A Systematic Review of Acupuncture for Chronic Fatigue Syndrome

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[Abstract]

Objectives: To evaluate and summarize the efficacy and safety of acupuncture treatment (AT) in chronic fatigue syndrome (CFS).

Methods: Fifteen databases (Pubmed, Cochrane, EMBASE, AMED, CINAHL, CNKI, Wanfang, and eight Korean databases) were searched up to September 2016. Only trials in which acupuncture was the sole treatment were included. Fatigue was used as the primary outcome measure, while the quality of life, pain, mood disorders, and adverse events were used as secondary outcome measures. We adopted three classifications: AT vs Sham AT, AT vs Wait-list, AT vs Western medication. The Cochrane risk of bias tool was used to assess the methodological quality.

Results: A total of 11 randomized controlled trials involving 869 participants were identified. In comparison with Sham AT, AT significantly alleviated fatigue and pain, but no conclusions about the quality of life and mood disorders could be drawn. In the Wait-list group and Western medication groups, patients with CFS might feel less fatigued following acupuncture treatment, but the evidence was insufficient due to lack of study. Nine of 11 RCTs (81.8%) reported adverse events and there were two cases of mild subcutaneous hemorrhage, but no serious adverse cases.

Conclusion: This review found evidence that patients with CFS may generally benefit from alleviation of symptoms by acupuncture treatment, and there is no evidence of worsening symptoms or causing of serious adverse events. A positive effect on fatigue and pain was observed, but no conclusion for improving quality of life and mood disorders.

Key words: Chronic fatigue syndrome; Acupuncture; Randomized controlled trials; Meta-analysis; Systematic review

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I. Introduction

Chronic fatigue syndrome (CFS) results in an unexplained fatigue that lasts for more than 6 months and is accompanied by various symptoms such as memory and concentration losses, post-exercise fatigue, sleep disorder, depression, and anxiety. Diagnostic criteria such as those of the Centers for Disease Control and Prevention (CDC; 1988)\(^3\), CDC (1994)\(^2\), Australian criteria\(^9\), and British criteria\(^4\) have been officially used. Among these, Fukuda’s CDC (1994) criteria were the most widely used. According to Wessely’s study where the literature related to CFS in several countries was reviewed, the prevalence of chronic fatigue was 7–21%, and the prevalence of patients who met the criteria for CFS was 0.5–2%\(^5\). In a prospective study of patients who visited a primary medical clinic, 1.2–2.6% of them were diagnosed with CFS: in particular, the patients who met the CDC (1994) criteria were 2.6%\(^5\). In general, the prevalence rate of CFS is reported to be 1–2%.

The cause and mechanism of CFS are so far unclear, and to date there is no officially recognized treatment. In Cochrane Reviews, several systematic reviews on exercise therapy\(^7\), cognitive behavior therapy\(^8\), and herbal medicine treatment\(^9\) have been reported. Furthermore, oriental medicine treatment\(^9\) and complementary and alternative medicine (CAM) therapies have also been reported\(^10\). However, no studies on acupuncture and CFS have been reported since the systematic review in China in 2009\(^9\), in which studies published until 2008 only in domestic databases were searched and methodological limitations in analyzing the effect of acupuncture treatment (AT) were noted.

Therefore, the purpose of the present review was to assess the efficacy and safety of AT by systematically summarizing data from randomized controlled trials (RCTs) of acupuncture in patients with CFS.

II. Methods

1. Search methods

We searched the following 15 databases up to September 2016 without language and publication type restrictions: PubMed, the Cochrane Library 2016 (Issue 9), Excerpta Medica Database (EMBASE), Alternative Medicine (AMED), the Cumulative Index to Nursing & Allied Health Literature (CINAHL), two Chinese databases (China National Knowledge Infrastructure (CNKI) and Wanfang), and eight Korean databases (KoreaMed, KMbase, NDSL, KISTI, KISS, RISS, Oasis, and Korean traditional knowledge portal). Additionally, relevant references from previous systematic reviews were also searched.

The following keywords were used for the search and were adjusted for each database: (“chronic fatigue syndrome” OR “myalgic encephalomyelitis” OR “myalgic encephalitis”) AND (“acupuncture” OR “electroacupuncture” OR “pharmaco-acupuncture” OR “acupressure” OR “acupoints” OR “acupoint injection” OR “dry needle” OR “needling”). The details are described in Appendix 1.

2. Study selection

1) Types of studies

We included all relevant RCTs and quasi-RCTs of any type of AT regardless of the study design, published language, number of participants, and blinding. Observational, uncontrolled, case-control, case series and laboratory studies were excluded.

2) Types of patients

Patients who were diagnosed by any defined diagnosis criteria of CFS such as CDC, Australian and British criteria were included regardless of sex, age, race, disease course, and severity.
3) Types of interventions

(1) Experimental interventions
All types of AT were included including electroacupuncture, scalp acupuncture, laser acupuncture, auricular acupuncture, acupressure, acupoint injection, and pharmaco-acupuncture. We only included trials in which acupuncture was the sole treatment. Studies with the following treatment were excluded: (1) AT combined with other complementary and alternative medicine (CAM) (e.g., [acupuncture + herbs] vs control); (2) two or more different types of AT in the experimental group (e.g., [electroacupuncture + Auricular acupuncture] vs control); and (3) uncontrolled interventions (e.g., using different acupoints in the same group according to the diagnostic pattern).

(2) Control interventions
Sham acupuncture (e.g., non-acupoints stimulation or placebo needle), Wait-list, and Western medications (e.g., steroids and vitamins) were included as control interventions. Studies that compared AT with other CAM treatments were excluded.

4) Types of outcome measures
We extracted the data of each measured outcome at the end of the treatment. The outcomes were divided into primary and secondary outcomes.

(1) Primary outcome
Fatigue measured by validated scales such as the Chalder fatigue scale (FS) and Fatigue Severity Scale (FSS) was applied as the primary outcome.

(2) Secondary outcomes
Studies using at least one of the following clinical outcome variables were included, while those only reporting laboratory outcomes were excluded. (1) Quality of life was measured by validated scales such as the Short Form–12 (SF–12), SF–20, SF–36, Somatic and Psychological Health Report (SPHERE), and World Health Organization Quality of Life–BREF (WHOQOL–BREF). (2) Pain was measured by validated scales such as the Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS). (3) Mood disorders were measured by validated scales such as the Beck Depression Index (BDI), Self–rating Anxiety Scale (SAS), and Self–rating Depression Scale (SDS). (4) Effective rates were measured by calculating the change in each score such as [(score before treatment – score after treatment) / score before treatment] × 100. (5) Adverse events were measured using any reporting system such as serious adverse reactions (SAEs).

5) Data extraction and quality assessment
Two independent reviewers participated in the process of literature search, selection, and data extraction. The literature was first searched through the titles and abstracts, and subsequently selected and included in this review by considering the full texts. Furthermore, the sample size, demographic characteristics, diagnostic criteria, treatment details, outcome measures, results, adverse events, and additional information about AT such as acupoints, meridians, retaining time, and De–Qi were also extracted. We resolved any disagreements between the two reviewers first through discussion and, when necessary, by seeking the opinion of a third reviewer.

The methodological quality was evaluated independently by two reviewers using the Cochrane risk of bias tool: if needed, a third reviewer was involved. The tool included seven criteria: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other potential biases (i.e., the baseline imbalance).
3. Data synthesis

To create a Summary of Findings table, we used the GRADEpro software (Grade Working Group) and data synthesis was performed by Review Manager (RevMan) Version 5.3.0 for Windows (Copenhagen, The Nordic Cochrane Center).

For the dichotomous data, we presented the effect size as the relative risk (RR) with 95% confidence interval (CI). For the continuous data, we calculated the weighted mean difference (WMD) when the same scale was used, while standardized mean difference (SMD) was calculated if different scales were used.

Meta-analysis was performed only when a quantitative synthesis was possible. We used the chi-square test and the Higgins I² test to assess the heterogeneity. Heterogeneity was considered at a $p < 0.1$. The fixed effect model was used unless there was evidence of heterogeneity. Subgroup analysis was performed according to different types of AT in the case of $I^2 > 50\%$. In addition, the funnel plot analysis was used to confirm publication bias, but failed due to the small number of studies.

III. Results

1. Study selection and description

A total of 1,277 studies were screened and 869 participants of 11 RCTs were finally included in this review. Fig. 1 illustrates the flow diagram of the
### Table 1. Summary of Included Studies

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Diagnosis</th>
<th>Sample size</th>
<th>Sex (M/F)</th>
<th>Mean age</th>
<th>Treatment period</th>
<th>AT</th>
<th>Sessions</th>
<th>Intervention group (regime)</th>
<th>Control group (regime)</th>
<th>Main outcomes</th>
<th>Intergroup differences</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hou (2016)</td>
<td>CDC (1988)</td>
<td>157/83</td>
<td>36.0</td>
<td>30 days</td>
<td>21</td>
<td>(A) AT (n = 89) (30 min, once daily, 7 times as a course, for three courses, with 3 days interval in between)</td>
<td>(B) Western medicine (n = 68) (Fluoxetine Hydrochloride cap. 20 mg/d for 30 days + Vit B6 20 mg/d for 3 weeks)</td>
<td>1) FS</td>
<td>1) ( p &lt; 0.05 )</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tang (2015)</td>
<td>CDC (1994)</td>
<td>17</td>
<td>34.9</td>
<td>4 wk</td>
<td>16</td>
<td>(A) AT (n = 8) (30 min, 5 times weekly for 2 weeks + 3 times weekly for 2 weeks)</td>
<td>(B) Sham AT (n = 9) (30 min, non-acupoint, Streitberger placebo needle, 5 times weekly for 2 weeks + 3 times weekly for 2 weeks)</td>
<td>1) CIS 2) SPHERE 3) SF-36</td>
<td>1) ( p &gt; 0.05 ) 2) ( p &gt; 0.05 ) (n.r.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lu (2014)</td>
<td>CDC (1994)</td>
<td>133/60/73</td>
<td>34.4</td>
<td>20 days</td>
<td>20</td>
<td>(A) AT (n = 47) (30 min, once daily)</td>
<td>(B) moxa-heated AT (n = 44) (moxa-heated AT 20 min + AT 30 min, once daily)</td>
<td>(C) Sham AT (n = 42) (30 min, non-acupoint, once every day)</td>
<td>1) FS</td>
<td>1) [AvsC] ( p &lt; 0.05 ) [BvsC] ( p &lt; 0.01 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ng (2013)</td>
<td>CDC (1994)</td>
<td>99/31/68</td>
<td>40.9</td>
<td>4 wk</td>
<td>8</td>
<td>(A) AT (n = 50) (30 min, 2 times weekly)</td>
<td>(B) Sham AT (n = 49) (30 min, acupoint, Streitberger placebo needle, 2 times weekly)</td>
<td>1) FS 2) SF-12 3) GHQ-12</td>
<td>1) [p] ( p &lt; 0.05 ) [m] ( p &lt; 0.01 ) [p] ( p &lt; 0.05 ) [m] ( p = 0.452 )</td>
<td>3) ( p = 0.766 )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Summary of Included Studies (Continued)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Diagnosis</th>
<th>Sample size</th>
<th>Sex (M/F)</th>
<th>Mean age</th>
<th>Treatment period</th>
<th>AT Sessions</th>
<th>Intervention group (regime)</th>
<th>Control group (regime)</th>
<th>Main outcomes</th>
<th>Intergroup differences</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim(^{10}) (2012) CDC (1994)</td>
<td>24</td>
<td>9/15</td>
<td>43.7</td>
<td>4 wk</td>
<td>(A) AT (n = 12) (20 min, 3 times weekly)</td>
<td>(B) no treatment (n = 12)</td>
<td>1) FSS 2) SRI 3) BDI 4) ISI 5) PGA</td>
<td></td>
<td>1) p &lt; 0.001 2) p &lt; 0.005 3) p = 0.0001 4) p &lt; 0.005 5) p &lt; 0.05</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Zhang(^{10}) (2012) CDC (1994)</td>
<td>72</td>
<td>30/42</td>
<td>34.0</td>
<td>4 wk</td>
<td>(A) AT (n = 47) (30 min, 5 times for 1 week, 3 times for the subsequent 2 weeks, 2 times for the last week)</td>
<td>(B) Sham AT (n=25) (30 min, acupoint, Streitberger placebo needle, 5 times for one week, 3 times for next 2 weeks, 2 times for last one week)</td>
<td>1) FSS 2) SPHERE 3) SF-36</td>
<td></td>
<td>1) p &lt; 0.005 2) p &lt; 0.05 3) p = 0.099</td>
<td>subcutaneous hematoma 2*</td>
<td></td>
</tr>
<tr>
<td>Zhang(^{10}) (2011) CDC (1994)</td>
<td>119</td>
<td>56/64</td>
<td>43.3</td>
<td>4 wk</td>
<td>(A) AT (n = 59) (20 min, once daily except weekend)</td>
<td>(B) Sham AT (n = 60) (20 min, non-acupoint, once daily except weekend)</td>
<td>1) FS 2) SF-20</td>
<td></td>
<td>1) p &lt; 0.01 2) p &lt; 0.05</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Chan(^{10}) (2010) CDC (1994)</td>
<td>53</td>
<td>23/30</td>
<td>38.7</td>
<td>2 wk</td>
<td>(A) AT (n = 27) (30 min, 3 times weekly)</td>
<td>(B) Sham AT (n = 26) (30 min, acupoint, Streitberger placebo needle, 3 times weekly)</td>
<td>1) WHOQOL 2) FS 3) Effective rate</td>
<td></td>
<td>1) p &lt; 0.01 2) p &lt; 0.01</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Author (year)</td>
<td>Diagnosis (year)</td>
<td>Sample size</td>
<td>Sex (M/F)</td>
<td>Mean age</td>
<td>Treatment period</td>
<td>AT</td>
<td>Sessions</td>
<td>Intervention group (regime)</td>
<td>Control group (regime)</td>
<td>Main outcomes</td>
<td>Intergroup differences</td>
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<tr>
<td>Wang (2009)</td>
<td>CDC (1994)</td>
<td>64</td>
<td>26/38</td>
<td>37.3</td>
<td>(n.r.)</td>
<td></td>
<td></td>
<td>(A) AT (n = 32) 30 min, 3 times weekly, 7 times as a course, for 2 courses, with 3-7 days interval in between</td>
<td>(B) Sham AT (n = 32) 30 min, non-acupoint, 3 times weekly, 7 times as a course, for 2 courses, with 3-7 days interval in between</td>
<td>1) WHOQOL</td>
<td>1) 2) 3) 4) 5)</td>
</tr>
<tr>
<td>Zhu (2008)</td>
<td>CDC (1994)</td>
<td>60</td>
<td>16/44</td>
<td>38.1</td>
<td>12 d</td>
<td></td>
<td>10</td>
<td>(A) EA (n = 30) 20 min, once daily, 5 times as a course, for 2 courses, with 2 days interval in between</td>
<td>(B) Sham EA (n = 30) 20 min, non-acupoint, once daily, 5 times as a course, for 2 courses, with 2 days interval in between</td>
<td>1) FSS</td>
<td>1) p &lt; 0.01</td>
</tr>
<tr>
<td>Wang (2007)</td>
<td>CDC (1994)</td>
<td>71</td>
<td>18/53</td>
<td>36.5</td>
<td>10 d</td>
<td></td>
<td>10</td>
<td>(A) EA (n = 36) 20 min, once daily</td>
<td>(B) Sham EA (n = 35) 20 min, non-acupoint, once daily</td>
<td>1) FSS</td>
<td>1) p &lt; 0.0001</td>
</tr>
</tbody>
</table>

* Not stated about the group.

selection process.

Among the 11 studies, nine were conducted in China\(^\text{13-15,18-23}\), one was in Hong Kong\(^\text{16}\), and one was in Korea\(^\text{17}\). The number of participants included in each study ranged between 17 and 157, with a mean age of 38.0 years and a men-to-women ratio of 1:1.5. The CDC criteria were used for diagnosis in all studies: one study used the 1988 CDC criteria\(^\text{13}\), while the other 10 studies used the 1994 CDC criteria (Fukuda criteria). Moreover, the FS was the most commonly used primary outcome\(^\text{13,15,16,19-21}\), while FSS was used in four studies\(^\text{17,18,22,23}\). As secondary outcomes, SF-36 was used in four studies\(^\text{14,18,22,23}\), SPHERE in four\(^\text{14,18,22,23}\), WHOQOL-BREF in two\(^\text{20,21}\), and various scales were used in each study (Table 1).

2. Interventions

1) Classification

The study design was classified into three categories based on the intervention in the control group. Among the 11 RCTs, nine studies\(^\text{14-16,18-23}\) were compared with Sham acupuncture, while the other two studies were compared to the Wait-list group\(^\text{17}\) and Western medication group\(^\text{13}\).

2) General characteristics of acupuncture treatment (Appendix 2)

(1) Types of acupuncture treatment

Among the 12 groups of the 11 selected studies, simple AT was used in nine groups\(^\text{13-21}\), electroacupuncture was used in two\(^\text{22,23}\), and moxa-heated needling was used in one\(^\text{15}\).

(2) Acupoints and meridians

A total of 21 acupoints were used. The most used acupoint was ST36, which was applied in eight studies\(^\text{14-16,18,20,21}\), followed by BL23 in seven studies\(^\text{13,14,17,18,20-23}\), BL18 in five studies\(^\text{13,14,17,18,21}\), CV4 in three studies\(^\text{13,15,21}\), CV6 in two studies\(^\text{13,15}\), ST40 in two studies\(^\text{18,23}\), and BL11\(^\text{15}\), BL13\(^\text{15}\), BL17\(^\text{18}\), BL22\(^\text{18}\), BL43\(^\text{18}\), and GB20\(^\text{17}\) in one study.

The Bladder meridian was the most used meridian (nine acupoints in eight studies\(^\text{13,14,17,18,20-23}\)), followed by Conception extra meridian (four acupoints in three studies\(^\text{13,15,20}\), Stomach meridian (one acupoint in eight studies\(^\text{14-16,18,20-23}\)), Governor extra meridian (one acupoint in five studies\(^\text{18-20,23}\), Spleen meridian (one acupoint in three studies\(^\text{15,16,20}\), Large Intestine meridian\(^\text{15,20}\), Gall Bladder meridian\(^\text{15}\) (one acupoint in one study), and Liver meridian\(^\text{15,20}\), Heart meridian\(^\text{14,19}\), and Kidney meridian\(^\text{15,20}\) (one acupoint in two studies).

(3) Treatment methods

In seven of the 11 RCTs\(^\text{13,14,16,18,20,21}\), the retaining time of AT was 30 minutes, while it was 20 minutes in the remaining four studies\(^\text{17,19,22,23}\).

De-Qi was performed in eight studies\(^\text{14-16,18,20-22}\), while one study\(^\text{17}\) did not perform it, and the remaining two studies\(^\text{13,23}\) did not describe it.

3. Risk of bias

The quality of the literature was evaluated by using the Cochrane risk of bias tool (Fig. 2 and 3). All the selected studies used randomization methods, but only eight RCTs\(^\text{14-16,18,20,21,23}\) presented a detailed methodological description, while the remaining three\(^\text{13,19,22}\) did not. Three RCTs\(^\text{17,21,23}\) adequately performed the allocation concealment, which was not described in the remaining studies\(^\text{13-16,18-20}\). Because of the nature of the AT, the practitioners cannot be blinded during the treatment. Therefore, all the included studies had a high risk of performance bias. The blinding of the evaluator was reported in six RCTs\(^\text{17,19,21,23}\), while four RCTs\(^\text{18,20,23}\) did not, and one\(^\text{13}\) implemented it inadequately. Six RCTs\(^\text{17,19,21-23}\) fully reported the reasons for dropouts and withdrawals, while two RCTs\(^\text{13,15}\) involving dropouts did not describe the reasons, and the remaining three RCTs\(^\text{17-19}\) did not involve any dropouts. Only one study\(^\text{17}\) had a pro-

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tocol that was followed adequately. Out of the 11 RCTs, there were no baseline differences in 10 trials, while the remaining study\textsuperscript{15} did not present the baseline data, and had thus a high risk of potential bias.

4. Summary of the main results

The efficacy of AT was analyzed in the following three categories: Acupuncture vs Sham acupuncture, Acupuncture vs Wait-list, and Acupuncture vs Western medicine treatment (Table 2, 3, and 4).

1) Acupuncture vs Sham acupuncture

(I) Fatigue

Both the FS and FSS were used as outcome variables. Three RCTs\textsuperscript{16,20,21} using the FS in the same study design were included in the meta-analysis and showed a significant fatigue reduction effect compared with the Sham acupuncture group (Fig. 4: \(n = 216\): WMD, -1.63: 95% CI, -2.55 to -0.72; \(p = 0.0005; \lambda^2 = 0\%\)). Moreover, two RCTs\textsuperscript{18,22} of different interventions, which applied the FSS, were quantitatively synthesized and showed a significant effect in the AT group (Fig. 5: \(n = 132\), WMD, -9.54: 95% CI, -17.20 to -1.89; \(p = 0.01; \lambda^2 = \)... \textsuperscript{10}
77%). Wang et al\textsuperscript{23} also reported a significant reduction in the FSS in the AT group (\(p < 0.0001\)), but FSS was not scored as continuous data but presented only as effective rates; thus, it was excluded from the quantitative synthesis.

(2) Quality of life

SPHERE, SF–12, SF–20, SF–36, WHOQOL–BREF, and General Health Questionnaire–12 items (GHQ–12) were used. Three RCTs\textsuperscript{14,18,22} of the same study design using SPHERE were synthesized and showed a significant effect compared with the Sham group (Fig. 6; \(n = 149\); WMD, –8.63 to –1.92; \(p = 0.002\); I\(^2\) = 61%). As defined earlier, subgroup analysis by intervention was performed to analyze the cause of heterogeneity.

Among five RCTs using SF–12\textsuperscript{16}, SF–20\textsuperscript{19}, and SF–36\textsuperscript{14,18,22}, two studies\textsuperscript{19,22} reported a significant improvement compared with the control group (SMD 1.22; IV, Random: 95% CI, 0.82 to 1.61 / SMD 1.84; IV, Random: 95% CI, 1.23 to 2.45). However, there were no significant differences between the two groups in the remaining three studies\textsuperscript{14,16,18}. In one\textsuperscript{16} of the studies, the effect of improving the quality of life was higher in the Sham acupuncture group, although not statistically significant. Meta-analysis was not performed due to the unexplained high heterogeneity (I\(^2\) = 89%). Wang et al\textsuperscript{23} was excluded from the quantitative synthesis because of insufficient data.

Three RCTs using WHOQOL–BREF\textsuperscript{20,21} and GHQ–12\textsuperscript{16} were quantitatively synthesized and indicated no significant difference between the two groups (Fig. 7; \(n = 216\); SMD 0.21; 95% CI, –0.06 to 0.48; \(p = 0.12\); I\(^2\) = 8%).

(3) Pain

Two RCTs\textsuperscript{21,22} using the VAS were included in the meta–analysis. There was a significant pain relief effect compared with the Sham group (Fig. 8; \(n = 124\); WMD, –11.81; 95% CI, –16.99 to –6.63; \(p < 0.00001\); I\(^2\) = 36%).
Fig. 6. Forest Plot: AT vs Sham AT (SPHERE)

Fig. 7. Forest Plot: AT vs Sham AT (QOL)

Fig. 8. Forest Plot: AT vs Sham AT (VAS)
(4) Mood disorder
One RCT reported about depression and anxiety using the SDS and SAS. Depression and anxiety symptoms in the AT group decreased more than in controls, but there was no significant difference between the two groups (n = 64; SDS: MD, -2.40; IV: Fixed; 95% CI, -6.79 to 1.99; p = 0.28 / SAS: MD, -0.44; IV: Fixed; 95% CI, -3.92 to 3.04; p = 0.80).

2) Acupuncture vs Wait-list
(1) Fatigue
Among the 11 selected studies, one RCT was compared with the Wait-list group and FSS was used as outcome variable. The AT group showed more significant fatigue reduction (n = 24; MD, -1.50; IV; Fixed; 95% CI, -2.25 to -0.75; p< 0.0001).

(2) Quality of life and pain
The quality of life and pain were not reported in comparing AT to the Wait-list group.

(3) Mood disorder
The Stress Response Inventory (SRI), BDI, and Insomnia Severity Index (ISI) were used as outcome variables to analyze the stress response, depression, and insomnia. The symptoms were significantly alleviated according to the scores in all three variables in the AT group compared with the Wait-list group (one study; n = 24; SRI: MD, -27.00; IV; Fixed; 95% CI, -38.17 to -15.83; p < 0.00001 / BDI: MD, -12.17; IV; Fixed; 95% CI, -19.09 to -5.25; p = 0.0006; ISI: MD, -7.42; IV; Fixed; 95% CI, -11.36 to -3.48; p = 0.0002).

3) Acupuncture vs Western medicine treatment
(1) Fatigue
In one RCT, AT was compared with Western medication treatment and FS was used as outcome variable. There was a significant fatigue reduction effect compared with the Western medicine group (n = 157; MD, -2.83; IV; Fixed; 95% CI, -5.23 to -0.43; p < 0.0001).

(2) Quality of life, pain, and mood disorder
The quality of life, pain, and mood disorder were not reported in comparing AT to the Western medication group.

4) Safety
Nine (81.8%) out of the 11 RCTs reported adverse events (Table 1). Among these nine studies, there were only two cases of mild subcutaneous hemorrhage in Zhang et al., but the group to which these cases belonged to was not reported. No other adverse events were reported in the remaining eight studies.

IV. Discussion
The CFS is a group of symptoms accompanied by severe fatigue, cognitive decline, pain, and insomnia. There are no definite diagnosis methods and the causes of CFS remain unclear. Therefore, various treatments are currently used to alleviate the fatigue and improve the quality of life.

In recent studies comparing individuals with CFS to healthy controls, the involvement of the central nervous system, neuro-hormone control system, chronic immune activity, and psycho-social factors has been reported. Based on this, a variety of therapies such as exercise, behavioral therapy, and CAM have been studied.

In particular, several studies have shown that AT is also effective in relieving fatigue. In the reactive oxygen mechanism, AT increases superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX), and decreases malonaldehyde (MDA). Furthermore, AT increases the lactate dehydrogenase (LDH), decreases creatine kinase (CK), enhances the muscle function by participating in Ca2+-ATPase activity in skeletal muscle cells, and activates the neuro-endocrine-immune system by controlling the hypothalamus-pituitary-adrenal axis and the immune system.
Although studies about the mechanism of acupuncture in reducing fatigue exist, there is no systematic review of acupuncture since 2009. In addition, there were several limitations in the previous review. Therefore, we attempted to systematically summarize the efficacy and safety of AT. A total of 1,277 studies were selected by searching 15 domestic and overseas databases. Finally, 11 RCTs with 869 patients with CFS were included and analyzed.

First, nine RCTs compared between AT and Sham acupuncture and demonstrated a statistically significant effect of AT in relieving fatigue and pain, but not in improving the quality of life and mood (Table 2). The evidence was unclear in the analysis of quality of life possibly due to the lack of consistency in the reported results, wide range of confidence intervals, small sample size, and the small number of studies that evaluated mood disorders such as depression and anxiety (i.e., one study).

Second, one RCT compared between AT and patients in the Wait-list group and showed a significant effect of AT in alleviating fatigue and mood disorders including stress response, depression, and insomnia; the results were not conclusive due to the low number of studies (Table 3).

Finally, one RCT compared between AT and Western medication and also showed a significant fatigue reducing effect of AT. This evidence was also inconclusive due to the low number of studies (Table 4).

Nine (81.8%) of the 11 RCTs reported adverse events, but there were no serious adverse cases except for two with mild subcutaneous hemorrhage.

The previous systematic review of AT in CFS also reported a significant effect of AT in alleviating the symptoms, but the search period was limited to the period between 1998 and 2008. Furthermore, the search was conducted in databases based in China except for core overseas databases such as Pubmed, Cochrane, and EMBASE. In addition, there was the limitation of including studies that compared AT with other CAM therapies, but not with Sham or Wait-list groups; thus, the conclusion in that review was limited. Therefore, we modified the search strategy in order to analyze clearly the efficacy of AT in CFS. We added the databases mentioned above that are related to the field and retrieved all RCTs until 2016. In addition, the selection criteria was strictly limited to assess the effect of AT alone, while we used the Cochrane risk of bias tool instead of the Jadad score for a detailed assessment of the quality of the literatures.

Nevertheless, our present review has several limitations. First, the number of studies included in the final analysis was relatively small due to the exclusion of various studies while strictly applying the selection criteria. Many studies that compared acupuncture with CAM therapy and those of combined therapy were excluded in the secondary selection process. As a result, a quantitative analysis was impossible for certain outcome variables due to insufficient number of studies. Moreover, the funnel plot analysis was not performed for the same reason. Second, the risk of bias of the included studies was generally unclear. The risk of performance bias was particularly high because of the nature of AT whereby the practitioner cannot be blinded for the treatment. Third, several of the selected studies that did not mention the details of the random sequence generation, allocation concealment, and blinding of the evaluator. Therefore, the quality of the literature was not properly evaluated. Fourth, there was a risk of potential reporting bias because only one study presented a study protocol. Fifth, nine of the 11 selected studies were conducted in China; thus there was a possibility of potential bias in publishing. Finally, there was a variety of symptoms in patients with CFS, which were evaluated as different outcome variables for each study. As a result, the number of participants included in the quantitative synthesis of each variable was insufficient and there was also a heterogeneity problem arising when different outcome measures were synthesized to-
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS (Fatigue)</td>
<td>The mean FS in the control groups was 12.16 points</td>
<td>The mean FS in the intervention groups was 1.63 lower (2.55 to 0.72 lower)</td>
<td>216 (3 studies)</td>
<td>⊗⊗⊗⊗ moderate*</td>
<td>Lower score indicates less fatigue</td>
</tr>
<tr>
<td>FSS (Fatigue)</td>
<td>The mean FSS in the control groups was 39.72 points</td>
<td>The mean FSS in the intervention groups was 9.54 lower (17.2 to 1.89 lower)</td>
<td>132 (2 studies)</td>
<td>⊗⊗⊗⊗ moderate*</td>
<td>Lower score indicates less fatigue</td>
</tr>
<tr>
<td>SPHERE (Quality of life)</td>
<td>The mean SPHERE in the control groups was 6.64 points</td>
<td>The mean SPHERE in the intervention groups was 5.27 lower (8.63 to 1.92 lower)</td>
<td>149 (3 studies)</td>
<td>⊗⊗⊗⊗ moderate*</td>
<td>Lower score indicates improved general health</td>
</tr>
<tr>
<td>SF-12,20,36 (Quality of life)</td>
<td>The SF score in the intervention groups was on average 0.65 SDs(0.04 lower to 1.34 higher) higher than in the control groups</td>
<td></td>
<td>367 (5 studies)</td>
<td>⊗⊗⊗⊗ very low*</td>
<td>As a rule of thumb, 0.2 SD represents a small difference, 0.5 a moderate, and 0.8 a large difference</td>
</tr>
<tr>
<td>QOL† (Quality of life)</td>
<td>The QOL score in the intervention groups was on average 0.21 SDs(0.06 lower to 0.48 higher) higher than in the control groups</td>
<td></td>
<td>216 (3 studies)</td>
<td>⊗⊗⊗⊗ low*</td>
<td>As a rule of thumb, 0.2 SD represents a small difference, 0.5 a moderate, and 0.8 a large difference</td>
</tr>
<tr>
<td>VAS (Pain)</td>
<td>The mean VAS in the control groups was 69.92 points</td>
<td>The mean VAS in the intervention groups was 11.81 lower (16.99 to 6.63 lower)</td>
<td>124 (2 studies)</td>
<td>⊗⊗⊗⊗ moderate*</td>
<td>Lower score indicates improved pain</td>
</tr>
<tr>
<td>SDS (Mood disorders)</td>
<td>The mean SDS in the control groups was 36.34 points</td>
<td>The mean SDS in the intervention groups was 2.4 lower (6.79 lower to 1.99 higher)</td>
<td>64 (1 study)</td>
<td>⊗⊗⊗⊗ very low*</td>
<td>Lower score indicates fewer depressive symptoms</td>
</tr>
<tr>
<td>SAS (Mood disorders)</td>
<td>The mean SAS in the control groups was 33.22 points</td>
<td>The mean SAS in the intervention groups was 0.44 lower (3.92 lower to 3.04 higher)</td>
<td>64 (1 study)</td>
<td>⊗⊗⊗⊗ very low*</td>
<td>Lower score indicates fewer anxiety</td>
</tr>
</tbody>
</table>

* The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (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).
† WHOQOL-BREF and GHQ-12.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

a Two studies have a high risk of incomplete outcome data and one study has a high risk of detection bias.

b The 95% CIs of two studies are wide, but all studies relatively have a consistency of MD and there is no heterogeneity (I²=0%).

c There is no high risk of bias, but several domains are unclear.

d Although there is a heterogeneity, two studies have same effect for alleviating fatigue.

e The I² score is large and heterogeneity is significant, but the heterogeneity is explained by subgroup analysis and all studies have a consistency of MD.

f One study has a high risk of detection bias and incomplete outcome data bias, and other studies are unclear in several domains.

g Unexplained heterogeneity (I²=90.5%) and there is no consistency of SMD.

h The CIs encompass benefit and harm.

Table 3. Summary of Findings: AT versus Wait-list

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed risk</th>
<th>Corresponding risk</th>
<th>Relative effect (95%CI)</th>
<th>Number of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSS (Fatigue)</td>
<td>The mean FSS in the control groups was 5.41 points</td>
<td>The mean FSS in the intervention groups was 1.5 lower (2.25 to 0.75 lower)</td>
<td>24 (1 study)</td>
<td>⊕⊕⊖⊖ low</td>
<td>Lower score indicates less fatigue</td>
<td></td>
</tr>
<tr>
<td>SRI (Mood disorders)</td>
<td>The mean SRI in the control groups was 61.5 points</td>
<td>The mean SRI in the intervention groups was 27 lower (38.17 to 15.83 lower)</td>
<td>24 (1 study)</td>
<td>⊕⊕⊖⊖ low</td>
<td>Lower score indicates lower stress-response</td>
<td></td>
</tr>
<tr>
<td>BDI (Mood disorders)</td>
<td>The mean BDI in the control groups was 16.42 points</td>
<td>The mean BDI in the intervention groups was 12.17 lower (19.09 to 5.25 lower)</td>
<td>24 (1 study)</td>
<td>⊕⊕⊖⊖ low</td>
<td>Lower score indicates fewer depressive symptoms</td>
<td></td>
</tr>
<tr>
<td>ISI (Mood disorders)</td>
<td>The mean ISI in the control groups was 15.67 points</td>
<td>The mean ISI in the intervention groups was 7.42 lower (11.36 to 3.48 lower)</td>
<td>24 (1 study)</td>
<td>⊕⊕⊖⊖ low</td>
<td>Lower score indicates lower severity of insomnia</td>
<td></td>
</tr>
</tbody>
</table>

SRI: Stress Response Inventory; BDI: Beck Depression Index; ISI: Insomnia Severity Index.

a This trial have a high risk of performance bias due to unblinded patients.
b The evidence was downgraded due to small number of participants of meta-analysis.

c Table 4. Summary of Findings: AT versus Western Medication

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed risk</th>
<th>Corresponding risk</th>
<th>Relative effect (95%CI)</th>
<th>Number of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS (Fatigue)</td>
<td>The mean FS in the control groups was 7.31 points</td>
<td>The mean FS in the intervention groups was 2.83 lower (3.18 to 2.48 lower)</td>
<td>157 (1 study)</td>
<td>⊕⊕⊖⊖ moderatea</td>
<td>Lower score indicates less fatigue</td>
<td></td>
</tr>
</tbody>
</table>

a Downgraded because of unblinded patients and unclear risk of bias in several domains.
together. Furthermore, there was a possibility that heterogeneity occurred according to the methodological quality because no comparisons were performed between strictly conducted and non-strictly conducted studies.

In future systematic reviews, more well-designed RCTs should be included in the final selection. Hence, the study design of each RCT including intervention and control group settings, random sequence generation, allocation concealment, blinding of patients and evaluators, and pre-protocol study registration should be made appropriately. In addition, in order to obtain a more clear evidence from the meta-analysis, larger studies should be included and unexplained heterogeneity should be minimized in the quantitative synthesis by additional subgroup analysis according to the study design. Moreover, future studies should standardize the outcome variables for the same symptom to reduce the heterogeneity.

V. Conclusion

This review established evidence that AT in patients with CFS may be beneficial in alleviating the symptoms, and showed that there are no indications of symptom deterioration or serious adverse events. A positive effect on fatigue and pain was also observed, but no conclusion regarding improvement in the quality of life and mood disorders could be drawn.

VI. References

12. Wang JJ, Song YJ, Wu ZC et al. A Meta-Analysis on Randomized Controlled Trials of Acupuncture Treatment of Chronic Fatigue Syndrome, Zhen...
with Chronic Fatigue Syndrome [dissertation], Beijing: China Academy of Chinese Medical Sciences, 2009, Chinese.

http://dx.doi.org/10.13045/acupunct.2017096 109
Appendix 1. Search Strategy

A. Pubmed (16–09–08)
#1 "fatigue syndrome, chronic"[mh] (n=4766)
#2 "myalgic encephalomyelitis" (n=579)
#3 "myalgic encephalitis" (n=30)
#4 #1 OR #2 OR #3 (n=5010)
#5 acup* OR "acupuncture"[mh] OR "acupuncture therapy"[mh] (n=26324)
#6 electroacup* OR electro-acup* OR "electroacupuncture"[mh] (n=4344)
#7 "auricular acup*" OR "ear acup*" OR "acupuncture, ear"[mh] (n=1160)
#8 "acupuncture points"[mh] (n=5094)
#9 "scalp acup*" (n=277)
#10 pharmacoacup* OR pharmaco-acup* (n=3)
#11 "laser acup*" (n=806)
#12 "acupoint injection" (n=125)
#13 "dry needle" OR 'dry needling' OR Needling (n=2085)
#14 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 (n=27158)
#15 #4 AND #16 (n=50)

B. Cochrane Library (16–09–08)
#1 chronic fatigue syndrome (n=1616)
#2 myalgic encephalomyelitis (n=33)
#3 myalgic encephalitis (n=7)
#4 #1 or #2 or #3 (n=1616)
#5 acup* (n=11237)
#6 electroacup* OR electro-acup* (n=1534)
#7 "auricular acup*" OR 'ear acup*' (n=456)
#8 "scalp acup*" (n=213)
#9 pharmacoacup* OR pharmaco-acup* (n=2)
#10 "laser acup*" (n=240)
#11 "acupoint injection" (n=304)
#12 needle OR 'dry needle' (n=1135)
#13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 (n=11632)
#14 #4 and #13 (n=153)

C. EMBASE (16–09–19)
#1 'chronic fatigue syndrome' (n=8877)
#2 'myalgic encephalomyelitis' OR 'myalgic encephalitis' (n=694)
#3 #1 OR #2 (n=9004)
#4 acup* (n=42262)
#5 electroacup* OR electro-acup* (n=6119)
#6 'auricular acup*" OR 'ear acup*' (n=847)
#7 'scalp acup*" (n=283)
#8 pharmacoacup* OR 'pharmaco-acup*' (n=8)
#9 'laser acup*" (n=399)
#10 'acupoint injection' (n=156)
#11 needle OR 'dry needle' (n=2803)
#12 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 (n=44088)
#13 #3 AND #12 (n=136)

D. CINAHL (EBSCO host) (16–09–08)
S1 TX chronic fatigue syndrome (n=3663)
S2 TX myalgic encephalomyelitis (n=449)
S3 TX myalgic encephalitis (n=42)
S4 or/1–3 (n=3752)
S5 TX acup* (n=23621)
S6 TX electroacup* or electro-acup* (n=1915)
S7 TX "auricular acup*" or 'ear acup*' (n=698)
S8 TX 'scalp acup*" (n=114)


S9 TX pharmacoacup* or pharmaco-acup* (n=5)
S10 TX "laser acup"** (n=288)
S11 TX "acupoint injection" (n=37)
S12 TX needling or "dry needl"** (n=1902)
S13 or/5-12 (n=24321)
S14 S4 and S13 (n=248)

E. AMED (EBSCO host) (16-09-08)
S1 TX chronic fatigue syndrome (n=1396)
S2 TX myalgic encephalomyelitis (n=99)
S3 TX myalgic encephalitis (n=5)
S4 or/S1-3 (n=1433)
S5 TX acup* (n=10195)
S6 TX electroacup* or electro-acup* (n=997)
S7 TX "auricular acup" or "ear acup" (n=486)
S8 TX "scalp acup"** (n=112)
S9 TX pharmacoacup* or pharmaco-acup* (n=0)
S10 TX "laser acup"** (n=76)
S11 TX "acupoint injection" (n=19)
S12 TX needling or "dry needl"** (n=804)
S13 or/S5-12 (n=10398)
S14 S4 and S13 (n=24)

F. CNKI (16-09-09)
1 SU= "chronic fatigue syndrome" or "myalgic encephalomyelitis" or "myalgic encephalitis" or "慢性疲劳综合征" (=937)
2 SU= "acupuncture" or "electroacupuncture" or "electro-acupuncture" or "auricular acupuncture" or "ear acupuncture" or "scalp acupuncture" or "pharmacocupuncture" or "pharmaco-acupuncture" or "laser acupuncture" or "acupoint injection" or "needling" or "干针" or "针法" or "针" or "电针" or "电针疗法" or "电针刺" or "穴位注射疗法" or "穴位注射" or "针灸" or "耳针" or "头针" (n=256285)
3 1 and 2 (n=386)

G. Wanfang (16-09-09)
1 标题:"chronic fatigue syndrome" or 标题:"myalgic encephalomyelitis" or 标题:"myalgic encephalitis" or 标题:"慢性疲劳综合征" (=937)
2 标题:"acupuncture" or 标题:"electroacupuncture" or 标题:"electro-acupuncture" or 标题:"pharmacocupuncture" or 标题:"pharmaco-acupuncture" or 标题:"auricular acupuncture" or 标题:"ear acupuncture" or 标题:"scalp acupuncture" or 标题:"laser acupuncture" or 标题:"acupoint injection" or 标题:"needling" or 标题:"干针" or 标题:"针法" or 标题:"针" or 标题:"电针" or 标题:"电针疗法" or 标题:"电针刺" or 标题:"穴位注射疗法" or 标题:"穴位注射" or 标题:"针灸" or 标题:"耳针" or 标题:"头针" (n=124158)
3 1 and 2 (n=277)
### Appendix 2. General characteristics of acupuncture treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Acupoints</th>
<th>De-Qi</th>
<th>Retaining time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hou 2016</td>
<td>AT</td>
<td>BL15, BL17, BL18, BL22, BL23, CV4, CV6, CV12, CV17</td>
<td>(n.r.)</td>
<td>30min</td>
</tr>
<tr>
<td>Tang 2015</td>
<td>AT</td>
<td>BL18, BL23, ST36, HT7, GV20</td>
<td>O</td>
<td>30min</td>
</tr>
<tr>
<td>Lu 2014</td>
<td>(A) AT</td>
<td>(A) GV20, CV17, CV6, ST36, LI4, LR3, SP6</td>
<td>(A) O</td>
<td>(AT) 30min</td>
</tr>
<tr>
<td></td>
<td>(B) Moxa-AT &amp; AT</td>
<td>(B) (Moxa-AT) GV20, CV6, CV4, ST36 (AT) CV17, LI4, LR3, SP6</td>
<td>(B) X</td>
<td>(Moxa-AT) 20min</td>
</tr>
<tr>
<td>Ng 2013</td>
<td>AT</td>
<td>GV20, ST36, SP6</td>
<td>O</td>
<td>30min</td>
</tr>
<tr>
<td>Kim 2012</td>
<td>AT</td>
<td>GV20, GB20, BL11, BL13, BL15, BL18, BL20, BL23</td>
<td>X</td>
<td>20min</td>
</tr>
<tr>
<td>Zhang 2012</td>
<td>AT</td>
<td>BL18, BL23, ST36, HT7</td>
<td>O</td>
<td>30min</td>
</tr>
<tr>
<td>Zhang 2011</td>
<td>AT</td>
<td>BL15, BL20, BL43</td>
<td>O</td>
<td>20min</td>
</tr>
<tr>
<td>Chan 2010</td>
<td>AT</td>
<td>ST36, KI3</td>
<td>O</td>
<td>30min</td>
</tr>
<tr>
<td>Wang 2009</td>
<td>AT</td>
<td>GV20, CV17, CV12, CV6, CV4, LI4, ST36, SP6, LR3, KI3, BL18, BL20, BL23</td>
<td>O</td>
<td>30min</td>
</tr>
<tr>
<td>Zhu 2008</td>
<td>EA</td>
<td>ST36, BL23</td>
<td>O</td>
<td>20min</td>
</tr>
<tr>
<td>Wang 2007</td>
<td>EA</td>
<td>ST36, BL23</td>
<td>(n.r.)</td>
<td>20min</td>
</tr>
</tbody>
</table>

AT: Acupuncture treatment, Moxa-AT: Moxa-heated needling, EA: Electro-acupuncture