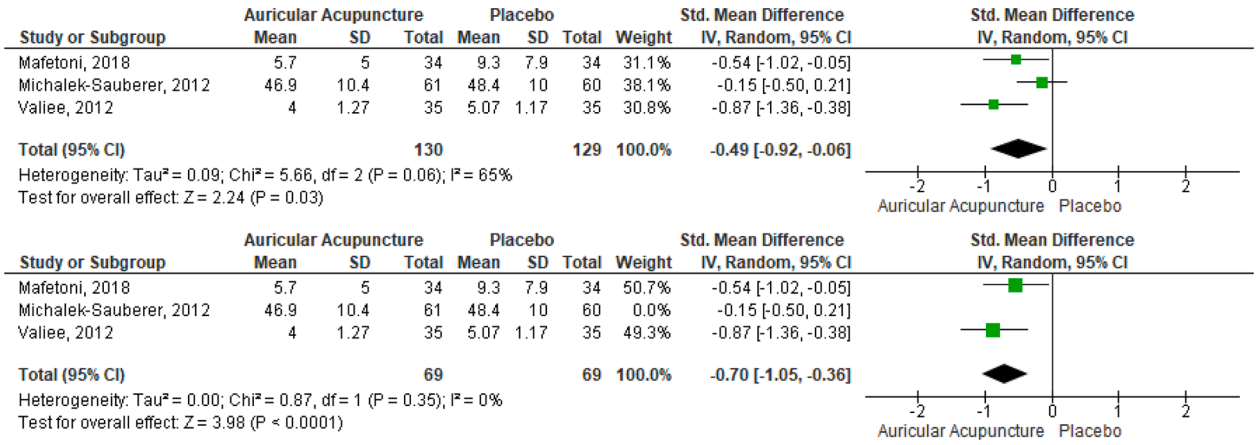

Fig. 8.. Forest plot of comparison: AA compared to placebo for pre-operatory anxiety, outcome: State-Trait-Anxiety, Visual Analogic Scale for anxiety and Hamilton Anxiety Rating Scale.

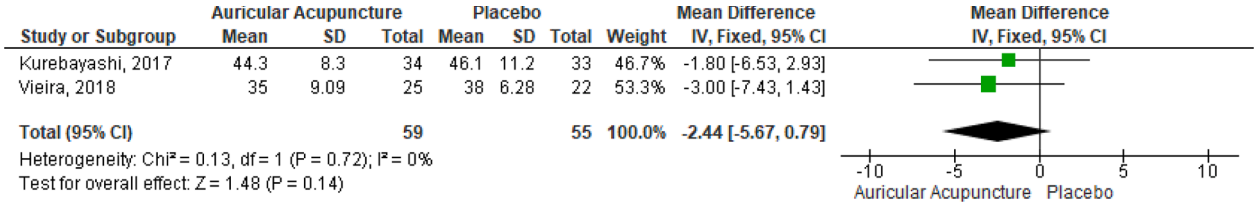

Fig. 9. - Forest plot of comparison: AA compared to placebo for exam anxiety in students, outcome: State-Trait-Anxiety Inventory.

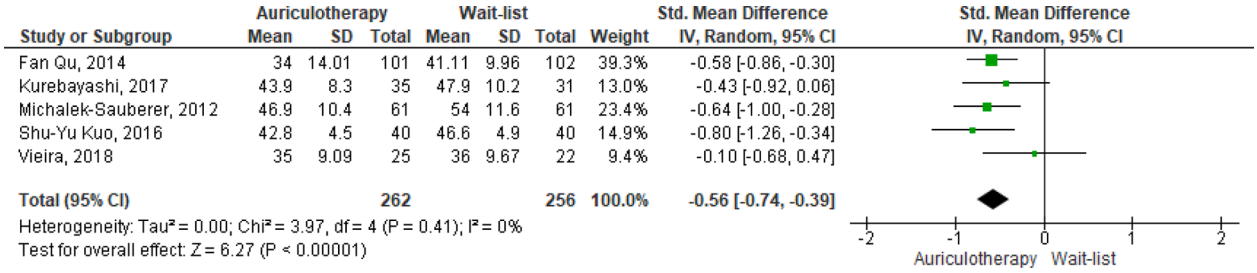

Fig. 10. – Forest plot of comparison: AA compared to waiting list for all types of anxiety, outcome: State-Trait-Anxiety Inventory.

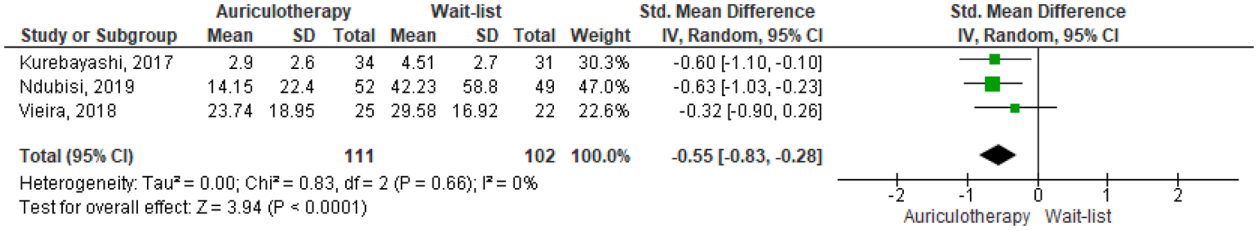

Fig. 11. - Forest plot of comparison: AA compared to waiting list for all types of anxiety, outcome: Visual analogic scale for anxiety.

acupuncture [53,56]. In 3 trials, treatment was delivered by practitioners working in General Heath care with AA training [32,58,60], only 1 trial used Traditional Chinese medicine physicians [52]. However, four trials did not report any details on the staff /practitioners providing the intervention [51,54,57,59].

Preoperative Anxiety was the most frequent type of anxiety [29,51,52,54,59,60,63], followed by anxiety in students [28,32,53] before examinations. We found only one trial on the use of AA for anxiety on the first-trimester abortion [57], one trial for anxiety in lactating mothers [56], one trial for anxiety used after in vitro fertilization [58], and only one trial focused on the use of AA for generalized AD [61]. Regarding follow-up, only Haddad-Rodrigues et al. [56], Kurebayashi et al. [32] mentioned high numbers of participants lost at follow-up, and Mafetoni et al. [60] reported no losses at follow up. Of all the included trials, only Prado et al. [53] cited the time frame for follow-up.

Unfortunately, most trials (10 studies) did not record or assess adverse effects [28,29,32,51-54,56,59,60]. Three trials did not identify or report any side effects [57,58,61] after AA.

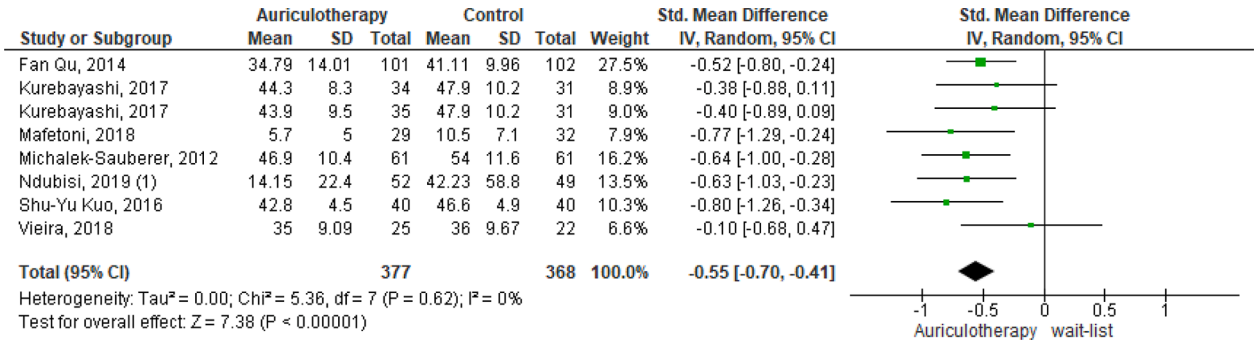

Fig. 12. - Forest plot of comparison: AA for all types of Anxiety, outcome: Anxiety scales.

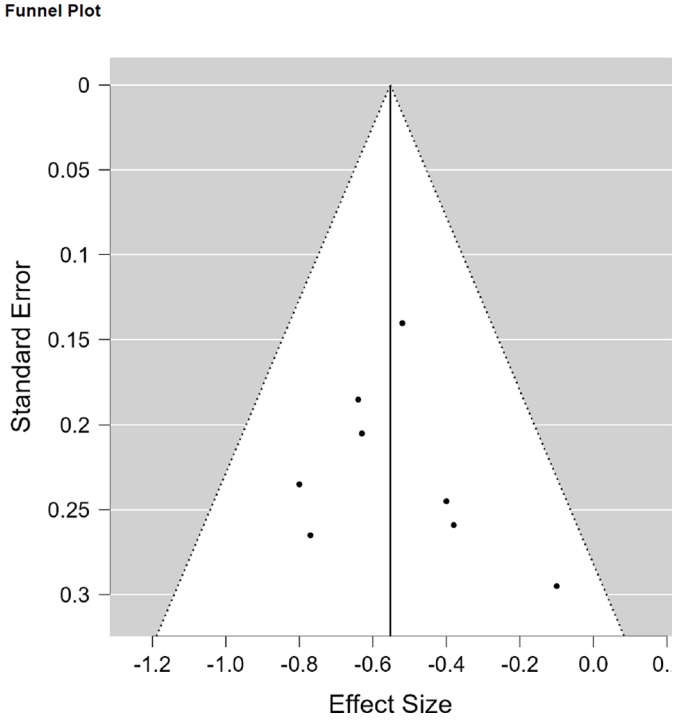

Fig. 13. - Funnel plot of comparison: Auriculotherapy compared with waiting list for all types of situational anxiety using all anxiety scales.

5.1. Risk of bias in included trials

Randomization and allocation concealment

The summary of the risk of bias (Fig. 4) shows that three trials did not provide information on the methods of randomization [53,54,61] and five trials did not report the allocation concealment used [53,54,57,59,61]. However, the risk of bias graph (Fig. 5) identified that around 75% of trials used a computer program to allocate participants to randomized groups, and the majority of these trials reported that allocations were concealed [29,32,51,52,56,58,60].

Attrition and reporting bias

As previously indicated, some trials presented their data and results statistically with p-values. However, most trials included complete data and had previously published their protocol [29,32,52,53,56-59]. We did not find evidence of a previously published protocol for four trials [51,54,60,61], so unclear risk was attributed. Only one trial was considered as having a high risk of attrition or reporting bias due to missing evidence of a previously published protocol [28].

Table 2
- Auriculotherapy compared to wait-list for situational anxiety

Patient or population: situational anxiety. **Intervention:** Auriculotherapy. **Comparison:** Wait-list

Outcomes	N° of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Anticipated absolute effects Risk difference with Auriculotherapy
Situational anxiety assessed with: State-Trait-Anxiety-Inventory	518 (5 RCTs)	⨁⨁⨁◯ Moderate[a,b]	SMD **0.56 SD lower** (0.74 lower to 0.39 lower)
Situational anxiety assessed with: State-Trait-Anxiety-Inventory and Visual Analogic Scale for anxiety	745 (8 RCTs)	⨁⨁⨁◯ Moderate[a,b]	SMD **0.55 lower** (0.7 lower to 0.41 lower)
Pre-operatory anxiety assessed with: State-Trait-Anxiety Inventory	198 (2 RCTs)	⨁⨁⨁◯ Moderate[cd]	MD **5.02 lower** (8.15 lower to 1.9 lower)
Students anxiety assessed with: State-Trait-Anxiety Inventory	113 (2 RCTs)	⨁⨁◯◯ Low[ce,f]	MD **2.53 SD higher** (5.99 higher to 0.94 higher)
Pre-operatory anxiety assessed with: Anxiety scales	266 (3 RCTs)	⨁⨁⨁◯ Moderate[c]	SMD **0.72 lower** (0.97 lower to 0.47 lower)
Exam anxiety assessed with: State-Trait-Anxiety Inventory	113 (2 RCTs)	⨁⨁◯◯ Llow[a,e]	MD **2.53 lower** (5.99 lower to 0.94 higher)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention; MD: mean difference; SMD: standardised mean difference. Explanations:

a. Selective reporting bias.

b. Some differences regarding the type of situational anxiety (students vs pre-operative).

c. Wide confidence intervals along on the included studies.

d. Different preoperative anxiety post-caesarean population versus dental surgery patients. e. Unclear blinding of participants and outcomes. Possible selective reporting.

f. Small sample size. GRADE Working Group grades of evidence. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

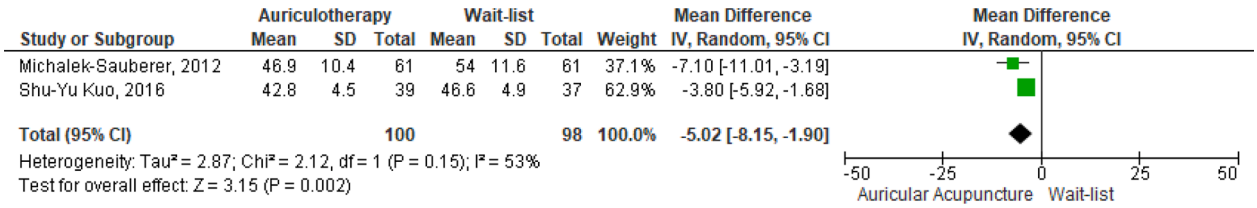

Fig. 14. - Forest plot of comparison: AA compared to waiting list for pre-operatory anxiety, outcome: State-Trait-Anxiety Inventory.

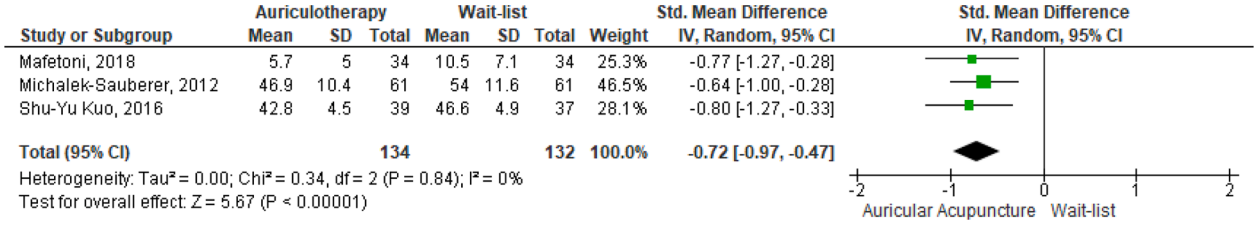

Fig. 15. – Forest plot of comparison: AA compared to waiting list for pre-operative anxiety.

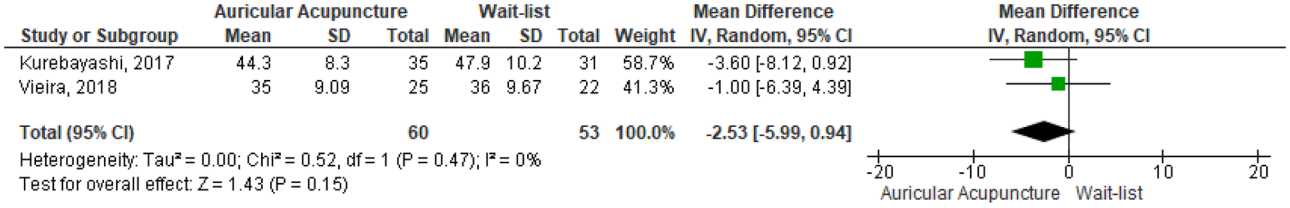

Fig. 16. - Forest plot of comparison: AA compared to waiting list for exam anxiety in students, outcome: State-Trait-Anxiety Inventory.

Table 3
- Auriculotherapy compared to usual care for generalized anxiety disorder

Patient or population: Generalized anxiety disorder. **Intervention:** Auriculotherapy. **Comparison:** usual care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Auriculotherapy
Nightmare	22 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 0.64** (0.25 to 1.62)	667 per 1000	**240 fewer per 1000** (500 fewer to 413 more)
Nervousness	22 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 0.62** (0.22 to 1.77)	538 per 1000	**205 fewer per 1000** (420 fewer to 415 more)
Sweating	10 (1 RCT)	⨁⨁◯◯ Low[a,b]	**OR 0.33** (0.01 to 8.18)	750 per 1000	**253 fewer per 1000** (721 fewer to 211 more)
Irritability	23 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 0.28** (0.05 to 1.64)	722 per 1000	**520 fewer per 1000** (686 fewer to 462 more)
Memory difficulty	24 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 0.23** (0.04 to 1.41)	722 per 1000	**556 fewer per 1000** (693 fewer to 296 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio. **Explanations:** a. Unclear selection, performance, detection and reporting biases. Small sample size and small number of events.

GRADE Working Group grades of evidence: High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Blinding

Due to the nature of the intervention, it was not possible to blind all the staff who delivered the intervention. Nevertheless, 75% of trials had ensured that participants and outcome assessment staff were "blinded", which was considered a low risk for personnel bias [28,29,52,54,56-58, 60].

Three trials were unclear regarding blinding of participants [32,59, 61] and, four trials were unclear about blinding outcome assessment [32,51,54,61]. Although Prado et al. [53] was the only trial reporting that the first author carried out data collection, we considered there was a high risk of detection bias.

Other Bias

Some trials have not reported any therapist competence, and adherence to the treatment protocol, so unclear risk was given [51,54, 57,59]. Although more than half of the trials have appropriate or reasonable therapist competence and adherence to the treatment protocol, consequently, a low risk of other bias was attributed.

5.2. AA compared to Placebo

5.2.1. Anxiety in general

Based on nine trials (Fig. 6), the AA group (386 patients) and the

placebo (group 382 patients) reported for all anxiety outcomes (STAI, VAS, Hamilton Anxiety Rating Scale) significant changes. Based on low Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.49$, df = 8 (P = 0.30); $I^2 = 16\%$ with a test for overall effect: Test for overall effect: Z = 5.42 (P < 0.00001), the pooled results showed a higher effect for AA group SMD -0.44 95% CI [-0.60, -0.28]. The estimation of the sample mean was optimally estimated from the sample size, median, and mid-quartile range based on Luo et al. [64] recommendation in medical research. Observing the funnel plot (Fig. 7) and by performing Egger's regression test, we considered the unlikely presence of publication bias p=0.961. Although we judged these as having moderate certainty of evidence (Table 1) due to different anxiety scales used in the analysis and there were some differences regarding the type of situational anxiety (students and pre-operative anxiety).

Pre-operative anxiety. The pooled results showed significant differences (Fig. 8) for outcomes STAI, Hamilton Anxiety Rating Scale, and VAS where the SMD was -0.49 [-0.92, -0.06], with high heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 5.66$, df = 2 (P = 0.06); $I^2 = 65\%$, Test for overall effect: Z = 2.24 (P = 0.03).

After conducting a sensitivity analysis, we realized that the heterogeneity vanished after removing Michalek-Sauberer [29] study (Fig. 8) and the effect size turned out to be higher: SMD= -0.70 [-1.05, -0.36]. This result could be either due to STAI outcome used while the other RCT used VAS and Hamilton AnxietyRating Scale or due to different preoperative conditions between studies. Although, both studies included in the second analysis had used similar auricular points (F5-6) with seeds in only one treatment session. Therefore, we have graded moderate certainty of evidence (Table 1).

Exam anxiety in students.. Only two trials with 59 students in AA group and 55 students in the placebo group reported a decrease on STAI scale for AA, MD= -2.44; 95% CI: -5.67, 0.79, Heterogeneity: $Chi^2 = 0.13$, df = 1 (P = 0.72); $I^2 = 0\%$, Test for overall effect: Z = 1.48 (P = 0.14), however there was not strong evidence that the intervention had an effect (Fig. 9). We decided to use fixed effects because those two trials shared a similar effect size, and a random effect would not change the results. Due to the wide confidence intervals among the included trials, different auricular points used, different sessions (between one and 10 sessions) and the small sample, this was graded as having a low certainty of evidence (Table 1).

5.3. AA compared to waiting list

Anxiety in general

Linking the treatment effectiveness of AA versus waiting list when we compared all included trials, either, the outcome STAI (Fig. 10) and VAS (Fig. 11) has decreased in the AA group (SMD -0.56; 95% CI: -0.74, -0.39; in five trials, Heterogeneity was not found: $Tau^2 = 0.00$; $Chi^2 = 3.97$, df = 4 (P = 0.41); $I^2 = 0\%$; Test for overall effect: Z = 6.27 (P < 0.00001)), and SMD -0.55; 95% CI [-0.83, -0.28], 3 trials, Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.83$, df = 2 (P = 0.66); $I^2 = 0\%$; Test for overall effect: Z = 3.94 (P = 0.0001) respectively. Both outcomes STAI and VAS were stastistically significant, and therefore decreased with an AA intervention. To investigate the effect using both scales (Fig. 12), we compared the AA (377 participants) versus waitinlist (368 participants) with 8 trials in total, the preference was towards the AA group in all trials, where the SMD is -0.55; 95% CI [-0.70, -0.41], Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.36$, df = 7 (P = 0.62); $I^2 = 0\%$, Test for overall effect: Z = 7.38 (P < 0.00001), also showing statistical significance. By performing sensitivity analysis and removing one study assessed as having a high risk of selective reporting [28], the results did not change but the effect was slighty higher (SMD -0.58 [-0.74, -0.43]). Observing the funnel plot (Fig. 13) and by performing Egger's regression test, we considered the unlikely presence of publication bias p=0.621. Although, due to different types of situational anxiety (pre-operatory and exam anxiety), selective reporting bias, unclear blinding of participants, we graded moderate certainty of evidence (Table 2).

Pre-operatory anxiety

There was only one study reporting the cortisol levels [52] where the authors found differences for AA group (n=39) MD= -0.48 [-0.94, -0.03] compared with waiting list (n=37), however meta-analyses was not possible for this outcome. Regarding anxiety based on scales, two trials with 100 patients in the AA group and 98 patients in the waiting list group reported significant changes for the outcome STAI. Based on the I^2 test-value (Fig. 14), Heterogeneity was considered moderate: $Tau^2 = 2.87$; $Chi^2 = 2.12$, df = 1 (P = 0.15); $I^2 = 53\%$ with a test for overall effect: Z = 3.15 (P < 0.002), the pooled results showed a significant effect for AA group MD = -5.02, 95% CI [-8.152, -1.90]. In this case, we decided to use the random-effects model because trials did not share a common effect size. Sensitivity analysis was not possible as both studies were considered low risk of bias, but different preoperative anxiety populations in both trials could lead to a high percentage of heterogeneity as distinct auricular points choosen (F6-5 versus G17, D2,3,19).

While Shu-yu Kuo[52] trial participants were post-caesarean women, Michalek-Sauberer [29] trial participants were dental surgery patients. Also, those results are corroborated without heterogeneity ($Tau^2 = 0.00$; $Chi^2 = 0.34$, df = 2,P = 0.84; $I^2 = 0\%$), if we add one more trial [60] to the analysis using the outcome Hamilton Rating Scale for Anxiety (Fig. 15). Therefore, with SMD= -0.72 95% CI [-0.97, -0.47], favorable for the AA group, and so, we consider moderate certainty of evidence (Table 2).

Exam anxiety in students.

Only two trials with 60 students in the AA group and 53 students in the waitinglist group reported a decrease (Fig. 16) on the STAI scale for AA (MD -2.53; 95% CI: -5.99, -0.94), Heterogeneity: $Chi^2 = 0.52$, df = 1 (P = 0.47); $I^2 = 0\%$, Test for overall effect: Z = 1.43 (P = 0.15). We decided to use fixed effects because those two trials shared a similar effect size, and a random effect would not change the results. In this case, due to small sample sizes, unclear blinding of participants/ outcomes, and possible selective reporting from Vieira et al. [28], different auricular points used, different sessions (between one and 10 sessions) and due to the small sample, this was graded as low certainty of evidence (Table 2).

5.4. Auriculotherapy alone or plus usual care versus usual care for anxiety disorder

We found only one trial [61] comparing AA (n=30) with Mexican Argemona seeds versus conventional therapy (clorodiazepóxido, 10 mg and trifluoperazine, 1mg; n=30) for generalized AD treatment. Rivadeneira et al. [61] performed a Self Assessment Inventory test (SAIT) and remission of anxiety symptoms after the 4th and 8th weeks. Those authors cited that "insomnia, irritability and memory symptoms decreased more remarkably in the group treated with AA". AA appeared to be more effective in treating anxiety which could potentially reduce the use of psychopharmacologic drugs. However, due to a lack of research in this area, comparison with other trials was impossible. Consequently, we have graded Low certainty of evidence (Table 3).

6. Discussion

Recently, Nielsen et al. [65] found that the most frequent risk of AA was infection, perichondritis, and chondritis from needles. We identified two trials that measured adverse events as a secondary outcome, and they did not find any serious adverse events. Nonetheless, using spheres in AA clinics will provide clinical benefits without the risks associated with needles [65]. Consequently, we strongly recommend the adverse effects reported in future research to establish if AA is safe for treatment

of anxiety.

More than half trials included in this review appeared to report appropriate/reasonable therapist competence and adherence to the treatment protocol. In six included trials, the acupuncturists were responsible for the treatment. The lack of reporting important information like therapist experience, training, and competence in treatment protocols remains problematic. However, the literature has frequently described that acupuncture is considered safe in the hands of well-trained practitioners [66].

We found only one trial [61] comparing Mexican Argemona seeds versus conventional therapy concerning generalized AD. Following that trial, AA was more effective in decreasing anxiety and reducing the use of psychopharmacologic drugs. Although, due to a lack of research in this field, comparisons with other trials were impossible. Our results follow Pilkington et al. [6] research, which also identified the challenge of interpreting the findings of acupuncture for generalized AD. Pilkington et al. [6] found two trials and these lacked methodological details. Moreover, when they compared acupuncture with drug therapy, no difference was observed because the trials were too weak to make a valid assessment and comparison [6]. Regarding the type of AA, we found only one trial [32] comparing AA using seeds versus semi-permanent needles for exam anxiety in students. The outcomes VAS and STAI were performed after the 4th and 8th weeks. Authors have reported that AA produced the best results for reducing state anxiety using needles compared with seeds. However, due to the lack of randomized controlled trials, we were unable to make comparisons.

Generally, our results support the systematic review done on acupuncture by Pilkington et al. [6], where all included trials reported positive findings, but lacked methodological detail. Similarly, they found that generally, the trials on perioperative anxiety were superior.

In our work, we did not find enough evidence to support the hypothesis that AA compared with placebo had a significant positive effect in reducing students' anxiety, but we did find that AA was better than a waiting list group. In fact, some researchers are against using placebo in AA trials [67], as the ear is tiny organ and has more than 93 documented active acupoints [68]. The stimulation of any point may produce physiological effects or affect the patient's belief [67]. Besides that, neurotransmitters such as endogenous opioids, dopamine and serotonin are also released, thereby modulating the individual's biological reactions [69].

On the other hand, there seems to be a continual tension between acknowledging the possible therapeutic utility of placebo prescription and the ethical issues surrounding its use [70]. The field of placebo research has accepted that a placebo might not be as distinctively defined as it is necessary for conducting a clinical trial in the non-pharmacological area [71]. Placebo effects are viewed as positive and valuable treatment factors, particularly in clinical practice, and are a part of every routine treatment [72].

Some results shown in our systematic review have clinically unimportant differences and low certainty, so we recommend different auricular approaches and more rigorous protocols to increase the certainty level of the results. The truth is that the type of auricular stimulation, type of method selected to choose the auricular points, number of sessions, and the treatment duration for anxiety varied between included studies has led to a lack of agreement on the optimal period of auricular therapy in the absence of consistency.

7. Limitations

The number of patients and the quality of trials included limited this review. One of the strengths of our study was that only RCTs were used to minimize the amount of bias. However, we excluded other studies with interventions that could have changed the results.

Moreover, as AA is widely used in traditional medicine, the results of this systematic review may be affected by the exclusion of Chinese databases (32) and, any unpublished trials. Nevertheless, we strongly recommend further updated analysis in the future with the inclusion of Chinese databases to corroborate these results.

8. Conclusion

Based on this systematic review, there is evidence that AA may reduce anxiety levels as measured by psychometrically robust scales of anxiety symptoms. Clinicians may consider AA as an adjunct or alternative when concerns about anxiety drug side effects are severe, contraindicated, or previously ineffective. Auriculotherpy can decrease cortisol levels, however only one study was found, thus, more research would be ideal. There is still a gap of reporting the AA adverse events and lack of research in AD following appropriate diagnosis. We found the area covered from (E3-5 and F5) referred to as "Shenmen point" or "Cosmonaut point", were the most frequent areas selected by most of the included trials. However the type of AA (e.g., needles vs seeds) and the methodology used behind the points chosen for anxiety treatment, also requires more research.

Authors' contributions

Andreia Vieira and Xiao-Yang (Mio) Hu provided the conception and design of the trial. Andreia Vieira, António Moreira, Jorge Pereira Machado, contributed to data collection, analysis, and interpretation of data. Nicola Robinson and, Xiao-Yang (Mio) Hu contributed to drafting the article and revising it critically for important intellectual content. Andreia Vieira prepared figures and tables. All authors reviewed the manuscript and approved the version to be published.

Financial support

There was no financial or other support or sponsors.

Declaration of Competing Interests

Nicola Robinson is Editor in Chief of this journal, and Xiao-Yang Hu is a member of the journal's editorial board. The author Andreia Vieira carried out this systematic review as part of her PhD work. There are no other conflicts of interests to declare.

Data availability

The authors have supplied the characteristics of the included trials in supplementary file.

Acknowledgments

This article is the result of work supported by Abel Salazar Institute of Biomedical Sciences of the University of Porto resources and facilities.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eujim.2022.102157.

References

[1] L. Notebaert, et al., Trait anxiety and the alignment of attentional bias with controllability of danger, Psychol. Res. 84 (3) (2020) 743–756.
[2] World Health Organization, Depression and Other Common Mental Disorders, World Health Organization, Geneva, Switzerland, 2017.
[3] E. Dean, Anxiety, Nurs. Stand. 30 (46) (2016) 15.
[4] J. Santabarbara, et al., Prevalence of anxiety in the COVID-19 pandemic: an updated meta-analysis of community-based studies, Prog. Neuropsychopharmacol. Biol. Psychiatry 109 (2021), 110207.
[5] V.W. Wong, et al., Lifestyle medicine for anxiety symptoms: a meta-analysis of randomized controlled trials, J. Affect. Disord. (2022).

[6] K. Pilkington, et al., Acupuncture for anxiety and anxiety disorders–a systematic literature review, Acupunct. Med. 25 (1–2) (2007) 1–10.
[7] A. Tan, et al., Efficacy and safety of acupuncture combined with western medicine for anxiety: a systematic review protocol, Medicine (Baltimore) 99 (31) (2020) e21445.
[8] D. Amorim, et al., Acupuncture and electroacupuncture for anxiety disorders: a systematic review of the clinical research, Complement. Ther. Clin. Pract. 31 (2018) 31–37.
[9] H.P. Correa, et al., Effects of auriculotherapy on stress, anxiety and depression in adults and older adults: a systematic review, Rev. Esc Enferm USP 54 (2020) e03626.
[10] G.N. Asher, et al., Auriculotherapy for pain management: a systematic review and meta-analysis of randomized controlled trials, J. Altern. Complement. Med. 16 (10) (2010) 1097–1108.
[11] B.J. Yates, P.S. Bolton, V.G. Macefield, Vestibulo-sympathetic responses, Comprehensive Physiol. 4 (2) (2014) 851–887.
[12] S.A. Mangold, M.D.J. Neuroanatomy, Reticular Formation, in StatPearls (2022). Treasure Island (FL.
[13] P. Rabischong, C. Terral, Scientific Basis of Auriculotherapy: State of the Art, Med. Acupunct. 26 (2014) 84–96.
[14] B.J. Kenny, B. Bordoni, Neuroanatomy, Cranial Nerve 10 (Vagus Nerve). StatPearls, 2022. : Treasure Island (FL).
[15] R.D. Sanders, The Trigeminal (V) and Facial (VII) Cranial Nerves: head and Face Sensation and Movement, Psychiatry (Edgmont) 7 (1) (2010) 13–16.
[16] M.T. Jobe, et al., Peripheral Nerve Injuries, Fourteenth Edition, Chapter 62, Campbell's Operative Orthopaedics, 2021 ed, ed. E. Inc.
[17] A.J. Fallgatter, et al., Far field potentials from the brain stem after transcutaneous vagus nerve stimulation, J. Neural Transm. (Vienna) 110 (12) (2003) 1437–1443.
[18] M.B. Sant'Anna, et al., Auriculotherapy for Chronic Cervical Pain, Med. Acupunct. 33 (6) (2021) 403–409.
[19] K. Wu, et al., Transcutaneous vagus nerve stimulation for the treatment of drug-resistant epilepsy: a meta-analysis and systematic review, ANZ J. Surg. 90 (4) (2020) 467–471.
[20] X.J. Li, et al., The effect of transcutaneous auricular vagus nerve stimulation on treatment-resistant depression monitored by resting-state fMRI and MRS: the first case report, Brain Stimul. 12 (2) (2019) 377–379.
[21] A. Straube, et al., Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): a randomized, monocentric clinical trial, J. Headache Pain 16 (2015) 543.
[22] S. Lui, et al., Auricular acupuncture for opiate dependence in substance misuse treatment programmes, Cochrane Database Syst. Rev. (4) (2009).
[23] S. Gates, L.A. Smith, D.R. Foxcroft, Auricular acupuncture for cocaine dependence, Cochrane Database Syst. Rev. (1) (2006), CD005192.
[24] J.I. Kim, et al., Acupuncture for the treatment of tinnitus: a systematic review of randomized clinical trials, BMC Complement. Altern. Med. 12 (2012) 97.
[25] J. Dietzel, et al., Auricular Acupuncture for Preoperative Anxiety-Protocol of Systematic Review and Meta-Analysis of Randomized Controlled Trials, Medicines (Basel) 7 (12) (2020).
[26] L. de Lorent, et al., Auricular Acupuncture Versus Progressive Muscle Relaxation in Patients with Anxiety Disorders or Major Depressive Disorder: a Prospective Parallel Group Clinical Trial, J. Acupunct. Meridian Stud. 9 (4) (2016) 191–199.
[27] T. Usichenko, et al., Auricular stimulation vs. expressive writing for exam anxiety in medical students - a randomized crossover investigation, PLoS One 15 (8) (2020), e0238307.
[28] A. Vieira, et al., Clinical effect of auricular acupuncture in anxiety levels of students prior to the exams: a randomized controlled trial, Eur. J. Integr. Med. 20 (2018) 188–192.
[29] A. Michalek-Sauberer, et al., Auricular acupuncture effectively reduces state anxiety before dental treatment–a randomised controlled trial, Clin. Oral Investig. 16 (6) (2012) 1517–1522.
[30] A. Vieira, et al., Is auriculotherapy effective and safe for the treatment of anxiety disorders? – Protocol for a systematic review, Eur. J. Integr. Med. 49 (2022), 101734.
[31] C. Klausenitz, et al., Auricular Acupuncture for Exam Anxiety in Medical Students-a Randomized Crossover Investigation, PLoS One 11 (12) (2016), e0168338.
[32] L.F. Kurebayashi, et al., Auriculotherapy to reduce anxiety and pain in nursing professionals: a randomized clinical trial, Rev. Lat. Am. Enfermagem 25 (2017) e2843.
[33] D. Moher, et al., Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (7) (2009), e1000097.
[34] L.J. Julian, Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A), Arthritis Care Res. (Hoboken) 63 (Suppl 11) (2011) S467–S472.
[35] C.D. Spielberger, R.C. Gorsuch, R.E. Lushene, Manual for the State-Trait Anxiety Inventory Psychologists, Consulting, Palo Alto: CA, 1970.
[36] Marques, L., Chosak, A., Simon, N.M., Phan, D.-M., Wilhelm, S., & Pollack, M., Rating Scales for Anxiety Disorders, H.O.C.R.S.A.A.I.P.A.M. Health, Editor. 2009. p. 37-72.
[37] A.S. Zigmond, R.P. Snaith, The hospital anxiety and depression scale, Acta Psychiatr. Scand. 67 (6) (1983) 361–370.
[38] E. Facco, et al., Toward the validation of visual analogue scale for anxiety, Anesth. Prog. 58 (1) (2011) 8–13.
[39] A.T. Beck, et al., An inventory for measuring clinical anxiety: psychometric properties, J. Consult. Clin. Psychol. 56 (6) (1988) 893–897.
[40] M. Hamilton, The assessment of anxiety states by rating, Br. J. Med. Psychol. 32 (1) (1959) 50–55.
[41] C. Kirschbaum, D.H. Hellhammer, Salivary cortisol in psychoneuroendocrine research: recent developments and applications, Psychoneuroendocrinology, 19 (4) (1994) 313–333.
[42] A Coomarasamy, W.H. Truchanowicz E, et al., Health Technology Assessment, No. 20.41, NIHR J. Lib. Southampton (UK) (2016).
[43] D. Moher, et al., CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials, Int. J. Surg. 10 (1) (2012) 28–55.
[44] J.P.T. Higgins, T.J. Chandler J, M. Cumpston, T. Li, M.J. Page, V.A. Welch, Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020), 2020. Cochrane, 2020. Available from, www.training.cochrane.org/handbook.
[45] GRADEpro G.D.T.: GRADEpro Guideline Development Tool [Software]. McMaster University, d.b.E.P., Inc.). Available from gradepro.org.
[46] M. Egger, et al., Bias in meta-analysis detected by a simple, graphical test, BMJ (Clin. Res. ed.) 315 (7109) (1997) 629–634.
[47] T.C. Collaboration, Review Manager (RevMan) [Computer program]. Version 5.4.1, 2020.
[48] W.S. Li, et al., Effect of assisted anesthesia of auricular point magnetic sticking on postoperative recovery of gynecological surgery, Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 33 (7) (2013) 648–652.
[49] W.S. Li, et al., Effects of magnetic auricular point-sticking on adjuvant anesthesia and postoperative recovery of body function, Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 31 (4) (2011) 349–352.
[50] P. Avisa, et al., Effectiveness of Acupressure on Dental Anxiety in Children, Pediatr. Dent. 40 (3) (2018) 177–183.
[51] A.G. Dellovo, et al., Effects of auriculotherapy and midazolam for anxiety control in patients submitted to third molar extraction, Int. J. Oral Maxillofac. Surg. 48 (5) (2019) 669–674.
[52] S.Y. Kuo, et al., Auricular acupressure relieves anxiety and fatigue, and reduces cortisol levels in post-caesarean section women: a single-blind, randomised controlled study, Int. J. Nurs. Stud. 53 (2016) 17–26.
[53] J.M. Prado, L.F. Kurebayashi, M.J. Silva, [Auriculotherapy effectiveness in the reduction of anxiety in nursing students], Rev. Esc Enferm USP 46 (5) (2012) 1200–1206.
[54] S. Wu, et al., Comparing the treatment effectiveness of body acupuncture and auricular acupuncture in preoperative anxiety treatment, J. Res. Med. Sci. 16 (1) (2011) 39–42.
[55] J.K. Wunsch, et al., Auricular acupuncture for treatment of preoperative anxiety in patients scheduled for ambulatory gynaecological surgery: a prospective controlled investigation with a non-randomised arm, Acupunct. Med. 36 (4) (2018) 222–227.
[56] M. Haddad-Rodrigues, et al., Acupuncture for anxiety in lactating mothers with preterm infants: a randomized controlled trial, Evid. Based Complement. Alternat. Med. 2013 (2013), 169184.
[57] C. Ndubisi, et al., Auricular acupuncture as an adjunct for pain management during first trimester abortion: a randomized, double-blinded, three arm trial, Contraception 99 (3) (2019) 143–147.
[58] F. Qu, et al., Auricular acupressure reduces anxiety levels and improves outcomes of in vitro fertilization: a prospective, randomized and controlled study, Sci. Rep. 4 (2014) 5028.
[59] S. Valiee, et al., Effect of acupressure on preoperative anxiety: a clinical trial, J. Perianesth. Nurs. 27 (4) (2012) 259–266.
[60] R.R. Mafetoni, et al., Effectiveness of auriculotherapy on anxiety during labor: a randomized clinical trial1, Rev. Lat. Am. Enfermagem 26 (2018) e3030.
[61] M. Rivadeneira, D; O, et al., Efectividad de la auriculoterapia en el tratamiento de la ansiedad en el adulto mayor, Rev. Electron (6) (2015) 40.
[62] D. Alimi, J.E. Chelly, New Universal Nomenclature in Auriculotherapy, J. Altern. Complement. Med. 24 (1) (2018) 7–14.
[63] J.K. Wunsch, et al., Auricular acupuncture for treatment of preoperative anxiety in patients scheduled for ambulatory gynaecological surgery: a prospective controlled investigation with a non-randomised arm, Acupunct. Med. 36 (4) (2018) 222–227.
[64] D. Luo, et al., Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range, Stat. Methods Med. Res. 27 (6) (2018) 1785–1805.
[65] A. Nielsen, S. Gereau, H. Tick, Risks and Safety of Extended Auricular Therapy: a Review of Reviews and Case Reports of Adverse Events, Pain Med. 21 (6) (2020) 1276–1293.
[66] J. McDonald, S. Janz, The Acupuncture Evidence Project - A Comparative Literature Review, Australian Acupuncture and Chinese Medicine Association Ltd (2017).
[67] C.S. Zhang, et al., Sham control methods used in ear-acupuncture/ear-acupressure randomized controlled trials: a systematic review, J. Altern. Complement. Med. 20 (3) (2014) 147–161.
[68] A.L. Jan, et al., Does Ear Acupuncture Have a Role for Pain Relief in the Emergency Setting? A Systematic Review and Meta-Analysis, Med. Acupunct. 29 (5) (2017) 276–289.
[69] L.R. Miller, F.G. Miller, Understanding placebo effects: Implications for nursing practice, Nurs. Outlook 63 (5) (2015) 601–606.
[70] D.G. Finniss, Placebo Effects: historical and Modern Evaluation, Int. Rev. Neurobiol. 139 (2018) 1–27.
[71] F. Musial, Acupuncture for the Treatment of Pain - a Mega-Placebo? Front. Neurosci. 13 (2019) 1110.
[72] A.W.M. Evers, et al., Implications of Placebo and Nocebo Effects for Clinical Practice: Expert Consensus, Psychother. Psychosom. 87 (4) (2018) 204–210.