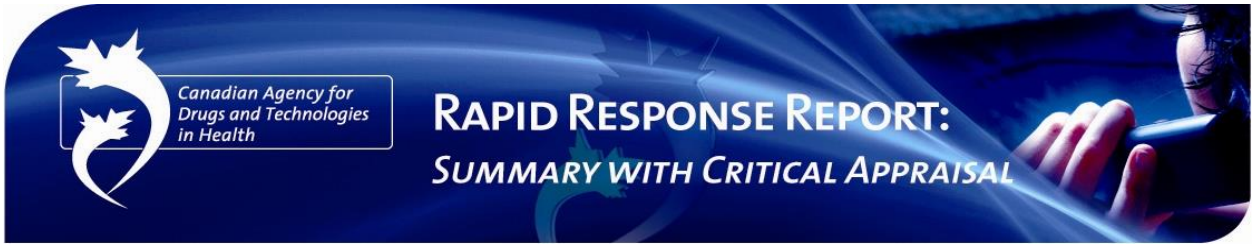

TITLE: Neurotrophic Stimulation Therapy for the Management of Generalized Anxiety Disorder and Depression: A Review of the Clinical Effectiveness

DATE: 20 August 2015

CONTEXT AND POLICY ISSUES

Neurotrophic stimulation therapy is an umbrella term that includes several non-invasive approaches intended to have a therapeutic effect in patients suffering from a variety of mental health disorders, including depression, anxiety, post-traumatic stress disorder (PTSD), traumatic brain injury, and substance withdrawal.[1] The primary components of neurotrophic stimulation therapy include acupuncture, neural auricular acupuncture, neural therapy, bio-acupuncture or acupoint injection therapy, and cranial electrostimulation.[1] The most well studied components of neurotrophic stimulation are acupuncture and transcranial direct current stimulation (tDCS). In Western society, acupuncture is generally considered a complementary or alternative treatment. It involves insertion of fine needles into various parts of the body.[2] Several different styles of administering acupuncture exist, including classical or traditional acupuncture, auricular acupuncture, trigger point acupuncture, electroacupuncture, and laser acupuncture.[2] Electroacupuncture refers to the process of applying an electrical current through the acupuncture needles and into the patient's body.[2,3] Different protocols for needle insertion points are used clinically. tDCS refers to a method of non-invasive brain stimulation with a low amplitude electrical current.[4] An anode and cathode are applied to opposite sides of the patient's scalp and a low intensity electrical current is delivered continuously for several minutes.[4] The exact physiologic mechanism for tDCS is not known; however, it has been postulated that the anode and cathode induce opposite effects to each other on cortical excitability.[4] Cranial electrotherapy stimulation (CES) is a non-invasive technique whereby electrodes are placed on the patient's earlobe and a pulsed low amplitude electrical current is delivered.[5]

Conventional therapies, such as cognitive behavior therapy or pharmacotherapy, have been demonstrated to be effective in managing several mental health disorders.[6-8] However, many patients remain symptomatic despite receiving conventional treatment.[7] This report focuses on two specific mental health disorders, depression and generalized anxiety disorder. Major depressive disorder (MDD) is defined as the presence of either depressed mood or anhedonia (loss of interest or pleasure in previously enjoyable activities) as well as inappropriate excessive

guilt, feelings of worthlessness, insomnia or hypersomnia, low self esteem, weight changes (gain or loss), loss of energy, psychomotor changes, or thoughts of suicide or self harm.[9,10] Symptoms must be present for most days over a two week period. MDD is a major public health concern and has a life-time prevalence of approximately 18%.[10,11] Generalized anxiety disorder (GAD) is defined as uncontrollable feelings of apprehension or fear about future events associated with somatic symptoms such as muscle tension.[11,12] Anxiety disorders have a lifetime prevalence of approximately 30%.[11] GAD and MDD are twice as common in women compared to men.[11]

Centers offering neurotrophic stimulation as an approach to managing mental health disorders are available in Canada.[1] The objective of this report is to review the literature for evidence of clinical effectiveness for the use of any component of neurotrophic stimulation alone or in combination with another component in patients with depression or GAD. A previous report addressed the clinical effectiveness of neurotrophic stimulation in PTSD and substance abuse disorders[13].

RESEARCH QUESTIONS

1. What is the clinical effectiveness of neurotrophic stimulation therapy for the management of depressive disorder?

2. What is the clinical effectiveness of neurotrophic stimulation therapy for the management of generalized anxiety disorder?

KEY FINDINGS

Evidence addressing the clinical effectiveness of neurotrophic stimulation therapy was limited to acupuncture or transcranial direct current stimulation in depression and acupuncture or cranial electrotherapy stimulation in anxiety. Evidence for other components was not identified in the literature search.

Two systematic reviews and one randomized controlled trial demonstrated that transcranial direct current stimulation reduced symptoms of depression and improved rates of response and remission over 6 months of follow-up in patients with major depressive disorder. The benefits of acupuncture on depressive symptoms were evaluated in four systematic reviews and six randomized controlled trials. Reduction in symptoms of depression was inconsistently demonstrated across the included studies.

One systematic review demonstrated that acupuncture may have positive effects in patients with anxiety disorders. One randomized controlled trial demonstrated a reduction in symptoms of anxiety and depression with cranial electrotherapy stimulation in patients with anxiety disorders over 5 weeks of follow-up.

METHODS

Literature Search Strategy

A focused search (with main concepts appearing in title or major subject heading) was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to the main focused search to limit the retrieval by study type. A second broader search (with main concepts appearing in the title, abstract or subject heading) was also included, however methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and randomized controlled trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and June 18, 2015.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria in Table 1.

Table 1: Selection Criteria

Population	Adult patients with GAD or Depression
Intervention	Neurotrophic stimulation therapy (acupuncture, NeuroTrophic Stimulation, Neural Auricular Acupuncture, Neural Therapy, Bio-Acupuncture/Acupoint Injection Therapy, Cranial Electrostimulation) Any component alone or in combination with each other
Comparator	Any comparator or no comparator
Outcomes	Symptom reduction, increased well-being, increased functional measures (such as a composite functional score or elements such as return to work), QoL
Study Designs	Health Technology Assessment / Systematic review / Meta-analysis/ Randomized Controlled Trials

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, or were published prior to 2011. Articles were also excluded if they were reported as part of an included HTA or systematic review.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The AMSTAR checklist[14] was used to critically appraise the systematic reviews. The Cochrane Collaboration's tool for assessing risk of bias[15] was used to critically appraise the randomized controlled trials.

For the critical appraisal, a numeric score was not calculated. Instead, the strengths and

limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 526 articles were identified from the literature search and two articles from the grey literature search for a total of 528 articles; after screening of titles and abstracts, 79 were selected for full-text screening. Fifteen of the references screened met the inclusion criteria.

A total of seven systematic reviews were identified: three that addressed the use of acupuncture in depression,[11,16,17] two that addressed the use of tDCS in depression,[18,19] one that addressed the use of CES in depression,[20] and lastly a systematic review of reviews that addressed the use of acupuncture in depression or anxiety.[21] A total of eight randomized controlled trials (RCT) were identified: six evaluating the role of acupuncture in depression,[22-27] one addressing the role of tDCS in depression[28], and one addressing the role of CES in anxiety.[5]

Appendix 1 describes the PRISMA flowchart of the included studies in the report.

Summary of Study Characteristics

Characteristics of the included systematic reviews and RCTs are summarized below and details are provided in Appendix 2 and 3.

Systematic Reviews

Seven systematic reviews addressed the clinical effectiveness of one or more components of neurotrophic stimulation in depression[11,16-21] or anxiety.[21] Three of the systematic reviews were a review of reviews.[16,17,21] Two were published in 2014,[18,20] one in 2013,[11] two in 2012,[19,21] and two in 2011.[16,17] Four systematic reviews were conducted in the United States of America (USA),[11,17,20,21] one in Brazil,[18] and two in the United Kingdom.[16,19]

Depression

Three systematic reviews addressed the use of acupuncture in depression.[11,16,17] Sniezek and colleagues[11] included six studies in their systematic review (five parallel RCTs and one cross over RCT). Four of these studies included only patients with MDD, one included only patients with an anxiety disorder and one included patients with depression or anxiety. The sample size of included studies ranged from 33 to 248 female participants 18 to 71 years of age. Sniezek et al. compared manual acupuncture to any control procedure (such as counseling, sham acupuncture, massage or no treatment) over a maximum of 6 months of follow-up. Ernst and colleagues[16] included eight reviews (six from China, one from the USA and two multinational studies, representing 71 unique studies) in their systematic review of reviews. The total sample size was 11,576 and all patients suffered from MDD. Ernst et al. compared acupuncture to sham acupuncture, pharmacotherapy, no treatment, or control. The duration of follow-up was not reported. Williams and colleagues[17] included two systematic reviews representing 28 RCTs and 2475 patients with depression in their systematic review. Williams et al. compared acupuncture to sham acupuncture, antidepressants, or wait-list control over up to 12 weeks of follow-up.

Two systematic reviews addressed the use of tDCS in depression.[18,19] Shiozawa and colleagues[18] included seven RCTs of patients with treatment resistant depression in their systematic review. A total of 259 patients were included and 58% were women. The mean age was 44 years and the mean number of previous antidepressants used was 2.16. Shiozawa et al. compared tDCS with or without pharmacotherapy to sham tDCS with or without pharmacotherapy. The follow-up period was not reported. Kalu and colleagues[19] included a total of ten studies in their systematic review: six RCTs and four open-label studies. The sample size of the included trials ranged from 10 to 64 and all patients suffered from MDD. Kalu et al. compared active tDCS to sham tDCS over 1 week to 1 month of follow-up.

One systematic review addressed the use of CES in depression.[20] The authors of this systematic review did not identify any trials that met their inclusion criteria. Lastly, Lee and colleagues[21] conducted a systematic review of reviews that addressed the use of acupuncture in depression or anxiety. Six systematic reviews representing 73 RCTs and 9,986 patients with depression were included.

Anxiety

One systematic review representing 10 RCTs and two uncontrolled trials with a total of 1,201 patients with anxiety were included. Lee et al.[21] compared any form of acupuncture (manual, electro, traditional Chinese, abdominal, and Western) to various comparators such as sham acupuncture, pharmacologic, behavioral, psychosocial, or no treatment. The total duration of follow-up was not reported.

Outcomes reported varied across all the systematic reviews but generally included symptom scales for depression or anxiety.

Randomized Controlled Trials

Eight RCTs addressed the clinical effectiveness of one or more components of neurotrophic stimulation in depression[22-28] or anxiety.[5] Two were published in 2014,[5,28] five in 2013,[22-26] and one in 2011.[27] Two RCTs were conducted in the United States of America,[5,27] two in Australia,[25,28] two in China,[23,24] one in the Netherlands[22] and one in the United Kingdom[26].

Depression

Six RCTs addressed the use of acupuncture in depression.[22-27] Bosch and colleagues[22] conducted an RCT which included 16 patients with depression. The mean age of participants was 51 years. Participants were allowed to continue antidepressant therapy. Bosch et al. compared weekly sessions of acupuncture to wait-list control over 12 weeks of follow-up. Wei-dong and colleagues[23] conducted an unblinded RCT including 60 patients with MDD. The mean age of participants was 49 years. Wei-dong et al. compared 20 minute sessions of electroacupuncture three times weekly to paroxetine 20mg per day over 24 weeks of follow-up. Sun and colleagues[24] conducted an RCT including 75 patients with MDD. The mean age of participants was 42 years. Sun et al. compared 30 minute sessions of electroacupuncture five times weekly to electroacupuncture control and fluoxetine 20 mg daily over 6 weeks of follow-up. Quah-Smith and colleagues[25] conducted an RCT including 47 patients with MDD of less than 2 years duration. No concomitant pharmacotherapy was allowed and 55% of participants had received acupuncture previously. Quah-Smith et al. compared laser acupuncture twice weekly for 4 weeks followed by once weekly for 4 weeks to placebo laser over 3 months of

follow-up. MacPherson and colleagues[26] conducted an RCT including 755 patients with moderate to severe MDD. The mean age of study participants was 44 years and 69% received concomitant pharmacotherapy. MacPherson compared 12 weekly acupuncture sessions plus usual care to both usual care alone and 12 weekly counseling session plus usual care. Patients were followed for a total of 12 months. Andreescu and colleagues[27] conducted an RCT including 53 patients with mild or moderate MDD. The mean age of participants was 48 years. Concomitant use of pharmacotherapy was not permitted. Andreescu et al. compared two 30 minute electoacupuncture sessions weekly for a total of 12 sessions to sham electroacupuncture over 8 weeks of follow-up.

One RCT addressed the use of tDCS in depression[28]. Segrave and colleagues conducted an RCT of 27 patients with MDD. The mean age of study participants was 40 years and 14 patients continued to take concomitant antidepressants during the study. Segrave et al. compared 24 minutes of tDCS combined with sham cognitive control training (CCT) to both CCT combined with sham tDCS, and tDCS combined with CCT, over 3 weeks of follow-up.

Outcomes reported varied across all RCTs but generally included symptom scales for depression or anxiety, most commonly the MADRS, HAM-D and Beck Depression Inventory (BDI) scales.

Anxiety

One RCT evaluated the role of CES in anxiety.[5] Barclay and colleagues[5] compared daily one hour sessions of CES to sham CES in patients with an anxiety disorder. The mean age of study participants was 42 years and 20% had concomitant depression. The majority of patients were female (68%) and 64% took concomitant pharmacotherapy. Patients were followed up over 5 weeks and evaluated for symptoms of depression and anxiety on the HAM-D and HAM-A symptom scales.

Summary of Critical Appraisal

Strengths and limitations of the systematic reviews and RCTs are provided in Appendix 4 and 5.

Systematic Reviews

Overall, the quality of the seven systematic reviews[11,16-21] was fair. In all seven systematic reviews the research question and inclusion criteria were established *a priori*. Comprehensive literature searches were performed and reported in all but one[18] of the systematic reviews. Grey literature searches were reported by Kaviraja et al.[20] and Shiozawa et al..[18] Sniezek et al.[11] did not search the grey literature. In the four remaining systematic reviews[16,17,19,21] it was unclear whether the authors had performed searches of the grey literature. Duplicate study selection and data abstraction was fully completed in five of the systematic reviews.[16,18-21] It was unclear whether Sniezek and colleagues[11] had undertaken study selection and data abstraction in duplicate. Williams and colleagues[17] undertook study selection in duplicate by independent reviewers but did not report that data abstraction was completed in duplicate. Only two of the systematic reviews[17,20] provided lists of both included and excluded studies; the remaining five systematic reviews[11,16,18,19,21] only provided a list of included studies. Kaviraja and colleagues[20] did not identify any studies for inclusion in their systematic review and as such did not report on study characteristics, quality assessment or statistical methods for combining study data. Five systematic reviews[11,16,18,19,21] reported study characteristics. Williams and colleagues[17] did not

report characteristics of included studies. Quality assessment was undertaken in five of the systematic reviews.[11,16-18,21] Quality assessment was not reported by Kalu and colleagues.[19] With the exception of the systematic review by Shiozawa and colleagues,[18] the remaining six systematic reviews incorporated the quality of studies when formulating their conclusions.[11,16,17,19-21] Appropriate statistical methods were reported to be used by two authors,[18,19] and three other authors did not report statistical methods as pooling of individual trial data was not undertaken.[16,17,20] Sniezek et al.[11] provided a narrative report of the outcomes of included studies and did not attempt meta-analysis. Lee et al.[21] did not undertake a meta-analysis because of the heterogeneity of the included trials. Publication bias was assessed in three of the systematic reviews;[18-20] the remaining four authors did not undertake assessment of publication bias.[11,16,17,21] One author[20] fully disclosed all conflicts of interest, and four of the authors[11,16,18,19,21] reported conflicts of interest for the systematic review only, not the individual trials. Williams and colleagues[17] did not report whether any conflicts of interest existed for either the systematic review or the individual studies.

Randomized Controlled Trials

The quality of the eight RCTs[5,22-28] varied across the included trials. Overall, one[27] of the included trials had a high risk of bias. The method of randomization was clearly reported in five of the six trials.[22-26,28] Barclay and colleagues[5] did not clearly report the method of randomization that was used in their trial. Allocation concealment was clearly reported in three of the RCTs[5,24,25] with a low risk of bias. Four RCTs[22,23,26,28] did not clearly report the method of allocation concealment and therefore had an unclear risk of bias. Two studies[25,28] clearly reported methods for blinding participants. Five of the authors did not clearly report the methods used to blind study participants.[5,22-24,26] The method of randomization, allocation concealment, and blinding of participants used by Andreescu and colleagues[27] was not reported and therefore represents a high risk of bias in this RCT. Outcome assessment was blinded in two of the included RCTs[22,28] and not clearly reported in the remaining six RCTs.[5,23-27] Two studies[5,25] had high follow-up rates and a low risk of attrition bias. Two of the RCTs[22,28] did not clearly report the number of study withdrawals or the number of participants included in the final analysis. Four of the studies[23,24,26,27] had large withdrawal rates and a high risk of incomplete outcome reporting. One of the RCTs[5] failed to report on all the predefined outcomes identified in their described methods, while the remaining seven studies[22-28] reported on all the predefined study endpoints.

Summary of Findings

The overall findings from the systematic reviews and RCTs are summarized below and details are available in Appendix 6 and 7.

Clinical effectiveness of neurotrophic stimulation therapy for the management of depressive disorder

Systematic Reviews

Kavirajan and colleagues[20] did not identify any RCTs that evaluated CES compared to sham CES in the management of acute depression that met the inclusion criteria for their review. Shiozawa and colleagues[18] found that active tDCS was significantly better than sham tDCS at reducing depression scores on the HAM-D or MADRS scales (standardized mean difference [SMD]=0.37, 95% confidence interval [CI] 0.04 to 0.7). tDCS also significantly increased the rate of response and remission compared to sham tDCS (SMD=0.4 95%CI 0.07 to 0.73). The

authors concluded that active tDCS was statistically superior to sham tDCS in the treatment of MDD. Kalu and colleagues[19] found that active tDCS reduced symptom severity significantly more than sham tDCS (Hedge's g=0.74, 95% CI 0.21 to 1.27, *P*=0.006). Symptom severity was reduced by 29% (range 15% to 60%), response was achieved in 20% (range 0% to 80%) and remission in 8.5% (range 0% to 24%) of patients who received active tDCS. The authors concluded that tDCS has a potential role in the management of depression, but larger studies with longer follow-up are required.

Sniezek and colleagues[11] found that based on one study in MDD, acupuncture reduced depression scores on the BDI and HAM-D scale significantly more than non-specific acupuncture (*P*<0.05). Remission rates in patients with MDD treated with acupuncture were similar to other interventions such as pharmacotherapy and psychotherapy. The authors concluded that there is a lack of high quality research supporting the use of acupuncture in women with depression or anxiety. Lee and colleagues[21] found that four systematic reviews had mixed or inconclusive results with the use of acupuncture in depression and two systematic reviews had positive results with acupuncture. The authors stated that no concrete conclusion could be drawn from these results but that acupuncture appears to be a promising option in the management of depression. Ernst and colleagues[16] found that all six systematic reviews from China had reported positive results for the efficacy of acupuncture in depression and that none of the non-Chinese systematic reviews had positive results. Compared to sham acupuncture, acupuncture showed positive results in seven studies, equivocal results in two studies and negative results in three studies. Compared to pharmacotherapy, acupuncture demonstrated positive results in 27 studies, equivocal results in 21 studies and negative results in four studies. Compared to no treatment or wait-list, acupuncture had positive results in three studies, equivocal results in two studies and no trials with negative findings. The authors concluded that the effectiveness of acupuncture in the management of depression remains unproven and no different than placebo. Williams and colleagues[17] found that acupuncture was significantly better than sham acupuncture at improving depression scores (HAM-D and BDI), (SMD= -0.65, 95%CI -1.18 to -0.11). However, no significant difference in response or remission rates were found with acupuncture compared to sham acupuncture, (relative risk [RR]=1.32, 95%CI 0.83 to 2.10 and RR=1.30, 95%CI 0.57 to 2.95, respectively). Compared to antidepressant therapy, acupuncture did not significantly reduce depressive symptoms (mean difference [MD]= -0.3,1 95%CI -0.94 to 1.56) or improve response rates (RR=1.09, 95%CI 0.92 to 1.30). When acupuncture was compared to sham acupuncture or wait-list control, no significant difference in response rates was found (*P*=NR). The authors concluded that acupuncture was more effective compared to sham acupuncture at improving depressive symptoms but did not improve rates of response or remission.

Randomized Controlled Trials

In a post-hoc analysis, Seagrave and colleagues[28] found that tDCS or CCT reduced depression symptom severity on the MADRS scale significantly after 5 sessions (*P*=0.04 and *P*=0.02 respectively). At 3 weeks follow-up the MADRS scores were no longer significantly different from baseline, P=NR. Patients who received tDCS or CCT had a significant reduction in their BDI scores after 5 sessions (*P*=0.005 and *P*=0.006). BDI scores returned to baseline after 3 weeks of follow-up in the CCT group but remained significantly lower than baseline in the tDCS group (*P*=0.02). No patients in the tDCS group were classified as responders (≥50% reduction in MADRS score) after 5 weeks of treatment or 3 weeks of follow-up. No statistical comparison between groups was made in the reduction of depressive symptoms or responder status. Remission rates (MADRS score <10) between groups did not reach statistical significance after

5 sessions or 3 weeks of follow-up. The authors concluded that tDCS may enhance the effects of CCT but more investigation is required.

Bosch and colleagues[22] found that over a 12 week follow-up period, acupuncture significantly improved sleep on the Pittsburgh Sleep Quality Index (*P*=0.003), while wait-list control did not (*P*=0.5). The authors concluded that acupuncture appears to improve sleep in patients with long standing psychiatric conditions. MacPherson and colleagues[26] demonstrated that symptoms of depression (measured on the Patient Health Questionnaire [PHQ]-9 scale) were significantly reduced at 3 months follow-up in patients who received acupuncture compared to usual care (MD= -2.46, 95%CI -3.72 to-1.21, I<0.001) but not significantly reduced compared to patients who received counseling (MD= -0.76, 95% CI -1.77 to 0.25, *P*=0.14). The difference in PHQ-9 score between acupuncture and usual care remained significant at 6 months (MD= -1.90, 95% CI -3.02 to -0.79, *P*=NR) but was no longer significant at 9 months follow-up (MD= -0.83, 95% CI -2.15 to 0.49, P=NR). The authors concluded that compared to usual care, acupuncture significantly reduced depressive symptoms over medium term follow-up. Wei-dong and colleagues[23] found that electroacupuncture reduced both objective and subjective measures of depression on the MADRS (*P*<0.05) and self-rating depression scales (*P*<0.01) respectively after 24 weeks of treatment. No statistical comparison between patients receiving electroacupuncture or paroxetine was undertaken. The authors concluded that electroacupuncture is an effective intervention for treating depression. Sun and colleagues[24] found that patients receiving either electroacupuncture or control had significantly lower scores for depressive symptoms on the HAM-D scale at 2 and 4 weeks follow-up, *P*=0.014 and *P*=0.003, respectively, compared to the patients who received fluoxetine. The differences between the three groups were not significant by week 6 (*P*=0.16). Significantly more patients who received electroacupuncture (75%) and control (75%) were responders (≥50% reduction in HAM-D score) compared to those who received fluoxetine (60%) (*P*<0.001). The authors concluded that electroacupuncture is as effective as fluoxetine in the treatment of depression, but larger scale trials are required. However, the conclusions on effectiveness did not appear to follow from the reported findings. Andreescu and colleagues[27] found no difference in depressive symptoms between electroacupuncture and control acupuncture over 8 weeks follow-up (HAM-D change from baseline: -7.4 vs. -7.9, *P*=0.81). The number of responders (HAM-D score <10 or 50% decrease from baseline) was not different between patients who received electroacupuncture or control acupuncture over 8 weeks (40% vs. 44%, *P*=0.77). Function assessed on the Global Assessment of Function scale was not significantly different between patients who received electroacupuncture or control over 8 weeks of follow-up (10.3 vs. 11.4, *P*=0.70). The authors concluded that electroacupuncture and control both resulted in similar improvements in symptoms of depression. Quah-Smith and colleagues[25] reported that laser acupuncture significantly reduced depressive symptoms on the HAM-D scale compared to placebo acupuncture over 8 weeks of follow-up (*P*=0.013). Compared to sham acupuncture, significantly more patients who received laser acupuncture experienced a >50% reduction in their HAM-D score from baseline (72% vs. 18%, *P*=0.0004). The authors concluded that laser acupuncture was associated with an objective improvement in depressive symptoms, but larger trials are needed to assess the long-term effects.

<u>Clinical effectiveness of neurotrophic stimulation therapy for the management of generalized anxiety disorder</u>

Systematic Reviews

Lee and colleagues[21] found that one systematic review demonstrated positive results for acupuncture in anxiety disorders using various endpoints such as HAM-A scale. No specific details regarding the changes in scores were provided by the authors. The authors concluded that acupuncture is a promising intervention in the management of anxiety but the safety is not well understood. Lee et al.[21] gave a weak GRADE recommendation for the use of acupuncture in the management of anxiety.

Randomized Controlled Trials

Barclay and colleagues[5] reported a significant reduction in symptoms of anxiety measured on the HAM-A scale with CES compared to sham CES, over 5 weeks of follow-up (13.3 vs. 20 *P*=0.001). A significant reduction in depressive symptoms measured on the HAM-D scale was also reported with CES compared to sham CES, over 5 weeks of follow-up (6.5 vs. 10 *P*=0.001). The authors concluded that CES is an effective treatment for anxiety with co-morbid depression.

Limitations

Studies addressing the clinical effectiveness of components of neurotrophic stimulation therapy for the treatment of depression included seven systematic reviews[11,16-21] and seven RCTs.[22-28] Four of the systematic reviews[11,16,17,21] and six of the RCTs[22-27] evaluated the use of various types and regimens of acupuncture in the treatment of depression. Two systematic reviews[18,19] and one RCT[28] evaluated the use of tDCS in the management of depression. The clinical effectiveness of other components of neurotrophic stimulation, alone or in combination, for the treatment of depression was not found as part of the literature search. The details of the quality assessment performed in five systematic reviews varied greatly. Shiozawa[18] reported that all seven of the trials included in their systematic review were randomized and outcome assessors were blinded to treatment allocation. The quality of the six studies included in the systematic review by Sniezek and colleagues[11] varied substantially. Quality ratings on the Jadad scale for the six trials ranged from 2 to 5. The Jadad scale is a tool to assist in quality assessment of RCTs. The Jadad scoring method accounts for randomization, allocation concealment, participant blinding and description of study withdrawals. Scores range from zero to five with scores of greater than three considered high quality.[29] Lee and colleagues[21] reported that five of the six RCTs included in their systematic review did a good job to minimize bias, whereas the sixth study had a higher risk of bias compared to the others. Ernst and colleagues [16] included eight systematic reviews in their systematic review of reviews. All eight systematic reviews were found to have minor or minimal flaws on the Overview Quality Assessment Questionnaire. Williams and colleagues[17] rated one of the included systematic reviews as “good” and the other as “fair” on the AMSTAR rating tool. Meta-analysis was under taken by Lee et al.[21] and Shiozawa et al.[18]. Both authors[18,21] undertook meta-analysis despite significant clinical heterogeneity both in the patient population and intervention. This makes the interpretation of the study findings challenging.

Overall, two of the RCTs[25,28] that evaluated the use of tDCS[28] or laser acupuncture[25] in the management of depression had a low risk of bias. Four of the RCTs[22-24,26] that evaluated the use of acupuncture[22,26] or electroacupuncture[23,24] in the management of depression had an unclear risk of bias. Three of the RCTs[22,23,26] had an unclear risk of selection and performance bias as they did not report the method used for allocation concealment or blinding of participants. Five of the RCTs[23-27] had an unclear risk of detection bias, as the methods of participant blinding was not reported. Four RCTs[23,24,26,27] had a high risk of attrition bias due to

the large number of participants who withdrew from the study. One RCT[27] that evaluated the use of electroacupuncture in depression had an overall high risk of bias.

Studies addressing the clinical effectiveness of components of neurotrophic stimulation therapy for the treatment of anxiety disorders included one systematic review of reviews[21] and one RCT[5]. The one systematic review[21] evaluated the use of acupuncture and the one RCT[5] evaluated the use of CES in anxiety. The clinical effectiveness of other components of neurotrophic stimulation, alone or in combination, for the treatment of anxiety disorders was not found as part of the literature search. Overall, the quality of the systematic review of reviews[21] was good. The quality of the systematic reviews included in the systematic review of reviews by Lee[21] had a low risk of bias. The risk of bias of the individual RCT[5] was unclear. There was a low risk of selection bias, but an unclear risk of performance and detection bias. The risk of reporting bias was high, secondary to selective outcome reporting.

Acupuncture regimens varied across all trials with respect to the location of needle insertion, frequency and duration of treatment, as well as number of acupuncture treatment sessions. As a result, the optimal acupuncture regimen for treating depression or anxiety is unclear. The sample sizes of RCTs for both depression and anxiety were small and the studies took place at a single center, with one exception[5]. The minimal clinically important difference for the scales used to assess the outcomes of the systematic reviews is unclear.

Overall, the main limitations of this review are the heterogeneity of the intervention and comparators as well as the variable risk of bias in the individual RCTs.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence addressing the clinical effectiveness of neurotrophic stimulation therapy in the management of depression and anxiety is limited to various forms of acupuncture, tDCS and CES. Two systematic reviews[18,19] found that compared to sham tDCS, tDCS decreased depressive symptoms and increased response and remission rates over up to 6 months of follow-up. In one small RCT by Seagrave et al.,[28] tDCS significantly decreased depressive symptoms compared to baseline after 5 sessions, although the benefit was lost at 3 weeks of follow-up. Remission rates were not significantly improved with five sessions of tDCS.

Overall, the evidence for the use of acupuncture in the management of depression has inconsistently demonstrated benefit. Four systematic reviews[11,16,17,21] demonstrated inconsistent benefits of acupuncture on reduction of depressive symptoms, response, or remission rates in comparison to control, pharmacotherapy, or psychotherapy. Three RCTs[23,24,26] found that manual-[26] or electroacupuncture[23,24] reduced depressive symptoms when compared to baseline symptom scores over 24 weeks, usual care after 6 months, or pharmacotherapy after 4 weeks. MacPherson and colleagues[23] did not find a significant difference in depressive symptoms over 3 months follow-up when acupuncture was compared to counseling. The difference in depressive symptom scores between electroacupuncture and fluoxetine found by Sun[24] were no longer present at 6 weeks of follow-up. Andreescu and colleagues[27] did not demonstrate any difference in response rates or depressive symptoms when they compared electroacupuncture to control. However, Quah-Smith and colleagues[25] found that laser acupuncture decreased depressive symptoms and improved responder rates compared to placebo over 3 months follow-up. One author[22] found that based on the results of a small RCT, acupuncture improved sleep over 12 weeks of follow-up compared to wait-list control.

The evidence supporting the use of neurotrophic stimulation in the management of anxiety is sparse compared to the volume of evidence for its use in depression. One systematic review[21] demonstrated positive results with the use of acupuncture on various symptom scales in patients with anxiety. One small RCT[5] demonstrated a significant reduction in symptoms of depression or anxiety with CES compared to sham CES over 5 weeks of follow-up.

Overall, the interpretation of the trials addressing neurotrophic stimulation therapy are limited by the use of a single intervention such as tDCS, acupuncture, or CES rather than a multimodal approach. The types of acupuncture and regimens used varied across studies, limiting the ability to draw conclusions regarding the optimal acupuncture regimen.

Neurotrophic stimulation therapy represents a novel approach to managing depression and anxiety. Presently, there is reasonable quality evidence that tDCS may improve depressive symptoms compared to sham treatment. Based on the available evidence, the role of acupuncture in the management of depression remains unclear. Presently, there a small amount of evidence supporting the use of neurotrophic stimulation in the management of anxiety. No evidence was identified which evaluated the benefit of neurotropic stimulation as a group of interventions in the management of depression or anxiety.

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REFERENCES

1. Last Door: breaking the chains of addiction [Internet]. Vancouver: Last Door Recovery Society. PTSD centered NeuroTrophic Stimulation Therapy, PTSD treatment addiction treatment program (NTST); 2014 Jul 8 [cited 2015 Jun 23]. Available from: http://www.lastdoor.org/ptsd-centered-neurotrophic-stimulation-therapy-ptsd-treatment-and-addiction-treatment-program-ntst/

2. Smith CA, Hay PP, MacPherson H. Acupuncture for depression. Cochrane Database Syst Rev. 2010;(1):CD004046.

3. Meade CS, Lukas SE, McDonald LJ, Fitzmaurice GM, Eldridge JA, Merrill N, et al. A randomized trial of transcutaneous electric acupoint stimulation as adjunctive treatment for opioid detoxification. J Subst Abuse Treat [Internet]. 2010 Jan [cited 2015 Jun 23];38(1):12-21. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2789908

4. Mondino M, Bennabi D, Poulet E, Galvao F, Brunelin J, Haffen E. Can transcranial direct current stimulation (tDCS) alleviate symptoms and improve cognition in psychiatric disorders? World J Biol Psychiatry. 2014 May;15(4):261-75.

5. Barclay TH, Barclay RD. A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression. J Affect Disord. 2014 Aug;164:171-7.

6. Chan YY, Lo WY, Li TC, Shen LJ, Yang SN, Chen YH, et al. Clinical efficacy of acupuncture as an adjunct to methadone treatment services for heroin addicts: a randomized controlled trial. Am J Chin Med. 2014;42(3):569-86.

7. Lua PL, Talib NS, Ismail Z. Methadone maintenance treatment versus methadone maintenance treatment plus auricular acupuncture: impacts on patient satisfaction and coping mechanism. J Pharm Pract. 2013 Dec;26(6):541-50.

8. Ralevski E, Olivera-Figueroa LA, Petrakis I. PTSD and comorbid AUD: a review of pharmacological and alternative treatment options. Subst Abuse Rehabil [Internet]. 2014 [cited 2015 Jun 23];5:25-36. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3953034

9. Brunoni AR, Valiengo L, Baccaro A, Zanao TA, de Oliveira JF, Vieira GP, et al. Sertraline vs. ELectrical Current Therapy for Treating Depression Clinical Trial--SELECT TDCS: design, rationale and objectives. Contemp Clin Trials. 2011 Jan;32(1):90-8.

10. Wu J, Yeung AS, Schnyer R, Wang Y, Mischoulon D. Acupuncture for depression: a review of clinical applications. Can J Psychiatry. 2012 Jul;57(7):397-405.

11. Sniezek DP, Siddiqui IJ. Acupuncture for treating anxiety and depression in women: a clinical systematic review. Med Acupunct [Internet]. 2013 Jun [cited 2015 Jun 23];25(3):164-72. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3689180

12. Errington-Evans N. Acupuncture for anxiety. CNS Neurosci Ther. 2012 Apr;18(4):277-84.

13. CADTH. Neurotrophic stimulation therapy for the management of post-traumatic stress disorder and substance abuse disorders: a review of the clinical effectiveness [Internet]. Ottawa (ON): CADTH; 2015 [cited 2015 Aug 18].

14. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007;7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

15. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.1.0. Oxford (UK): The Cochrane Collaboration; 2011. Table 8.5.a: The Cochrane Collaboration's tool for assessing risk of bias [cited 2015 Jul 3]. Available from: http://handbook.cochrane.org/index.htm#chapter_8/table_8_5_a_the_cochrane_collaborations_tool_for_assessing.htm

16. Ernst E, Lee MS, Choi TY. Acupuncture for depression?: A systematic review of systematic reviews. Eval Health Prof. 2011 Dec;34(4):403-12.

17. Williams JW Jr., Gierisch JM, McDuffie J, Strauss JL, Nagi A. An overview of complementary and alternative medicine therapies for anxiety and depressive disorders: supplement to efficacy of complementary and alternative medicine therapies for posttraumatic stress disorder [Internet]. Washington (DC): Department of Veterans Affairs; 2011 Aug [cited 2015 Jun 23]. (VA Evidence-based Synthesis Program Reports). Available from: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0033505/pdf/TOC.pdf

18. Shiozawa P, Fregni F, Bensenor IM, Lotufo PA, Berlim MT, Daskalakis JZ, et al. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. Int J Neuropsychopharmacol [Internet]. 2014 Sep [cited 2015 Jun 23];17(9):1443-52. Available from: http://ijnp.oxfordjournals.org/content/ijnp/17/9/1443.full.pdf

19. Kalu UG, Sexton CE, Loo CK, Ebmeier KP. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychol Med. 2012 Sep;42(9):1791-800.

20. Kavirajan HC, Lueck K, Chuang K. Alternating current cranial electrotherapy stimulation (CES) for depression. Cochrane Database Syst Rev. 2014;7:CD010521.

21. Lee C, Crawford C, Wallerstedt D, York A, Duncan A, Smith J, et al. The effectiveness of acupuncture research across components of the trauma spectrum response (tsr): a systematic review of reviews. Syst Rev [Internet]. 2012 [cited 2015 Jun 23];1:46. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3534620

22. Bosch P, van Luijtelaar G, van den Noort M, Lim S, Egger J, Coenen A. Sleep ameliorating effects of acupuncture in a psychiatric population. Evid Based Complement Alternat Med [Internet]. 2013 [cited 2015 Jun 23];2013:969032. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3678454

23. Wang WD, Lu XY, Ng SM, Hong L, Zhao Y, Lin YN, et al. Effects of electro-acupuncture on personality traits in depression: a randomized controlled study. Chin J Integr Med. 2013 Oct;19(10):777-82.

24. Sun H, Zhao H, Ma C, Bao F, Zhang J, Wang DH, et al. Effects of electroacupuncture on depression and the production of glial cell line-derived neurotrophic factor compared with fluoxetine: a randomized controlled pilot study. J Altern Complement Med [Internet]. 2013 Sep [cited 2015 Jun 23];19(9):733-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3768227

25. Quah-Smith I, Smith C, Crawford JD, Russell J. Laser acupuncture for depression: a randomised double blind controlled trial using low intensity laser intervention. J Affect Disord. 2013 Jun;148(2-3):179-87.

26. MacPherson H, Richmond S, Bland M, Brealey S, Gabe R, Hopton A, et al. Acupuncture and counselling for depression in primary care: a randomised controlled trial. PLoS Med [Internet]. 2013 [cited 2015 Jun 23];10(9):e1001518. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3782410

27. Andreescu C, Glick RM, Emeremni CA, Houck PR, Mulsant BH. Acupuncture for the treatment of major depressive disorder: a randomized controlled trial. J Clin Psychiatry. 2011 Aug;72(8):1129-35.

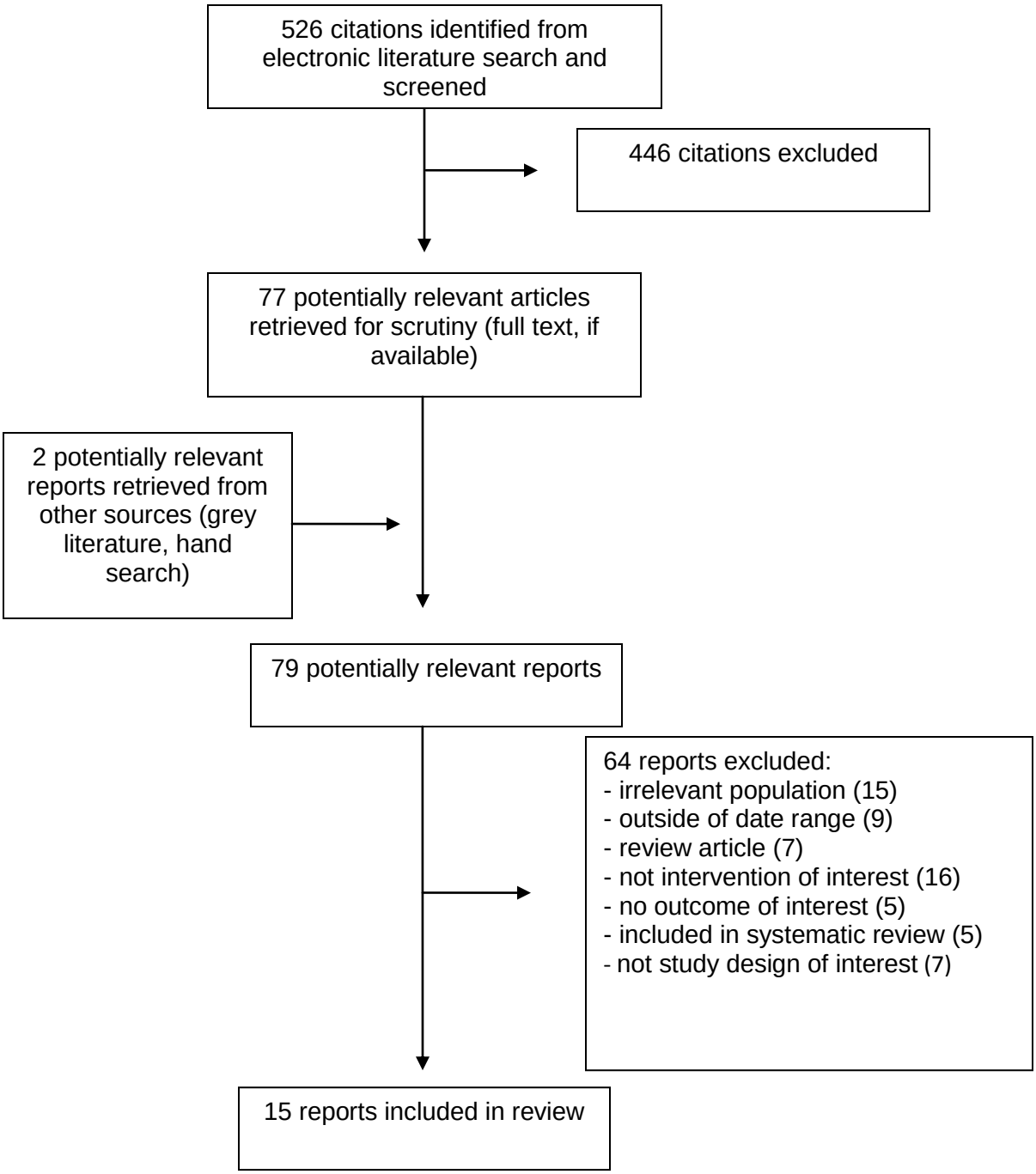
28. Segrave RA, Arnold S, Hoy K, Fitzgerald PB. Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. Brain Stimul. 2014 Mar;7(2):325-31.

29. Boyuan Z, Yang C, Ke C, Xueyong S, Sheng L. Efficacy of acupuncture for psychological symptoms associated with opioid addiction: a systematic review and meta-analysis. Evid Based Complement Alternat Med [Internet]. 2014 [cited 2015 Jun 23];2014:313549. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4235186

ABBREVIATIONS

tDCS	transcranial direct current electrostimulation
CES	cranial electrotherapy stimulation
MDD	major depressive disorder
GAD	generalized anxiety disorder
RCT	randomized controlled trial
MADRS	Mongomery-Asberg Depression Rating Scale
HAM-D	Hamilton Depression Rating Scale
HAM-A	Hamilton Anxiety Scale
BDI	Beck Depression Inventory
PSQI	Pittsburg Sleep Quality Index
PHQ-9	Patient Health Questionnaire
MD	mean difference
NR	not reported
SDS	self-rating depression scale

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Kavirajan[20], 2014, USA	Systematic Review Follow-up (range): NA	Acute depression No included studies	CES	Sham CES	Symptoms of depression Tolerability of CES
Shiozawa[18], 2014, Brazil	Systematic Review Follow-up (range): NR	7 included studies (RCT) Treatment resistant depression N=259 Age (mean): 44 years (SD=10) 58% women # previous antidepressants=2.16 (SD=1.7)	tDCS+/- pharmacotherapy (3 trials were w/o concomitant pharmacotherapy, 4 trials were with concomitant therapy)	Sham tDCS+/- pharmacotherapy	Depression scores, response, remission
Sniezek[11], 2013, USA	Systematic Review Follow-up (range): up to 6 months	6 included studies (5 parallel RCT, 1 cross over RCT) MDD=4 studies Anxiety=1 study Depression + Anxiety=1 study Sample size (range): 33 to 248 Age (range): 18 to 71 years Women only (2 studies included only pregnant women)	Manual Acupuncture	Any control procedure (counseling, psychotherapy, sham acupuncture, massage, patient education)	Depression scores
Kalu[19], 2012, United Kingdom	Systematic Review Follow-up (range): 1 week to 1 month (NR in some studies)	10 included studies (6 RCT, 4 open-label studies) All patient had major depression (bipolar or unipolar) Sample size: 10 to 64	Active tDCS	Sham tDCS	Depressive symptoms (HAM-D, MADRS)

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Lee[21], 2012, USA	Systematic Review of Reviews Follow-up: NR	Depression n=6 systematic reviews (73 RCTs included, n=9,986 patients) Anxiety trials n= 1 systematic review (10 RCTs and two controlled trials, n=1,201 patients)	Acupuncture (manual, electro, ear, traditional Chinese, abdominal, Western medical)	Various (sham, no treatment, pharmacologic, behavioral, psychosocial)	Various symptom scales (HAM-D, HAM-A, BDI)
Ernst[16], 2011, United Kingdom	Systematic Review of Systematic Reviews Follow-up: NR	All patients had depression N=8 systematic reviews; 6 from China, 1 from USA, 2 multinational (71 unique primary studies) Sample size (range): 11,576 (477 to 3678)	Acupuncture	Sham acupuncture, pharmacotherapy, no treatment, wait-list control	NR
Williams[17], 2011, USA	Systematic Review Follow-up: up to 12 weeks	Patients with depression (2 SR of 28 RCTs, n=2475) or anxiety (0 SR)	Acupuncture	Sham acupuncture Antidepressant Wait-list control	Symptoms of depression, anxiety or PTSD Functional status or HRQOL

NA=not applicable; **CES**=cranial electrotherapy stimulation; **SD**=standard deviation; **tDCS**=transcranial direct current stimulation; **w/o**=without; **USA**=United States of America; **HAM-D**=Hamilton Depression Rating Scale; **MADRS**=Montgomery-Asberg Depression Rating Scale; **NR**=not reported; **CAM**=complementary and alternative medicine; **HAM-A**=Hamilton Anxiety Scale; **PTSD**=post-traumatic stress disorder; **HRQOL**=health related quality of life

APPENDIX 3: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Segrave[28], 2014 Australia	RCT Follow-up: 3 weeks	Major Depressive Disorder N=27 (10 female) Age (mean): 40.44 SD±14.52 MADRS score at baseline (range): 19-40 Concomitant antidepressants n=14	tDCS (24 minutes of 2mA) +sham CCT	CCT+sham tDCS tDCS+CCT	MADRS Beck Depression Inventory
Barclay[5], 2014 USA	RCT Follow-up: 5 weeks	Anxiety Disorder (20% had concomitant depression) N=115 67.8% female Age (mean): 42.3 SD±14.6 Concomitant pharmacotherapy = 63.5%	CES (100μA daily x 1 hour)	Sham CES (daily x 1 hour)	HAM-D, HAM-A
Bosch[22], 2013 Netherlands	RCT Follow-up: 12 weeks	Depression N=16 (12 women) Age (mean): 50.94 SD 1.33 Patients were allowed to continue their antidepressants	Acupuncture (once weekly x 12 weeks)	Wait-list	Quality & Quantity of sleep (PSQI)
Wei-dong[23], 2013 China	RCT (unblinded) Follow-up: 24 weeks	MDD N=60 (33 women) Age (mean): 48.5	Electroacupuncture (20 minutes with intermittent electrical impulses of 40Hz, 3 x per week for 24 weeks)	Paroxetine (20mg/day)	SDS, SAS,MADRS

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Sun[24], 2013 China	RCT Follow-up: 6 weeks	MDD N=75 (47 women) Age: 42	Electroacupuncture (5 x per week 30 minutes per day with 3Hz x 6 weeks) Acupoints: Baihui & Zusanli	Electroacupuncture control group Acupoints: Taichong, Sanyinjiao, Neiguan, Shenmen Fluoxetine (20mg/day)	HAM-D
Quah-Smith[25], 2013 Australia	RCT Follow-up: 3 months	MDD (<2 years duration) N=47 (72% women) No concomitant pharmacotherapy was allowed 55% previous acupuncture	Laser Acupuncture (2 x per week x 4 weeks, then 1 x per week for 4 weeks with 100mW low intensity infra-red 808nm) Acupoints LR14, CV14, LR8, HT7, KI3)	Placebo laser	HAM-D, QID-SR, QIDS-CL
MacPherson[26] 2013 United Kingdom	RCT Follow-up: 12 months	MDD (moderate to severe) N=755 (73.4% female) Age (mean): 43.5 SD 13.4 Concomitant pharmacotherapy = 68.7%	Acupuncture (12 weekly sessions) + usual care	Usual care Counseling (12 weekly sessions) + usual care	PHQ-9, BDI-II
Andreescu[27], 2011 USA	RCT Follow-up: 8 weeks	Mild or Moderate MDD N=53 (72% female) Age (mean): 47.5 Concomitant use of pharmacotherapy was not allowed	Electroacupuncture (12 sessions total: 2x30 minute sessions per week with 3-5mA current & 2Hz frequency) Acupoints: (verum acupuncture regimen): Du 20, Yintang	Sham electrostimulation (12 sessions total: 2x30 minute sessions per week)	HAM-D, MOS-SF-36, GAF

RCT=randomized controlled trial; **SD**=standard deviation; **MADRS**=Montgomery-Asberg Depression Rating Scale; **tDCS**=transcranial direct current stimulation; **CCT**=cognitive control training; **USA**=United States of America; **HAM-A**=Hamilton Rating Scale for Anxiety; **HAM-D**=Hamilton Depression Rating Scale; **CES**=cranial electrotherapy stimulation; **PSQI**=Pittsburgh Sleep Quality Index; **SDS**=self-rating depression scale; **SAS**=self-rating Anxiety scale; **MDD**=major depressive disorder; **QID-SR**=Quick Inventory for Depression-Self Reporting; **QIDS-CL**=Quick Inventory for Depression-Clinician; **MA**=manual acupuncture; **SDS**=Self-rating depression scale; **PHQ-9**=Patient Health Questionnaire; **BDI-II**=Beck Depression Inventory II; **MOS-SF-36=**Medical Outcomes Study 36-item Short-Form Health Survey; **GAF**=Global Assessment of Functioning

APPENDIX 4: Critical Appraisal of Included Systematic Reviews

First Author, Publication Year	A priori design	Duplicate study selection & Data Abstraction	Comprehensive literature search	Grey literature searched	List of studies (included & excluded)	Included study characteristics	QA completed	QA in conclusion	Appropriate Statistical methods	Publication bias assessed	Conflict of Interest
Kavirajan [20], 2014	+	+	+	+	+	NA	NA	+	NA	+	+
Shiozawa [18], 2014	+	+	-	+	/ (included only)	+	+	-	+	+	/ (only for SR)
Sniezek [11], 2013	+	?	+	-	/ (included only)	+	+	+	?	-	/ (only for SR)
Kalu [19], 2012	+	+	+	?	/ (included only)	+	-	+	+	+	/ (only for SR)
Lee [21], 2012	+	+	+	?	/ (included only)	+	+	+	+	-	/ (only for SR)
Ernst [16], 2011	+	+	+	?	/ (included only)	+	+	+	NA	-	/ (only for SR)
Williams [17], 2011, USA	+	/	+	?	+	-	+	+	NA	-	-

+=done -=not done ?=unclear NA=not applicable /=partial

APPENDIX 5: Critical Appraisal of Included Randomized Controlled Trials

First Author, Publication Year	Random sequence generation	Allocation Concealment	Blinding of participants	Blinding of outcome assessment	Incomplete Outcome Data	Selective Reporting
Segrave[28], 2014	L	?	L	L	?	L
Barclay[5], 2014	?	L	?	?	L	H
Bosch[22], 2013	L	?	?	L	?	L
Wei-dong[23], 2013	L	?	?	?	H	L
Sun[24], 2013	L	L	?	?	H	L
Quah-Smith[25], 2013	L	L	L	?	L	L
MacPherson[26] 2013	L	?	?	?	H	L
Andreescu[27], 2011	H	H	H	?	H	L

L=low risk of bias H=high risk of bias ?=unclear risk of bias NA=not applicable

APPENDIX 6: Main Study Findings and Authors' Conclusions (Depression)

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Systematic Reviews		
Kavirajan[20], 2014	There were no RCTs evaluating CES vs. sham CES in the management of acute depression that met the inclusion criteria for this review.	There is a paucity of rigorously designed trials evaluating the efficacy of CES in acute depression
Shiozawa[18], 2014	Depression Scores (HAM-D or MADRS): Active vs. Sham tDCS SMD=0.37 95%CI 0.04, 0.70 Response and Remission: Active vs. Sham tDCS SMD=0.4 95%CI 0.07,0.73 Response Rates Active vs. Sham tDCS OR=1.63 95%CI 1.26,2.12 Remission Rates Active vs. Sham tDCS OR=2.5 95%CI 1.26,2.5	Active tDCS was statistically superior to sham tDCS in the treatment of major depression. Previous trials have mixed results and trial size is small. Therefore clinicians should rely on established treatments for depression as there is not enough evidence to support the immediate use of tDCS
Sniezek[11], 2013	Depression Scores (1 study in MDD) Acupuncture vs. non-specific acupuncture Significant greater reduction in both BDI and HDS with treatment acupuncture (P<0.05) Remission (1 study in MDD) Remission rates in patients with MDD treated with acupuncture were similar to other treatments (pharmacotherapy, psychotherapy)	There is a lack of high quality research supporting the use of acupuncture in women with depression or anxiety. The novel QSAT quality assessment tool requires validation but offers a promising approach to evaluating the standards of acupuncture trails.
Kalu[19], 2012	Reduction in Symptom Severity % reduction in symptom severity (weight mean) with active tDCS= 28.9% (open-label=24.8%, RCT=32.3%), range=14.6% to 60% Responders % responders with active tDCS (weighted mean)=19.8% (open-label=17.5%, RCT=21.8%), range=0% to 80% Remission % achieving remission with active tDCS (weighted mean) =8.5% (open-label=10%, RCT=6.1%), range=0% to 23.8% Reduction in Symptom Severity Active tDCS vs. sham tDCS=Hedges' g=0.74 95%CI 0.21, 1.27, P=0.006	tDCS has a potential benefit in the management of depression. Larger studies with longer follow-up are required.
Lee[21], 2012, USA	Acupuncture in Depression 4 SR had mixed or inconclusive results 2 SR had positive results with acupuncture Acupuncture in Anxiety 1 SR demonstrated positive results for acupuncture in anxiety disorders	Acupuncture appears promising for the management of depression but no definitive conclusions can be drawn. Weak GRADE recommendation in favour of acupuncture in the management of depression.

First Author, Publication Year	Main Study Findings	Authors' Conclusions
		Acupuncture appears promising for the management of anxiety, but safety is not well understood. Weak GRADE recommendation in favour of acupuncture in the management of anxiety. Larger trials are needed
Ernst[16], 2011, United Kingdom	All 6 SR from China had positive conclusions regarding the efficacy of acupuncture in the treatment of depression. None of the non-Chinese trials reported positive outcomes. (statistics NR) <u>Acupuncture vs. Sham Acupuncture:</u> 12 primary studies; 7 positive, 2 equivocal, 3 negative <u>Acupuncture vs. Pharmacotherapy</u> 52 primary studies; 27 positive, 21 equivocal, 4 negative <u>Acupuncture vs. no treatment or wait-list</u> 5 primary studies; 3 positive, 2 equivocal, 0 negative	The effectiveness of acupuncture in the management of depression remains unproven and appear indistinguishable from the effects of placebo.
Williams[17], 2011, USA	Outcomes were reported as narratives from each individual study. <u>Acupuncture vs. Sham acupuncture (Depression 1 RCT n=477)</u> Depression scores (HAM-D, BDI): SMD -0.65 95%CI -1.18, -0.11 Response rates (≥50% reduction in symptoms, 6 RCTs) RR=1.32 95%CI 0.83, 2.10 Remission rates (4 RCTs) RR=1.30 95%CI 0.57,2.95 <u>Acupuncture vs. antidepressant pharmacotherapy (Depression, 9RCTs n=662)</u> Depressive symptoms MD -0.31 95%CI -0.94,1.56 Response rates RR 1.09 95%CI 0.92, 1.30 <u>Acupuncture compared to sham acupuncture, wait-list or as an adjunct:</u> NS difference in response rates	Acupuncture was more effective at improving depressive symptoms compared to sham acupuncture, but did not improve rates of response or remission. Acupuncture did not differ compared to antidepressants.
Randomized Controlled Trials		
Segrave[28], 2014 Australia	<u>Reduction in Symptom Severity</u> MADRS score decreased significantly after 5 sessions (post-hoc analysis) tDCS+sham CCT P=0.04 sham tDCS+ CCT P=0.02	tDCS may enhance antidepressant effects when combined with CCT but warrants further investigation

<table>
<tr><th>First Author, Publication Year</th><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td></td><td>MADRS score at 3 weeks follow-up was not longer significantly reduced in patients who received tDCS+shamCCT or shamDCT+CCT

<u>Response Rate</u> (≥50% reduction in MADRS score)
Completion of five sessions
Sham tDCS+ CCT=44%
tDCS+sham CCT=0 patients
At 3 weeks follow-up
Sham tDCS+ CCT=11%
tDCS+sham CCT=0 patients

Remission rates (MADRS <10) between groups did not reach statistical significance either after 5 sessions nor 3 weeks f/u.

<u>BDI after 5 sessions (post-hoc)</u>
Change from baseline tDCS+sham CCT (P=0.005) and sham tDCS+CCT (P=0.006)

<u>BDI after 3 weeks f/u (post-hoc)</u>
Sham tDCS+CCT returned to baseline
tDCS+sham CCT remained significantly lower than baseline (P=0.02)</td><td></td></tr>
<tr><td>Bosch[22], 2013

Netherlands</td><td>PSQI Total Score<table><tr><th>Intervention</th><th>BL</th><th>Wk 12</th><th>P-value</th></tr><tr><td>Acupuncture</td><td>8.5</td><td>6.88</td><td>0.003</td></tr><tr><td>Wait-list</td><td>9.63</td><td>9</td><td>0.493</td></tr></table></td><td>Acupuncture seems to improve sleep in patients with long standing psychiatric conditions in a convenience sample.</td></tr>
<tr><td>Wei-dong[23], 2013

China</td><td>Electroacupuncture<table><tr><th>Scale</th><th>Pre-Tx (SD)</th><th>Post-Tx (SD)</th><th>P-value</th></tr><tr><td>MADRS</td><td>24.7 (5.9)</td><td>13.8 (6.2)</td><td><0.05</td></tr><tr><td>SDS</td><td>64.6 (9.3)</td><td>52.2 (11.5)</td><td><0.01</td></tr></table>No comparison to paroxetine before or after treatment was made</td><td>Electroacupuncture is an effective method of treating depression</td></tr>
<tr><td>Sun[24], 2013

China</td><td>Hamilton Depression Rating Scale<table><tr><th></th><th>EA (n= 20)</th><th>Control (n=16)</th><th>Fluoxetine (n=25)</th><th>P-value</th></tr><tr><td>BL</td><td>23.8</td><td>22.8</td><td>23.3</td><td>0.36</td></tr><tr><td>Wk 2</td><td>18.8</td><td>18.9</td><td>21.8</td><td>0.014</td></tr><tr><td>Wk 4</td><td>14.3</td><td>14.1</td><td>17.4</td><td>0.003</td></tr><tr><td>Wk 6</td><td>9.5</td><td>9.9</td><td>12.1</td><td>0.16</td></tr></table></td><td>Electroacupuncture has the same therapeutic effect as fluoxetine in the treatment of depression. Confirmation in larger scale trials is required.</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year</th><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td></td><td>
<table>
<tr><td>P-value</td><td>0.00</td><td>0.00</td><td>0.00</td><td></td></tr>
</table>

Responders (≥50% reduction in HAM-D)
EA Treatment: 75%
EA Control: 75%
Fluoxetine: 60%
P<0.001</td><td></td></tr>
<tr><td>Quah-Smith[25], 2013

Australia</td><td>
<table>
<tr><th></th><th>Placebo Acupuncture (n=22)</th><th></th><th>Laser Acupuncture (n=25)</th><th></th><th>P-value</th></tr>
<tr><th></th><th>BL</th><th>8 wks</th><th>BL</th><th>8wks</th><th></th></tr>
<tr><td>HAM-D</td><td>21</td><td>14</td><td>21</td><td>9</td><td>0.013</td></tr>
<tr><td>QID-CL</td><td>21</td><td>13</td><td>21</td><td>8</td><td>0.016</td></tr>
<tr><td>QID-SR</td><td>19</td><td>11</td><td>18</td><td>12</td><td>0.390</td></tr>
<tr><td>HAM-D >50 % reduction</td><td>NA</td><td>4/22 (18.2 %)</td><td>NA</td><td>18/25 (72%)</td><td>0.0004</td></tr>
</table>
Laser acupuncture
QIDS-SR at 1 month (n=18) & 3 month (n=16) follow-up were significantly reduced from baseline, P=0.001</td><td>Laser acupuncture is associated with objective improvement in depression. Larger trials are needed to assess the long term effects.</td></tr>
<tr><td>MacPherson[26] 2013

United Kingdom</td><td>PHQ-9 at 3 months
<u>Acupuncture vs. Usual Care</u>
N=452
MD= -2.46 95%CI -3.72, -1.21 P<0.001
<u>Acupuncture vs. Counseling</u>
N=603
MD= -0.76 95%CI -1.77,0.25 P=0.140

PHQ-9 at 6 months
<u>Acupuncture vs. Usual Care</u>
N=350
MD= -1.90 95%CI -3.02, -0.79 P=NR
<u>Acupuncture vs. Counseling</u>
N=371
MD= 0.45 95%CI -0.58,1.49 P=NR

PHQ-9 at 9 months
<u>Acupuncture vs. Usual Care</u>
N=348
MD= -0.83 95%CI -2.15, 0.49 P=NR</td><td>Compared to usual care, acupuncture significantly reduces the symptoms of depression in medium term follow-up</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year</th><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td></td><td><u>Acupuncture vs. Counseling</u>
N=360
MD= -0.25 95%CI -0.25, 2.19 P=NR

PHQ-9 at 12 months
<u>Acupuncture vs. Usual Care</u>
N=347
MD= -0.99 95%CI -2.53,0.55 P=NR
<u>Acupuncture vs. Counseling</u>
N=361
MD= 0.721 95%CI -0.82, 2.01 P=NR

BDI-II at 12 months
<u>Acupuncture vs. Usual Care</u>
N=445
MD= -2.88 95%CI -5.68, -0.08 P=NR
<u>Acupuncture vs. Counseling</u>
N=401
MD= 0.59 95%CI -1.93, 3.11 P=NR</td><td></td></tr>
<tr><td>Andreescu[27], 2011

USA</td><td>Change from Baseline to 8 weeks, mean (SD)
<table>
<tr><th>Measure</th><th>Electro (n=23)</th><th>Control (n=22)</th><th>P-value</th></tr>
<tr><td>HAM-D</td><td>-7.4 (6.2)</td><td>-7.9 (7.4)</td><td>0.81</td></tr>
<tr><td colspan="4">MOS-SF-36, component scores</td></tr>
<tr><td>Physical</td><td>0.5 (6.9)</td><td>-1.7 (8.0)</td><td>0.32</td></tr>
<tr><td>Mental</td><td>6.2 (13.6)</td><td>14.1 (17.5)</td><td>0.09</td></tr>
<tr><td>Bodily Pain</td><td>-1.0 (18.3)</td><td>6.8 (19.7)</td><td>0.17</td></tr>
<tr><td>GAF</td><td>10.3 (10.3)</td><td>11.4(8.8)</td><td>0.70</td></tr>
</table>
Responders (HAM-D score <10 or 50% decrease from BL)
Electroacupuncture (n=23)=40%
Sham Acupuncture (n=22)=44%
P=0.77</td><td>Electroacupuncture and control acupuncture both demonstrated similar improvements in symptoms of depression</td></tr>
<tr><td colspan="3">RCT=randomized controlled trial; CES=cranial electrotherapy stimulation; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; SDM=standard mean difference; OR=odds ratio; MDD=major depressive disorder; BDI=Beck Depression Inventory; HDS=Hamilton Rating Scale; QSAT=Quality Score for Acupuncture Trials; GRADE=Grading of Recommendations, Assessment, Development and Evaluation; NS=not significant; MD=mean difference; PSQI=Pittsburgh Sleep Quality Index; BL=baseline; SDS=self-rating depression scale; EA=electroacupuncture; QID-SR=Quick Inventory for Depression-Self Reporting; QIDS-CL=Quick Inventory for Depression-Clinician; NA=not applicable; PHQ-9=Patient Health Questionnaire; BDI-II=Beck Depression Inventory II; MOS-SF-36=Medical Outcomes Study 36-item Short-Form Health Survey; GAF=Global Assessment of Functioning</td></tr>
</table>

APPENDIX 7: Main Study Findings and Authors' Conclusions (Anxiety)

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Randomized Controlled Trials		
Barclay[5], 2014 USA	HAM-A Scores (5 weeks) CES (n=57)=13.37 Sham CES (n=51) = 19.98 P=0.001 HAM-D Scores (5 weeks) CES (n=58)=6.47 Sham CES (n=49) = 9.96 P=0.001	CES is an effective treatment for anxiety with co-morbid depression

RCT=randomized controlled trial; **CES**=cranial electrotherapy stimulation; **HAM-D**=Hamilton Depression Rating Scale; **MADRS**=Montgomery-Asberg Depression Rating Scale; **SDM**=standard mean difference; **OR**=odds ratio; **MDD**=major depressive disorder; **BDI**=Beck Depression Inventory; **HDS**=Hamilton Rating Scale; **QSAT**=Quality Score for Acupuncture Trials; **GRADE**=Grading of Recommendations, Assessment, Development and Evaluation; **BDI**=Beck Depression Inventory; **SMD**=standardized mean difference; **NS**=not significant; **MD**=mean difference