SOUTH BAYLO UNIVERSITY

Acupuncture for Primary Dysmenorrhea:

A Systematic Review and Meta-Analysis

By

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ABSTRACT

Primary Dysmenorrhea (PD) is defined as painful menstruation in the absence of underlying pathology. Characterized by recurrent, crampy, spasmodic, lower abdominal or pelvic pain during menstruation with or without radiation to the back or upper thigh or both, it is the most common reason for gynecologic visits, affecting 50% to 90% of women, half of whom describe their pain as moderate to severe. The aim of this systemic review and meta-analysis is to evaluate the outcomes of the randomized controlled trials (RTCs) regarding the therapeutic effect of acupuncture on alleviating pain in patient with PD. The search for studies was performed in databases including PubMed, Cochrane Collaboration, EBSCO, Google Scholar and other relevant sources. The inclusion criteria was randomized controlled trials in women with PD, published from 2011 to 2021. Articles not related to the treatment of PD with acupuncture were excluded. And finally ten eligible studies were screened. . The primary outcome were the Visual Analog Scale (VAS), Cox Retrospective System (RSS), a menstrual symptom measure that has been shown to

have high reliability, validity, and sensitivity, gives two scores, a Total Frequency Ratings score (RSS COX1) and an Average Severity Ratings score (RSS COX2). Lower scores indicate better health and secondary outcome were adverse effects (AEs), self-rating anxiety scale (SAS), and self-rating depression scale (SDS). Mean difference (*MD*) and standardized mean difference (*SMD*) for continuous data were used with associated confidence intervals (*CI*s). VAS pain score [MD -1.00] showed significant improvement, however, RSS-COX1 [MD -1.33], RSS-COX2 [MD -0.74], SAS [MD 1.41] and SDS [MD -2.97] did not show significance. As a conclusion, acupuncture is an alternative option for relieving dysmenorrhea, especially when the pharmaceutical drugs are not favorable choices. It is safe and effective treatment for patient with PD.

Keyword: acupuncture, primary dysmenorrhea, randomize controlled trial

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

I. INTRODUCTION

1. Dysmenorrhea in western point of views

Dysmenorrhea, defined as painful menstruation, is the most common gynecologic condition affecting women. Reported prevalence varies widely, ranging from 17% to as high as 90% (Ferries-Rowe et al., 2020). It can be classified as primary and secondary dysmenorrhea. 1) Primary dysmenorrhea (PD) is a lower abdominal pain happening during the menstrual cycle, in the absence of underlying diseases or pathology, with initial onset six to 12 months after menarche. 2) Secondary dysmenorrhea (SD) presentation is a clinical situation where menstrual pain can be due to an underlying disease, disorder, or structural abnormality either within or outside the uterus. The often cause of SD is endometriosis, other possible causes include, Pelvic inflammatory disease (PID), Uterine fibroids, Abnormal pregnancy (for instance, miscarriage, ectopic), Infection, tumors, or polyps in the pelvic cavity.

Primary dysmenorrhea

The pathophysiology of PD is not well understood. Nevertheless, the identified cause is due to the hypersecretion of the prostaglandins (PGs) from the uterine inner lining. Prostaglandin F2alpha (PGF-2a) and Prostaglandin PGF 2. The time of the endometrial shedding during the beginning of menstruation is when the endometrial cells release PGF. Prostaglandins cause uterine contractions, and the intensity of the cramps is proportionate to the amount of PGs released after the sloughing process that started due to dropping hormonal surge. Also, vasopressin has been linked to primary dysmenorrhea. Vasopressin increases the uterine contractility and can cause ischemic pain due to its vasoconstriction effects (Nagy et al., 2021).

Characteristic symptoms of PD include lower abdominal or pelvic pain with or without radiation to the back or upper thighs or both. Patients describe pain that is crampy, spasmodic and of fluctuating intensity, with the onset of pain shortly before or at the onset of bleeding and lasting up to 72 hours. Pain intensity usually peaks at 24–36 hours from the onset of menses, and the duration is rarely longer than a few days. Other associated symptoms may include headache, diarrhea or constipation, fatigue, bloating and nausea or vomiting.

With a typical history consistent with PD, normal findings from pelvic examination and negative results on urinary human chorionic gonadotropin pregnancy test, further diagnostic evaluation is not needed. In many instances, it is preferable to confirm the diagnosis through a therapeutic trial of NSAIDs. At least partial relief of pain with NSAID therapy is so predictable in women with PD that failure to respond should raise doubts about the diagnosis.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered first-line treatment for PD. NSAIDs are classified as prostaglandin synthetase inhibitors. The various formulations of NSAIDs have comparable efficacy for PD, and pain relief is successfully achieved in 64–100% of women. Mild and moderate dysmenorrhea usually responds well to NSAIDs. Severe dysmenorrhea still responds to NSAIDs but may require higher doses or using combination/adjuvant therapy. In the women who are not respond to, or are intolerant to PG-inhibitors, oral contraceptives often are used as second-line therapy. The synthetic hormones in oral contraceptives suppress ovulation and reduce the thickness of the endometrial lining of the uterus, thereby reducing the volume of menstrual fluid, PG synthesis and dysmenorrheic pain. Hormonal intrauterine devices have also been shown to reduce the severity of menstrual pain. Other currently available therapeutic approaches for the management of dysmenorrheic pain include: transcutaneous electric nerve

stimulation, transdermal nitroglycerin patches, acupuncture/acupressure and surgical interventions such as laparoscopic uterosacral nerve ablation surgery (Iacovides et al., 2015).

2. Dysmenorrhea in TCM point of views

In TCM, the word 痛经 (Painful Periods or Dysmenorrhea) indicates menstrual pain that occurs before, during or after menstruation may occur in the lower abdomen or sacral region and sometimes extend to the legs. In severe cases, there may be nausea and vomiting or even fainting. The Liver, Penetrating Vessel and Directing Vessel are responsible for the physiology of menstruation. Proper movement of Blood relies on the free flow of Liver-Qi and of the Qi of the Penetrating Vessel.

There are four etiology factors associate with dysmenorrhea. 1) Emotional strain is the very important etiological factor in painful periods. Anger, frustration, resentment, hatred: all may lead to Liver-Qi stagnation. In women, Liver-Qi stagnation causes Blood to stagnate in the Uterus leading to painful periods. 2) Excessive exposure to cold and dampness may cause Cold to invade the Uterus. Cold contracts and causes stasis of Blood in the Uterus and therefore painful periods. 3) Physical overwork or a chronic illness leads to deficiency of Qi and Blood, so that the Blood has no force to move properly thus causing stagnation and pain. 4) The Liver and Kidneys are weakened by excessive sexual activity (which affects women somewhat less than men), too many childbirths too close together, and sexual activity starting too early. A deficiency of Liver and Kidneys induces emptiness of the Penetrating and Directing Vessels so that they cannot move Qi and Blood properly, thus causing painful periods.

The most important pathological factor in painful periods is stagnation of Qi and/or Blood, which may arise by itself or be caused by Cold in the Uterus. Even Deficiency types of painful periods, caused by Blood or Liver/Kidney deficiency, involve an element of stagnation as the deficient Blood fails to move properly.

From the point of view of Manifestation (biao) the central pathology of Painful Periods is a disharmony of the Penetrating Vessel and Sea of Blood. Hence the main principle of treatment for the Manifestation is to regulate the Qi and Blood of the Penetrating Vessel. To treat the Root in Painful Periods, must clearly between Heat, Cold, Deficiency and Excess. First identify the prevailing pattern, then treat it in order to treat the Root. During the period concentrates on treating the Manifestation. At other points in the cycle treats the Root. A deficiency, in particular, is best treated during the 2 weeks after the period. The main patterns causing the Root of Painful Periods are therefore: 1) Stagnation of Qi 2) Stasisof Blood 3) Stagnation of Cold (of the Empty- or Full-type) 4) Damp-Heat (with Blood-Heat) 5) Stagnant Liver-Qi turning into Fire 6) Qi and Blood deficiency 7) Yang and Blood deficiency 8) Kidney- and Liver-Yin deficiency.

Table 1. TCM Dysmenorrhea patterns with treatment principles

Patterns	Treatment Principles
Full types	
Stagnation of Qi	Move Qi and Blood, eliminate stagnation, stop pain.
Stasis of Blood	Invigorate Blood, eliminate stasis, stop pain.

Stagnation of Cold (of the Empty- or Full-type)	Warm the Uterus, expel Cold, invigorate Blood.
Damp-Heat (with Blood-Heat)	Clear Heat, resolve Dampness, eliminate stasis.
Stagnant Liver-Qi turning into Fire	Clear Heat, pacify the Liver, eliminate stagnation, stop pain.
Empty types	
Qi and Blood deficiency	Tonify Qi, strengthen the Spleen, nourish Blood.
Yang and Blood deficiency	Warm the Yang, nourish Blood, strengthen the Centre and stop pain.
Kidney- and Liver-Yin deficiency	Nourish Yin, benefit the Kidneys, nourish the Liver.

Both acupuncture and Chinese herbs either one or in combination give excellent results in painful periods and the majority of cases can be cured. In any menstrual problem, it takes a minimum of three menstrual cycles to regulate Blood and the Directing and Penetrating Vessels. Three months is therefore the shortest possible time for the treatment to be successful.

OBJECTIVES

The purpose of this study is to assess the effectiveness of acupuncture in the treatment of primary dysmenorrhea. This will be achieved through analysis of the reported scores used for assessment of the patients' pain level.

LITERATURE REVIEW

To corporate with western doctors, acupuncturists need evidence-based medicine to prove that acupuncture is effective. In the last 10 years, there are a decent amount of studies that considered acupuncture is safe and effective treatment modality for the management of PD. Acupuncture is an alternative option for relieving primary dysmenorrhea compare with non-acupuncture and Ibuprofen. But when compare with Combined Oral Contraceptive Pill (COC), COC caused greater reduction in maximal pain scores than acupuncture but acupuncture did not cause any hormone-related side effects as COC did.

Acupuncture is better than non-acupuncture. In Liu et al., 2011's study, the primary comparison of VAS scores demonstrated that patients receiving acupuncture (-15.56 mm, 95% CI -22.16 to -8.95, P<0.001), unrelated acupoint (-18.14 mm, 95% CI -24.81 to -11.47, P<0.001), and nonacupoint (-10.96 mm, 95% CI -17.62 to -4.30, P=0.001) treatment presented significant improvements compared with no acupuncture group. There were no significant differences among the four groups with respect to secondary outcomes. Acupuncture was better than no acupuncture for relieving the pain of dysmenorrhea following a single point of acupuncture, but no differences were detected between acupoint acupuncture and unrelated acupoint acupuncture, acupoint acupuncture and nonacupoint acupuncture.

Acupuncture with Ibuprofen, acupuncture was shown to be associated with a significantly lower pain intensity and decreased symptom severity of primary dysmenorrhea as compared with ibuprofen (p<0.05). A significantly higher responder rate was found in the acupuncture group as

compared with the control group (p<0.05). No serious adverse events were reported by patients in either group.

Acupuncture with COC. Sriprasert et al., 2015, Both acupuncture and COC had resulted in significant improvement over baselines in all outcomes, that is, maximal dysmenorrhea pain scores, days suffering from dysmenorrhea, amount of rescue analgesic used, and quality of life assessed by SF-36 questionnaire. Over the three treatment cycles, COC caused greater reduction in maximal pain scores than acupuncture, while improvements in the remaining outcomes were comparable. Responders were defined as participants whose maximal dysmenorrhea pain scores decreased at least 33% below their baseline. Response rates following both interventions at the end of the study were not statistically different. Acupuncture commonly caused minimal local side effects but did not cause any hormone-related side effects as did COC. In conclusion, acupuncture is an alternative option for relieving dysmenorrhea, especially when COC is not a favorable choice.

II. MATERIALS AND METHODS

Search Criteria (PICO)

Randomizes controlled Trial only

Table 2. PICO elements and keywords

PICO elements	Keywords
Participants	Women with PD
Intervention	Acupuncture with/without electro-stimulator
Comparison	No intervention, sham acupuncture, Combined Oral Contraceptive Pill or ibuprofen
Outcomes	*Primary*: Visual Analog Scale (VAS), Cox Retrospective System (RSS) gives two scores, a Total Frequency Ratings score (RSS COX1) and an Average Severity Ratings score (RSS COX2). *Secondary*: adverse effects (AEs), self-rating anxiety scale (SAS), and self-rating depression scale (SDS).

Eligibility criteria

Retrieved studies are marked as included if they meet the following inclusion criteria: 1) studies that are randomized controlled trials, 2) population: women with primary dysmenorrhea, 3) intervention: acupuncture with/without electro-stimulator, 4) comparator: placebo acupuncture, sham acupuncture, Combined Oral Contraceptive Pill and ibuprofen, and 5) primary outcome:

Visual Analog Scale (VAS), Cox Retrospective System (RSS) gives two scores, a Total Frequency Ratings score (RSS COX1) and an Average Severity Ratings score (RSS COX2), secondary outcomes: adverse effects (AEs), self-rating anxiety scale (SAS), and self-rating depression scale (SDS). The following studies were excluded: 1) non-randomized controlled trials, 2) women receiving acupressure, laser acupuncture, moxa, cupping, tuina, scrapping and Chinese herbal medicine, 3) studies with no accessible data, conference abstracts, and animal studies.

Literature search

Electronic databases of PubMed, Cochrane Collaboration, EBSCO, Google Scholar and other relevant sources were utilized. The timeframe for the publication of article was set from 2011 to 2021. The searched terms were “acupuncture”, “primary dysmenorrhea” and “randomized controlled trial”. The systemic review and meta-analysis was limited to randomized control trail (RTCs) with clear hypotheses, objectives, setting, participants, assessments, interventions, outcome, and conclusion.

Data collection and analysis

Screening and result

Following the literature search of all included databases, eligible studies and relevant controlled trials were exported and screened in two steps. The first step was title and abstract screening to exclude other study designs and animal trials. The second step was full-text screening to ensure that the controlled trials met the inclusion criteria. The complete screening yielded a total of 96 studies for acupuncture treatment for PD as shown in Figure 1. After screening the 96 studies

through titles and abstracts, 47 studies were selected for full-text article review to ensure that the controlled trials met the inclusion criteria and 10 RCT studies were chosen for the meta-analysis.

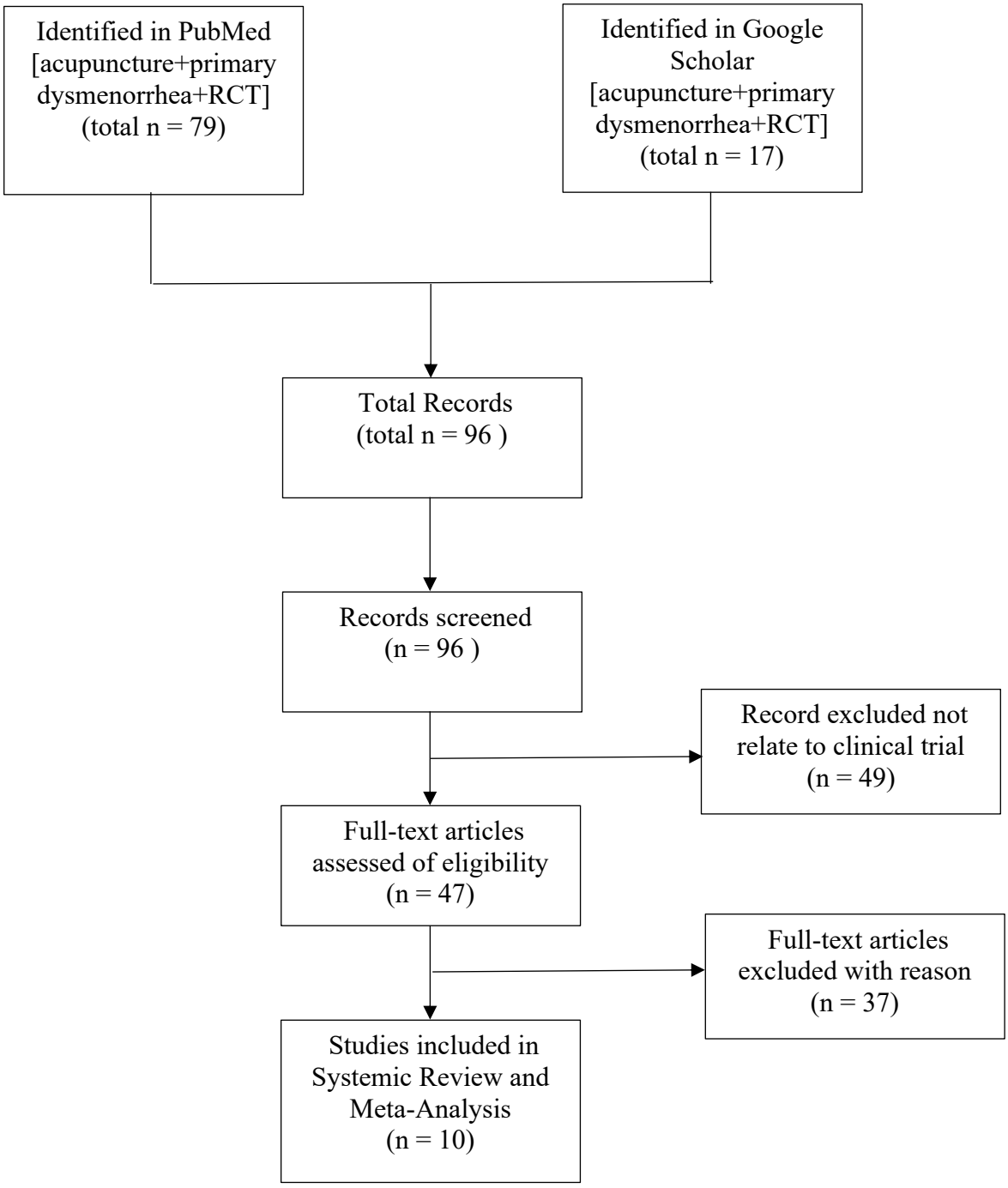

Figure 1. RCT Data-selection flow diagram

Data Analysis:

The characteristics of the RCTs on primary dysmenorrhea included in this review were analyzed and summarized by the order of Author and Year, Sample Size and Subject Data, Research Methods, P-Values and Outcome.

Data extraction

Following the P-I-C-O method, information of Literature Information, Methods, Participants, Interventions and Outcomes were extracted from each study and summarized as a tables.

1) Data extraction items

Extracting data for systematic review and meta-analysis from selected literature research information include: literature information, methods, participants and intervention, outcomes and others as shown in Table 3.

2) Conversion of data

Mean value, median difference, standard mean deviation, standard error, odds ratio, relative risk of the extracted data. Quantitative results of the same concept were derived by checking the basic values of Meta-analysis. The mean difference and 95% CI (confidence interval) value of the change, values of the intervention group, and the control group are used as default value and entered into Cochrane Collaboration's Review Manager 5.4 (RevMan 5.4).

Assessment of Risk of Bias (RoB)

Bias in the randomized comparative clinical trial literature selected for systematic review. For risk assessment, use the RoB (Risk of Bias) software provided by RevMan 5.4. The risk of bias when conducting systematic reviews and meta-analyses that to be extracted from the literature and the evaluation criteria are: Random sequence generation, Allocation concealment, Blinding of participants and personnel, Blinding of outcome assessment, incomplete outcome data, and Selective reporting.

Heterogeneity Assessment

The level of heterogeneity across the studies was estimated by overlapping CI in forest plots, and the value of the I^2 statistics for heterogeneity test and the chi-squared test for statistical heterogeneity. P value <0.05 were considered to indicate statistical significance in all the results. The analysis of the effective treatment was performed in the meta-analysis using the RevMan 5.4. the outcome of thirteen subgroups in the ten documents, was meta-analyzed and shown as a forest plot. (Figure 4-8)

Higgins's I^2 statistics 30

To quantify inconsistencies, Higgins's I^2 statistics was used. The degree of heterogeneity was depended on the I^2.

The criteria are as follows in order to analyze the heterogeneity.

$0\% \leq I^2 \leq 40\%$: may not be significant heterogeneity

$30\% \leq I^2 \leq 60\%$: may be moderate heterogeneity

$50\% \leq I^2 \leq 90\%$: may be substantially heterogeneity

$75\% \leq I^2 \leq 100\%$: significant heterogeneity

Reporting Bias Assessment

In order to identified bias such as publication bias, time lag bias, multiple publication bias, location bias, citation, reporting bias, language bias, and outcome reporting bias, the funnel plot was attained by Review Manager 5.4 for preventing the overestimation of summary estimates in the effectiveness of the treatment.

Meta-Analysis

Meta-Analysis Outcome measures for the analysis of the review were Visual Analog Scale (VAS), Cox Retrospective System (RSS), gives two scores, a Total Frequency Ratings score (RSS COX1) and an Average Severity Ratings score (RSS COX2), Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) by using the RevMan 5.4. The outcome of 13 subgroups in the 10 documents was meta-analyzed and shown as a forest plot. (Figure 4-8). All of the data in the review were continuous, and end-point scores were expressed as SMDs for different scales with associated 95% Cl.

III. RESULT

Data Extraction and Conversion

1) Data extraction items

Extracting data for systematic review and meta-analysis from selected literature, Research information, research methods, research subjects, comparative interventions, results and others as shown in Table 3, were extracted according to the P-I-C-O method.

2) Conversion of outcome data

Among the result data for each item extracted from the selected 10 documents, the clinical significance basic values such as mean value, median value, standard deviation, standard error, odds ratio, relative risk from the extracted data were derived comparing the value. The Cochrane Man Review 5.4 (RevMan 5.4) was applied in this meta-analysis using the standard mean difference (SMD) and the 95% confidence interval (CI) in the experiment group and control group.

Table 3. Data Items Being Extracted from the Selected Literature

Data Component	Data Item
Literature Information	Cun-Zhi Liu et al 2011a
Methods	Double-Blinded, RTCs
Participants	200 participants with; 1) primary dysmenorrhea (onset <3 years after menarche); 2) aged from 15 to 30 years with a history of regular menstrual cycle (28-day cycle ± 7 day); 3) experienced menstrual pain of moderate or severe intensity, varying from 40 mm to 100 mm on the Visual Analog Scale (VAS), for at least 6 months before study entry; 4) refrained from the use of any analgesics 24 hours before the trial
Interventions	Acupoint Group vs. No acupuncture Group
Outcomes	The primary outcome was pain intensity as measured by a 100-mm visual analog scale (VAS) at baseline; 5, 10, 30, and 60 minutes following the start of the first intervention. Cox retrospective symptom scale (RSS), verbal rating scale (VRS), pain total time, and proportion of participants using analgesics were also recorded during three menstrual cycles VAS scores demonstrated that patients receiving Acupuncture (-15.56 mm, 95% CI -22.16 to -8.95, P < 0.001) treatment presented significant improvements compared with No Acupuncture Group There were no significant differences among the two groups with respect to secondary outcomes
Others	Participants were recruited from Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, China-Japan Friendship Hospital, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University, and the First Hospital affiliated to Tianjin College of Traditional Chinese Medicine between November 2007 and September 2008

Table 3. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Cun-Zhi Liu et al 2011b
Methods	Double-Blinded, RTCs
Participants	200 participants with; 1) primary dysmenorrhea (onset <3 years after menarche); 2) aged from 15 to 30 years with a history of regular menstrual cycle (28-day cycle ± 7 day); 3) experienced menstrual pain of moderate or severe intensity, varying from 40 mm to 100 mm on the Visual Analog Scale (VAS), for at least 6 months before study entry; 4) refrained from the use of any analgesics 24 hours before the trial
Interventions	Unrelated Acupoint Group vs. No Acupuncture Group
Outcomes	The primary outcome was pain intensity as measured by a 100-mm visual analog scale (VAS) at baseline; 5, 10, 30, and 60 minutes following the start of the first intervention. Cox retrospective symptom scale (RSS), verbal rating scale (VRS), pain total time, and proportion of participants using analgesics were also recorded during three menstrual cycles VAS scores demonstrated that patients receiving Unrelated Acupoint (-18.14 mm, 95% CI -24.81 to -11.47, P < 0.001) treatment presented significant improvements compared with No Acupuncture Group There were no significant differences among the two groups with respect to secondary outcomes
Others	Participants were recruited from Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, China-Japan Friendship Hospital, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University, and the First Hospital affiliated to Tianjin College of Traditional Chinese Medicine between November 2007 and September 2008

Table 3. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Cun-Zhi Liu et al 2011c
Methods	Double-Blinded, RTCs
Participants	200 participants with; 1) primary dysmenorrhea (onset <3 years after menarche); 2) aged from 15 to 30 years with a history of regular menstrual cycle (28-day cycle ± 7 day); 3) experienced menstrual pain of moderate or severe intensity, varying from 40 mm to 100 mm on the Visual Analog Scale (VAS), for at least 6 months before study entry; 4) refrained from the use of any analgesics 24 hours before the trial
Interventions	Nonacupoint Group vs. No Acupuncture Group
Outcomes	The primary outcome was pain intensity as measured by a 100-mm visual analog scale (VAS) at baseline; 5, 10, 30, and 60 minutes following the start of the first intervention. Cox retrospective symptom scale (RSS), verbal rating scale (VRS), pain total time, and proportion of participants using analgesics were also recorded during three menstrual cycles VAS scores demonstrated that patients receiving Nonacupoint (-10.96 mm, 95% CI -17.62 to -4.30, P = 0.001) treatment presented significant improvements compared with No Acupuncture Group There were no significant differences among the two groups with respect to secondary outcomes
Others	Participants were recruited from Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, China-Japan Friendship Hospital, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University, and the First Hospital affiliated to Tianjin College of Traditional Chinese Medicine between November 2007 and September 2008

Table 3. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Caroline A. Smith et al 2011
Methods	Single-Blinded, RTCs
Participants	92 women, aged 14–25 years with a diagnosis of primary dysmenorrhea. The criteria for establishing a diagnosis of primary dysmenorrhea was based on self-reported severe incapacitating pain for at least one day of menses in two menstrual cycles classified by a pre-defined pain score of ≥6/10 on the short form of the McGill questionnaire and a visual analog scale, and pain that did not respond well to analgesics
Interventions	Acupuncture Group vs. Control Group (Sham Acupuncture)
Outcomes	The primary outcomes were menstrual pain intensity and duration, overall improvement in dysmenorrhea symptoms and reduced need for additional analgesia, measured at 3, 6 and 12 months from trial entry At 3 months although pain outcomes were lower for women in the acupuncture group compared with the control group, there was no significant difference between groups. Women receiving acupuncture reported a small reduction in mood changes compared with the control group, relative risk (RR) 0.72, 95% confidence interval (CI) 0.53–1.00, P = .05. Follow-up at 6 months found a significant reduction in the duration of menstrual pain in the acupuncture group compared with the control group, mean difference –9.6, 95% CI –18.9 to –0.3, P = .04, and the need for additional analgesia was significantly lower in the acupuncture group compared with the control group, RR 0.69, 95% CI 0.49–0.96, P = .03, but the follow-up at 12 months found lack of treatment effect
Others	Women were recruited for the study from the community through their general practitioner, gynecologist or by advertising in the media in South Australia between February 2003 and August 2005

Table 3. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Cun-Zhi Liu et al 2014a
Methods	Single-Blinded, RTCs
Participants	501 participants were required to be between 15 and 30 years, with a history of regular menstrual cycles (28-day cycle±7 days) and primary dysmenorrhea (onset <3 years after menarche). Menstrual cramping pain had to be of moderate to severe intensity, varying from 40 mm to 100 mm on a visual analog scale (VAS), and for at least 6 months before study entry. Participants agreed to refrain from the use of any analgesics 24 hours before the first intervention
Interventions	Classic Acupoint Group vs. Unrelated Acupoint Group
Outcomes	The primary outcome was subjective pain as measured by a 100-mm visual analog scale (VAS). Measurements were obtained at 0, 5, 10, 30, and 60 minutes following the first intervention. In addition, patients scored changes of general complaints using Cox retrospective symptom scales (RSS-Cox) and 7-point verbal rating scale (VRS) during three menstrual cycles The primary comparison of VAS scores following the first intervention demonstrated that classic acupoint group was more effective than Unrelated Acupoint (−4.0 mm, 95% CI −7.1 to −0.9, P = 0.010) Group However, no significant differences were detected among the two acupuncture groups for RSS-Cox or VRS outcomes. The per-protocol analysis showed similar pattern. No serious adverse events were noted
Others	This study was designed as a multicenter randomized controlled trial in six large hospitals of China and was conducted between December 2008 and December 2009

Table 3. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Cun-Zhi Liu et al 2014b
Methods	Single-Blinded, RTCs
Participants	501 participants were required to be between 15 and 30 years, with a history of regular menstrual cycles (28-day cycle±7 days) and primary dysmenorrhea (onset <3 years after menarche). Menstrual cramping pain had to be of moderate to severe intensity, varying from 40 mm to 100 mm on a visual analog scale (VAS), and for at least 6 months before study entry. Participants agreed to refrain from the use of any analgesics 24 hours before the first intervention
Interventions	Classic Acupoint Group vs. Nonacupoint Group
Outcomes	The primary outcome was subjective pain as measured by a 100-mm visual analog scale (VAS). Measurements were obtained at 0, 5, 10, 30, and 60 minutes following the first intervention. In addition, patients scored changes of general complaints using Cox retrospective symptom scales (RSS-Cox) and 7-point verbal rating scale (VRS) during three menstrual cycles The primary comparison of VAS scores following the first intervention demonstrated that classic acupoint group was more effective than nonacupoint (−4.0 mm, 95% CI −7.0 to −0.9, P = 0.012) groups However, no significant differences were detected among the two acupuncture groups for RSS-Cox or VRS outcomes. The per-protocol analysis showed similar pattern. No serious adverse events were noted
Others	This study was designed as a multicenter randomized controlled trial in six large hospitals of China and was conducted between December 2008 and December 2009

Table 3. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Intira Sriprasert et al 2015
Methods	Single-Blinded, RTCs
Participants	52 women aged between 18 and 35 years. During a run- in period of one month, participants were instructed to discontinue all treatments for dysmenorrhea with the exception of the rescue analgesic drug prescribed by the investigator. Inclusion criteria were a history of dysmenorrhea within the previous three consecutive months with a numeric rating scale (NRS) of 5 or more, a verbal multidimensional scoring system (VMSS) of grade 2 or more, and the use of rescue analgesic drug for dysmenorrhea (at least 1 tablet during the run-in period)
Interventions	Acupuncture vs. Combined Oral Contraceptive (COC)
Outcomes	Five variables were measured: (1) maximal dysmenorrhea pain scores assessed by a NRS ranging from 0 to 10 with 0 described as no pain and 10 described as maximal pain; (2) number of days suffering from dysmenorrhea; (3) amount of rescue analgesic used for relief of dysmenorrhea; (4) quality of life assessed by the Short Form Health Survey (SF-36) questionnaire; (5) verbal multidimensional scoring system (VMSS) for assessment of dysmenorrhea evaluated from three domains including ability to work, systemic symptoms, and use of analgesics By the end of the study, both treatments had resulted in significant improvement over baselines in all outcomes, that is, maximal dysmenorrhea pain scores, days suffering from dysmenorrhea, amount of rescue analgesic used, and quality of life assessed by SF-36 questionnaire Over the three treatment cycles, COC caused greater reduction in maximal pain scores than acupuncture, while improvements in the remaining outcomes were comparable. Responders were defined as participants whose maximal dysmenorrhea pain scores decreased at least 33% below their baseline. Response rates

	following both interventions at the end of the study were not statistically different. Acupuncture commonly caused minimal local side effects but did not cause any hormone-related side effects as did COC
Others	This trial was conducted during the period from January 2013 to February 2014 at the Center of Thai Traditional and Complementary Medicine (TTCM), Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Table 3. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Geetha B. Shetty et al 2018
Methods	Double-Blinded, RTCs
Participants	60 participants aged 17-23 years were recruited from a residential college. Female participants with the history of primary dysmenorrhea at least for the past 1 year, regular menstruation with periods varied from 21 to 35 days, and no history of use of oral contraceptive pills, intrauterine devices, and any particular medicine for primary dysmenorrhea for the past 6 months before the commencement of the study
Interventions	Study Group (Acupuncture Group) vs. Control Group (No Acupuncture Group)
Outcomes	The primary outcome variable of the study was pain Intensity. The secondary outcome variable such as muscle cramping was assessed using a 4-point numerical rating scale, the systemic symptoms such as headache, dizziness, diarrhea, faint, mood change, tiredness, nausea, and vomiting. Baseline, during, and post assessments were taken on the 1st day; 30th and 60th day; and 90th day, respectively This study showed a significant reduction in all the variables such as the visual analog scale score for pain, menstrual cramps, headache, dizziness, diarrhea, faint, mood changes, tiredness, nausea, and vomiting in the study group compared with those in the control group
Others	The study was conducted in the Department of Acupuncture, SDM College of Naturopathy and Yogic Sciences, Karnataka

Table 3. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Haijun Wang et al 2019
Methods	Single-Blinded, RTCs
Participants	64 eligible participants (1) aged from 18 to 35 years without history of delivery; (2) normal menstrual cycle (28 ± 7 days) in previous 3 months; (3) diagnosed with PD according to the Primary Dysmenorrhea Consensus Guidelines and confirmed no significant organ pathologies with ultrasound B and with different pattern based on the revised Chinese National Guideline; (4) moderate to severe menstrual pain intensity with a score of >40 mm on the Visual Analog Scale (VAS); and (5) able to understand the whole study and agree with all procedures by signing a written informed consent
Interventions	Acupuncture Treatment Group vs. Ibuprofen Group
Outcomes	The primary outcome was the intensity of menstrual pain measured by using the visual analogue scale at the completion of treatment. Secondary outcomes included the severity of symptoms associated with menstrual pain, responder rate, and safety of acupuncture treatment. The clinical outcomes were measured on each menstrual cycle at baseline, treatment course (3 cycles), and follow-up period At trial completion, acupuncture was shown to be associated with a significantly lower pain intensity and decreased symptom severity of primary dysmenorrhea as compared with ibuprofen ($p<0.05$). A significantly higher responder rate was found in the acupuncture group as compared with the control group ($p < 0.05$). No serious adverse events were reported by patients in either group
Others	Patients mainly were recruited from Shanxi University of Traditional Chinese Medicine by poster advertisement

Table 3. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Siyi Yu et al 2020
Methods	Single-Blinded, RTCs
Participants	54 patients with Primary dysmenorrhea (PDM). The inclusion criteria for patients with PDM were (1) a regular menstrual cycle (27–32 days); (2) a history of PDM longer than 1 year; (3) no exogenous hormones or centrally acting medication in the last 6 months; (4) lower quadrant abdominal pain (including cramping, swelling, tingling, etc.) during menstruation in the last 6 months rated higher than 4 on a visual analog scale (VAS) (0 = not at all, 10 = the worst pain sensation); and (5) right-handedness, as confirmed by the Edinburgh Handedness Inventory
Interventions	Real Acupuncture Treatment vs. Sham Acupuncture Treatment
Outcomes	The primary outcome assessed in this trial was abdominal pain severity, as measured by the 0–10 VAS rom "no pain at all" to "unbearable pain. In addition, the self- rating anxiety scale (SAS) and self-rating depression scale (SDS) were applied as secondary outcomes to evaluate the anxiety and depression levels of the PDM patients. All clinical outcomes were measured at baseline and after completion of three sessions of treatment during the periovulatory phase (days 12–16 of the menstrual cycle) Pain-related functional connectivity (FC) matrices were constructed at baseline and post-treatment period. The different neural mechanisms altered by real and sham acupuncture were detected with multivariate analysis of variance. Multivariate pattern analysis (MVPA) based on a machine learning approach was used to explore whether the different FC patterns predicted the acupuncture treatment response in the PDM patients. There were no significant differences in age, BMI, duration of disease, and baseline the self- rating anxiety scale (SAS), self-rating depression scale (SDS) or VAS scores between the real and sham acupuncture treatment groups (all $P > 0.05$). The VAS at the

	post-treatment period was lower in the real group than in the sham group, and the VAS change score and VAS change rate were significantly higher in the real acupuncture treatment group than in the sham acupuncture treatment group. Paired t-tests showed that the VAS change in the real acupuncture treatment group was significant ($t = 9.90$, $P < 0.01$), while the VAS change in the sham acupuncture group was not significant ($t = 2.10$, $P = 0.06$). In addition, there were no significant associations between duration of disease and baseline VAS, SDS, and SAS scores and post-treatment VAS score changes in either group (all $P > 0.05$) The results showed that real and sham acupuncture displayed differences in FC alterations between the descending pain modulatory system (DPMS) and sensorimotor network (SMN), the salience network (SN) and SMN, and the SN and default mode network (DMN). Furthermore, MVPA found that these FC patterns at baseline could predict the acupuncture treatment response in PDM patients
Others	This work was supported by the programs of the National Natural Science Foundation of China (Nos. 81574089, 81973960, 81973966, and 81590951), the Fok Ying-Tong Education Foundation (No. 151043), the Initiative Postdocs Supporting Program (No. BX20190046), and the China Postdoctoral Science Foundation Grant (No. 2019M663454)

Table 3. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Yanan Wang et al 2021
Methods	Single-Blinded, RTCs
Participants	44 patients with Primary dysmenorrhea (PDM) were recruited. The inclusion criteria were as follows: (1) right-handed nulliparous women aged 18–30 years; (2) meeting the diagnostic criteria for PDM of the Society of Obstetricians and Gynecologists of Canada; (3) normal menstrual cycle (27 to 32 days); (4) fulfillment of a menstrual cycle dysmenorrhea diary; (5) average pain intensity score of ≥4 on a visual analog scale (VAS) for three consecutive menstrual cycles; (6) fMRI scan performed on days 1–3 of menstruation and a VAS pain score of ≥ 4 before the scan; and (7) responsive to acupuncture and able to attain the feeling of *De qi*
Interventions	Real Acupuncture Group vs. Sham Acupuncture Group
Outcomes	Visual Analog Scale (VAS) scores were recorded before and after the fMRI scan to evaluate the degree of dysmenorrhea immediately before and after acupuncture The clinical characteristics of the patients during their menstrual period were collected, and imaging scans were performed during the first 3 days of the patients' menstrual period. The researchers analyzed task and resting functional magnetic resonance imaging (fMRI) data to investigate the potential central mechanism of the immediate effect of acupuncture intervention on the intensity of PDM pain There were no significant differences between the two groups regarding the pre-treatment VAS score ($p = 0.493$) and post-treatment VAS score ($p = 0.069$), but the reduction in the pain intensity after treatment was significantly greater in the real acupuncture group than the sham acupuncture group. Furthermore, the pain intensity change [(post-treatment VAS score minus pre-treatment VAS score)/pre-treatment VAS score] was significantly

	greater in the real acupuncture group than the sham acupuncture group ($p = 0.010$) The task fMRI study found that the rostral anterior cingulate cortex (rACC) and right supplemental motor area were activated during real acupuncture. Using the resting- state functional connectivity (FC) method, they found a post-versus pre-treatment change in the FC of the rACC and left precentral gyrus in the comparison of real acupuncture versus sham acupuncture. In addition, the FC of the rACC–left precentral gyrus at baseline was negatively correlated with short-term analgesia, while the change in the FC of the rACC–left precentral gyrus was positively correlated with short-term analgesia after acupuncture treatment
Others	This trial was financially supported by the National Natural Science Foundation of China (Grant Nos. 81973966 and 81303060) and China National Postdoctoral Program for Innovative Talents (Grant No. BX20190046)

Table 3. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Cheng-Hao Tu et al 2021
Methods	Single-Blinded, RTCs
Participants	35 patients with Primary Dysmenorrhea (PDM) were recruited. The inclusion criteria for subjects were as follows: (a) aged 20–35 years; (b) right- handed; (c) regular menstrual cycle of 27–32 days; and (d) average menstrual pain level in the past 6 months > 4 points on a 10-point numerical rating scale
Interventions	Verum Acupuncture Group vs. Sham Acupuncture Group
Outcomes	The Chinese version of the McGill Pain Questionnaire (MPQ) was used to assess the multidimensional menstrual pain experience. The total score of the pain rating index represents the menstrual pain experience, whereas that of the present pain intensity represents menstrual pain intensity. In addition, the Chinese version of Spielberger's State-Trait Anxiety Inventory (STAI) and the Chinese version of Beck's Depression Inventory II (BDI II) were used to assess the level of anxiety and depression, respectively No significant interaction effect was found on menstrual pain experience or intensity between group and time factors. The main effect analysis revealed no effect on the group factor but a significant effect on the time factor. The post hoc analysis (controlled with Sidak correction) revealed that both menstrual pain experience and intensity significantly declined in the early stage of the intervention (weeks 0 to 4) and during the entire intervention (weeks 0 to 8), but no significant change was found in the late stage (weeks 4 to 8) J. Clin. Med. 2021, 10, x FOR PEER REVIEW 7 of 14. Furthermore, no significant difference was observed in psychological status and gonadal hormone level Resting-state functional magnetic resonance imaging was conducted before, during, and after the intervention to measure the spontaneous activity in brain. After the 8-week intervention, both

	verum and sham groups reported decreased menstrual pain. However, the cessation of decreased functional connectivity (FC) between periaqueductal gray matter and the regions associated with affective pain modulation and attention-related pain modulation were found in the verum but not in the sham group after the 8-week intervention. More decreased FC has been found in the region associated with non-specific effects of acupuncture intervention after the early stage of acupuncture intervention
Others	This work was supported by the Ministry of Science and Technology, Taiwan (MOST 106- 2314-B-039-012, 107-2314-B-039-058-MY2, and 109-2320-B-039-043) and the China Medical University, Taiwan (CMU 102-ASIA-19, 107-N-24, 108-MF-03, and 109-MF-56)

Table 3. Data Items Being Extracted from the Selected Literature (Continued)

Data Component	Data Item
Literature Information	Shin-Lei Peng et al 2021
Methods	Single-Blinded, RTCs
Participants	25 right-handed female patients with Primary Dysmenorrhea (PDM) were recruited through advertisements. Inclusion criteria for patients were as follows: (1) age in the range 20–30 years old; (2) regular menstrual cycle of 27–32 days; and (3) average menstrual pain level (including cramping, swelling, tingling, etc.) in the last 6 months rated higher than 4 points on a 10-point visual analog scale (0 = not at all and 10 = the worst pain sensation)
Interventions	Verum Acupuncture Treatment vs. Sham Acupuncture Treatment
Outcomes	Pain rating index (PRI), Cerebral Blood Flow (CBF), and gonadal hormone levels were acquired before and after 8-week treatments. Both verum and sham acupuncture treatments exert its analgesic effect on PDM after intervention as PRI reduced ($p < 0.05$). Blood gonadal levels were not significantly different after acupuncture in both groups (all $p > 0.05$). In the verum group, intervention-related decreases in CBF were observed in the right dorsal anterior cingulate cortex. In the sham group, regions identified as showing reductions in CBF after acupuncture included the left ventromedial prefrontal cortex, left caudate, and left insula. Patients with higher baseline CBF in the left precuneus and right hippocampus were accompanied with worse treatment response to acupuncture intervention. Mechanisms of verum and sham acupuncture treatments are dissimilar as manifested by different brain responses
Others	The financial support from Ministry of Science and Technology, Taiwan (MOST 109-2320-B-039-043, MOST 107-2314-B-039-058-MY2, and MOST 106-2314-B-039-012) and China Medical University, Taiwan (CMU109-S-43, CMU108-MF-03, and CMU107-N-24)

Assessment of Risk of Bias (RoB)

I evaluated the risk of bias in the ten clinical trial literature selected for systematic review. Using software provided by RevMan 5.4 for the types of risk of bias evaluated according to the criteria. The summary of the comprehensive qualitative evaluation is shown in Figure 2.

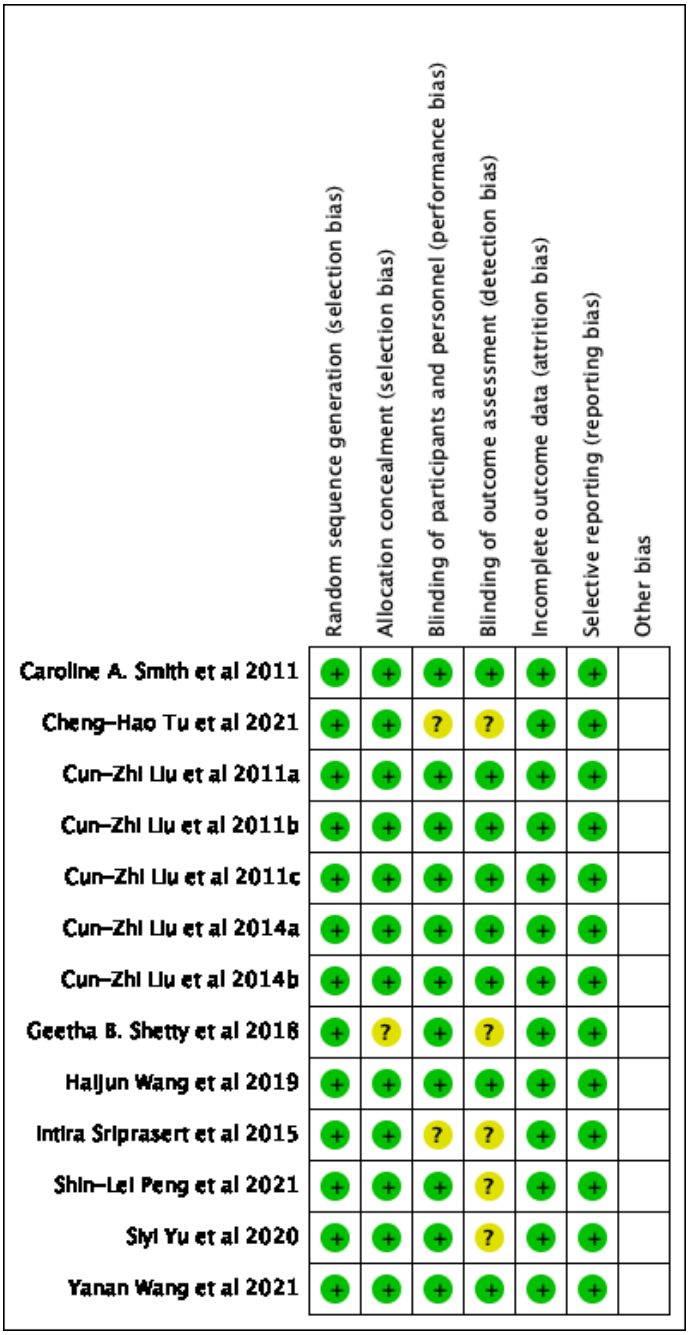

Figure 2. Risk of bias summary

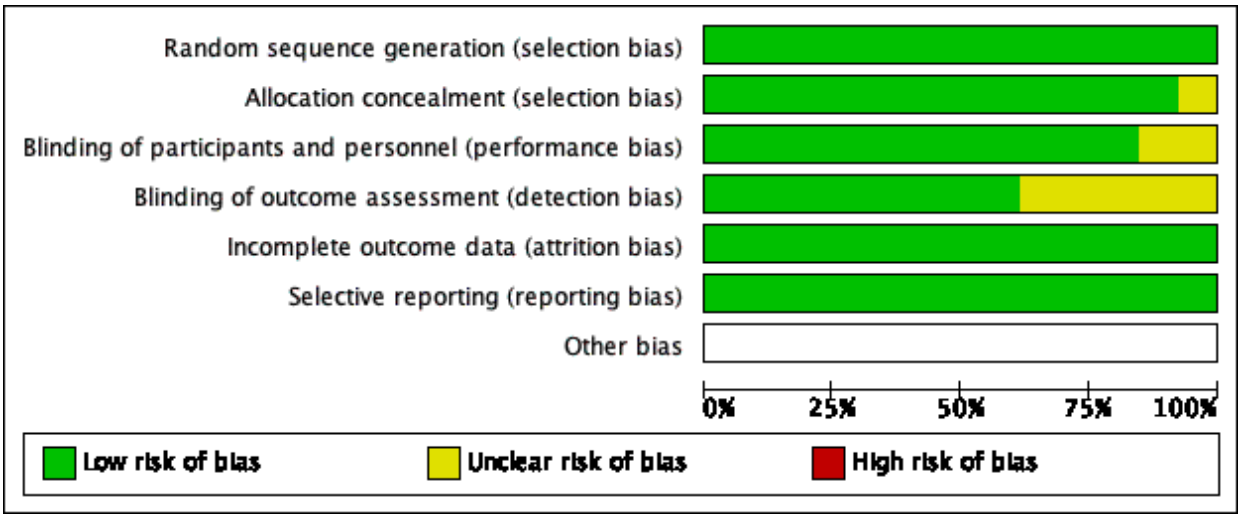

Figure 3. Risk of bias distribution graph

In the allocation concealment 1 out of 13 cases (7.69%) unclear risk because there was not mention about allocation (Geetha B. Shetty et al 2018).

In the blinding of participants and personnel 2 out of 13 cases (15.38%) unclear risk because there were not mention about blinding of participant and personnel (Cheng-Hao Tu et al 2021, and Intira Sriprasert et al 2015).

In the blinding of outcome assessment 5 out of 13 cases (38.46%) unclear risk because there were not mention about blinding of outcome assessment (Cheng-Hao Tu et al 2021, Geetha B. Shetty et al 2018, Intira Sriprasert et al 2015, Shin-Lei Peng et al 2021 and Siyi Yu et al 2020). (Figure. 3)

Heterogeneity analysis

In the outcomes of Caroline A. Smith et al 2011, Cheng-Hao Tu et al 2021, and Cun-Zhi Liu et al 2011, etc.

To examine whether the confidence intervals and the directionality of the treatment effect values overlap, Heterogeneity test, the Chi^2 statistics and Higgins's I^2 was used. The result is shown in Table 4. The heterogeneity test was performed in 3 individual result items including Visual Analog Scale (VAS), A Total Frequency Ratings Score (RSS-COX1), An Average Severity Ratings Score (RSS-COX2) and the remaining items were excluded from the analysis.

As shown in Table 4, Visual Analog Scale (VAS) in I^2 value was 92%, indicating significant heterogeneity. In A Total Frequency Ratings Score (RSS-COX1) and An Average Severity Ratings Score (RSS-COX2) I^2 value were 0%, indicating no significant heterogeneity.

On the other hand, the p-value was statistically significant at (p-value < 0.05) only 1 item, which is Visual Analog Scale (VAS), p-value = 0.0001 was significant. As above, the fixed effect models were analyzed.

Table 4. Heterogeneity of Outcomes from Caroline A. Smith et al 2011, Cheng-Hao Tu et al 2021, and Cun-Zhi Liu et al 2011, etc.

Outcome	Q	df	p-value	I^2
Visual Analog Scale (VAS)	141.25	12	<0.00001	92%
An Average Severity Ratings Score (RSS-COX1)	0.41	4	0.98	0%
An Average Severity Ratings Score (RSS-COX2)	0.37	4	0.98	0%

Meta-analysis

Using the RevMan 5.4, the outcome of thirteen subgroups in the ten trails, were meta-analysis and show as a forest plot for Visual Analog Scale (VAS), A Total Frequency Ratings Score (RSS-COX1), An Average Severity Ratings Score (RSS-COX2), Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS). (Figure 4 to 8).

The Visual Analog Scale (VAS) for pain is a straight line with one end meaning no pain and the other end meaning the worst pain imaginable. A patient marks a point on the line that matches the amount of pain she feels. (Appendix 1).

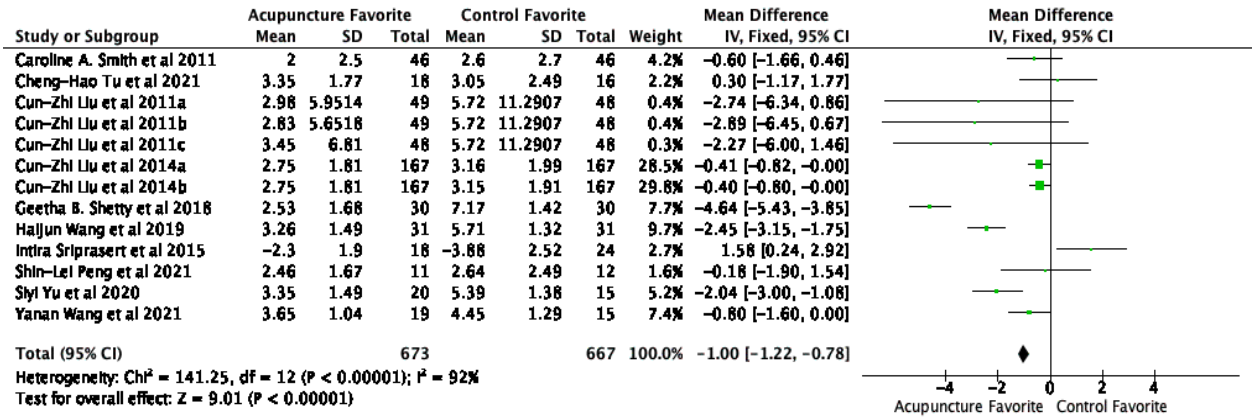

Figure 4. Effect of acupuncture therapy on the VAS pain score, Forest plot

The thirteen subgroups in ten trails (Caroline A. Smith et al 2011, Cheng-Hao Tu et al 2021, and Cun-Zhi Liu et al 2011, etc.) involving 1340 patients were included in the meta-analysis. The results indicated that the improvement in the total effectiveness rate among the different control groups the VAS pain score were significant lower in the acupuncture groups than in the control groups [MD -1.00 (-1.22, -0.78), 95% CI, $p<0.00001$) The level of heterogeneity (I^2) in VAS pain score was 92%. Although significant difference was observed, there are two studied

Cheng-Hao Tu et al 2021 and Intira Sriprasert et al 2015 did not reach statistically significant (Figure 4).

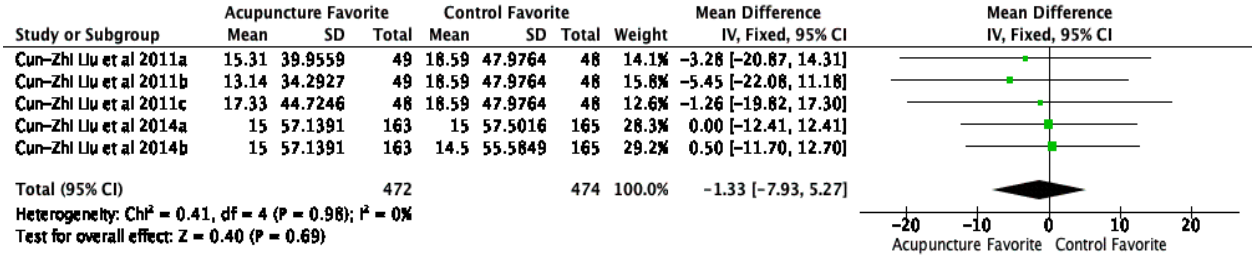

Figure 5. Effect of acupuncture therapy on A Total Frequency Ratings Score (RSS-COX1), Forest plot

Cox retrospective symptom scale (RSS), a menstrual symptom measure that has been shown to have high reliability, validity, and sensitivity, gives two scores, a Total Frequency Ratings score (RSS-COX1) and an Average Severity Ratings score (RSS-COX2). Lower scores indicate better health.

The five subgroups in two trials (Cun-Zhi Liu et al 2011 and Cun-Zhi Liu et al 2014) involving 946 patients were included in the meta-analysis. The results indicated that the RSS-COX1 were not significant difference between the acupuncture groups and the control groups [MD -1.33 (-7.93, -5.27), 95% CI, p=0.98). The level of heterogeneity (I^2) in RSS-COX1 was 0% (Figure 5).

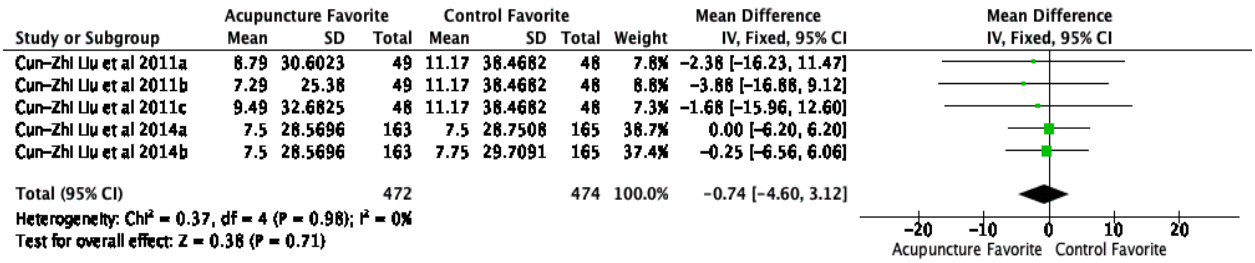

Figure 6. Effect of acupuncture therapy on an Average Severity Ratings score (RSS-COX2), Forest plot

The five subgroups in two trials (Cun-Zhi Liu et al 2011 and Cun-Zhi Liu et al 2014) involving 946 patients were included in the meta-analysis. The results indicated that the RSS-COX2 were not significant difference between the acupuncture groups and the control groups [MD -0.74 (-4.60, 3.12), 95% CI, p=0.98). The level of heterogeneity (I^2) in RSS-COX2 was 0% (Figure 6).

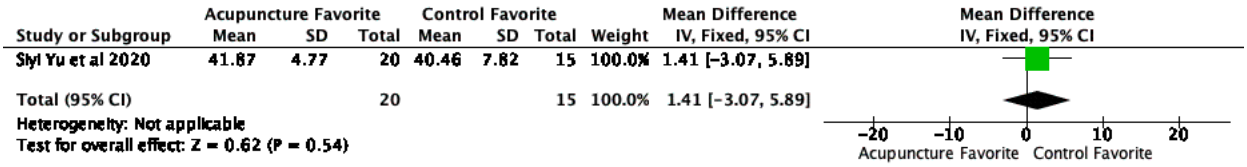

Figure 7. Effect of acupuncture therapy on Self-Rating Anxiety Scale (SAS), Forest plot

The Zung Self-Rating Anxiety Scale (SAS) is a well-accepted instrument for adults and adolescents to make self-report measurement of anxiety in both clinical and research settings, which includes four groups of manifestations: motor, autonomic, cognitive, and central nervous system symptoms (Zhanyu Pang et al, 2019) (Appendix 2).

In Siyi Yu et al 2020, involving 35 patients were included in the meta-analysis. The results indicated that there was no statistic significant difference in SAS between the acupuncture group

and the control group [MD 1.41 (-3.07, 5.89), 95% CI, p=0.54]. The level of heterogeneity (I^2) in SAS was not applicable (Figure 7).

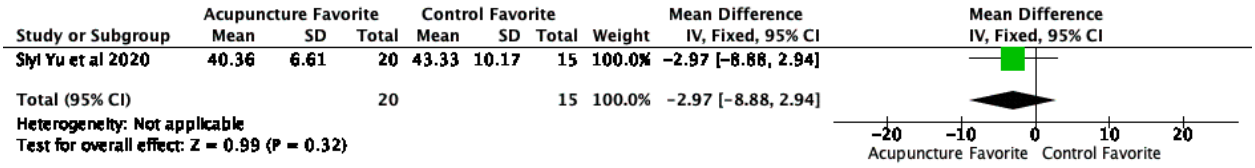

Figure 8. Effect of acupuncture therapy on Self-Rating Depression Scale (SDS), Forest plot

The Zung Self-Rating Depression Scale (SDS) is a commonly utilized norm-referenced scale. The SDS is a 20-item Likert scale covering symptoms that were identified in factor analytic studies of the syndrome of depression (Debra A. Dunstan, 2018) (Appendix 3).

In Siyi Yu et al 2020, involving 35 patients were included in the meta-analysis. The results indicated that SDS were not significant in the acupuncture groups than in the control groups [MD -2.97 (-8.88, 2.94), 95% CI, p=0.32]. The level of heterogeneity (I^2) in SDS was not applicable (Figure 8).

Identification of Reporting Bias

In order to check for reporting bias such as Visual Analog Scale (VAS), A Total Frequency Ratings Score (RSS-COX1), An Average Severity Ratings Score (RSS-COX2), Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) by performing a funnel plot of 5 result items overestimation of the summary estimate of treatment effect was prevented. In these analyses, the shape of each funnel plot appeared almost symmetrical, meaning that publication bias was mildly evident across all studies. But only Figure 9. Funnel Plot Comparison of Visual Analog Scale (VAS), the result was significant because the number of synthesized documents was greater than 10. The rest of the funnel plots, the number of synthesized documents were less than 10, therefore the results were not significant (Figure 9 to 13).

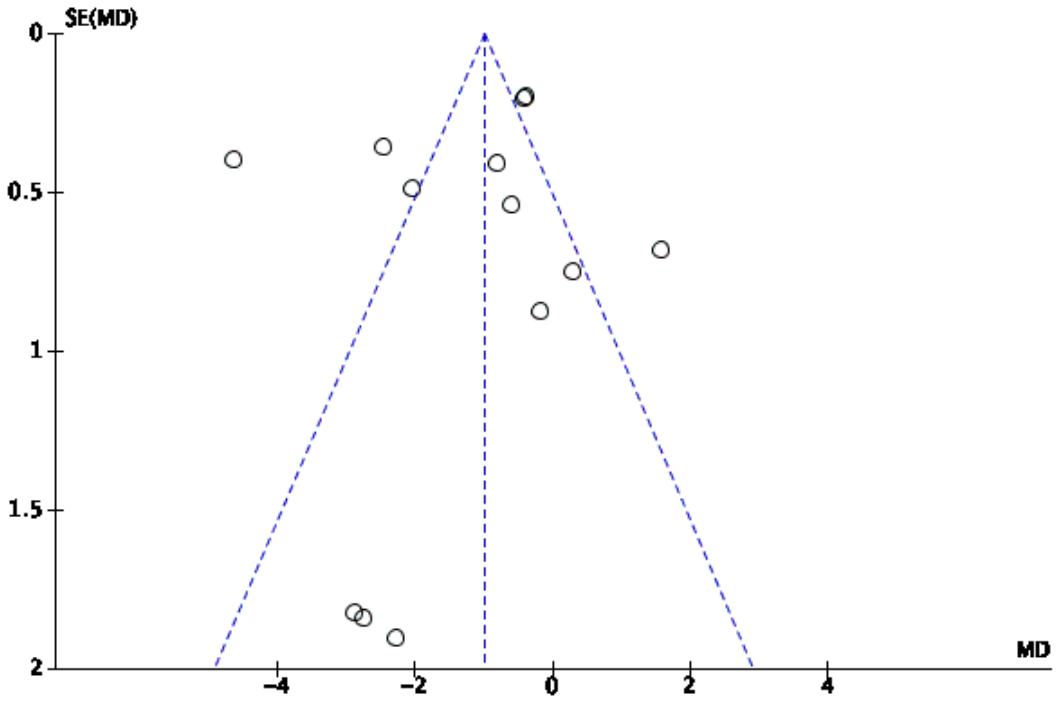

Figure 9. Funnel Plot Comparison of Visual Analog Scale (VAS)

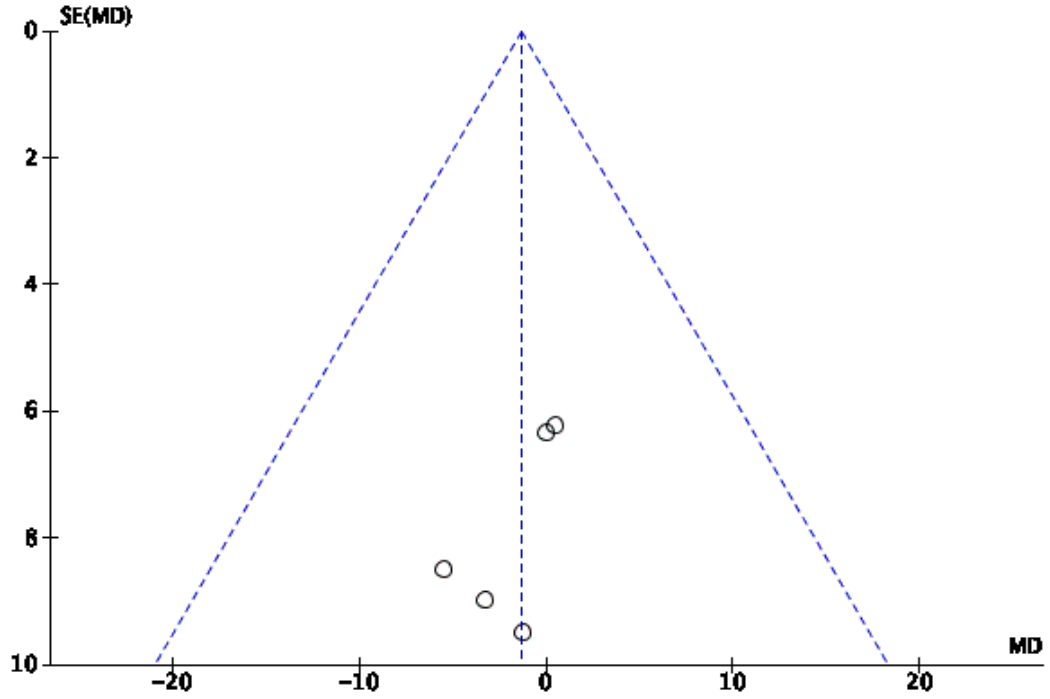

Figure 10. Funnel Plot Comparison of A Total Frequency Ratings Score (RSS-COX1)

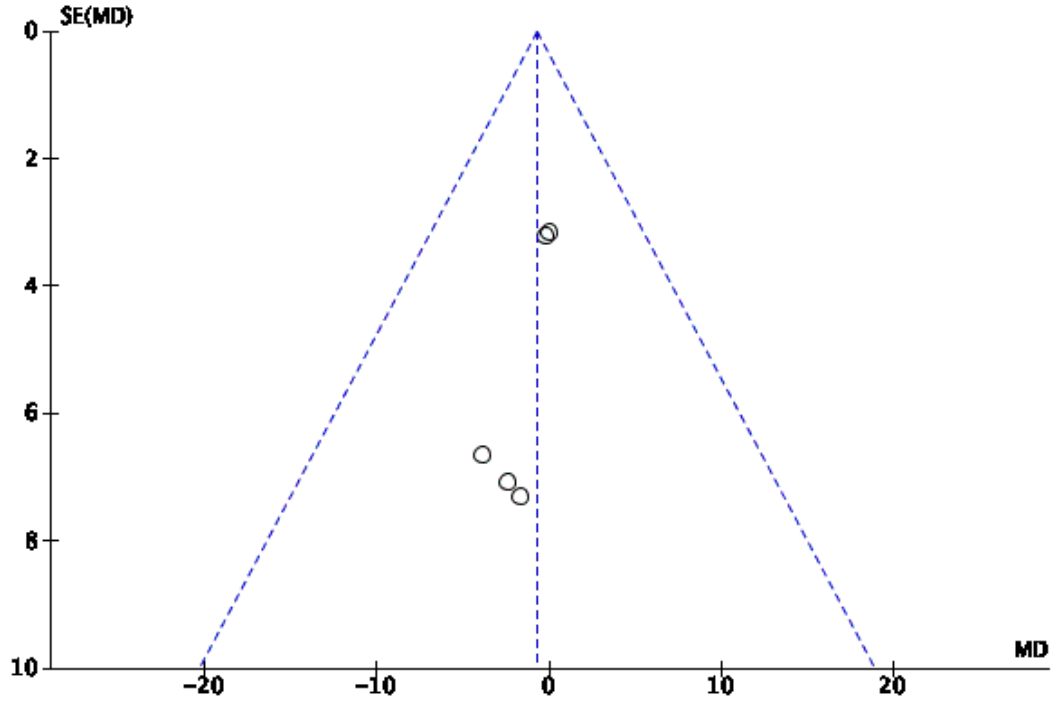

Figure 11. Funnel Plot Comparison of An Average Severity Ratings Score (RSS-COX2)

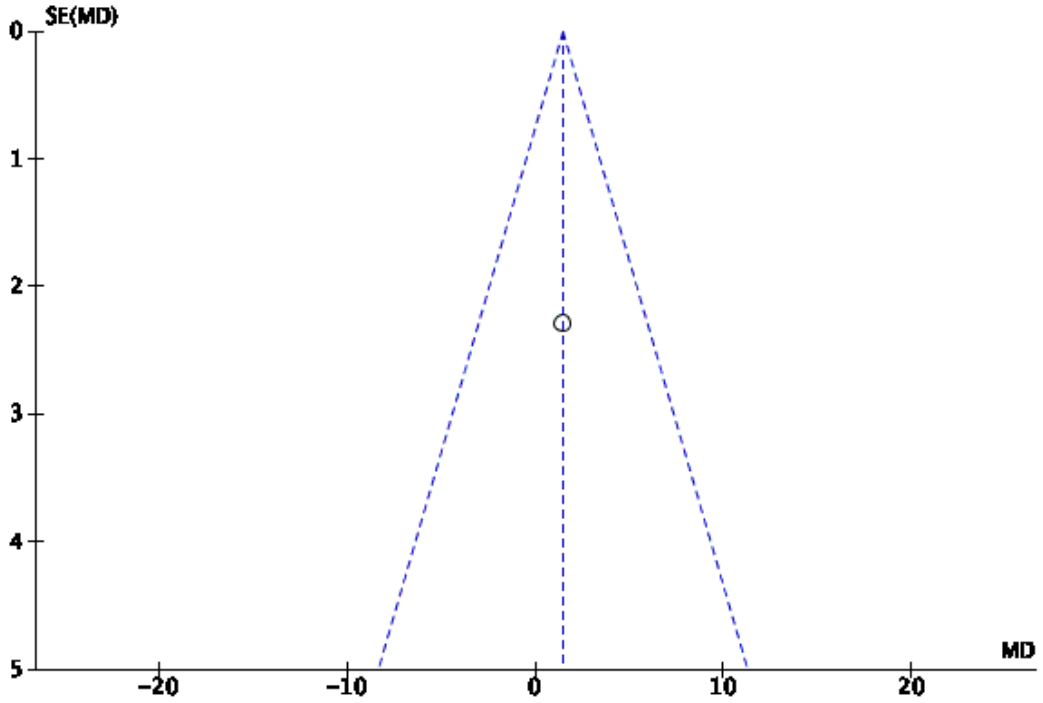

Figure 12. Funnel Plot Comparison of Self-Rating Anxiety Scale (SAS)

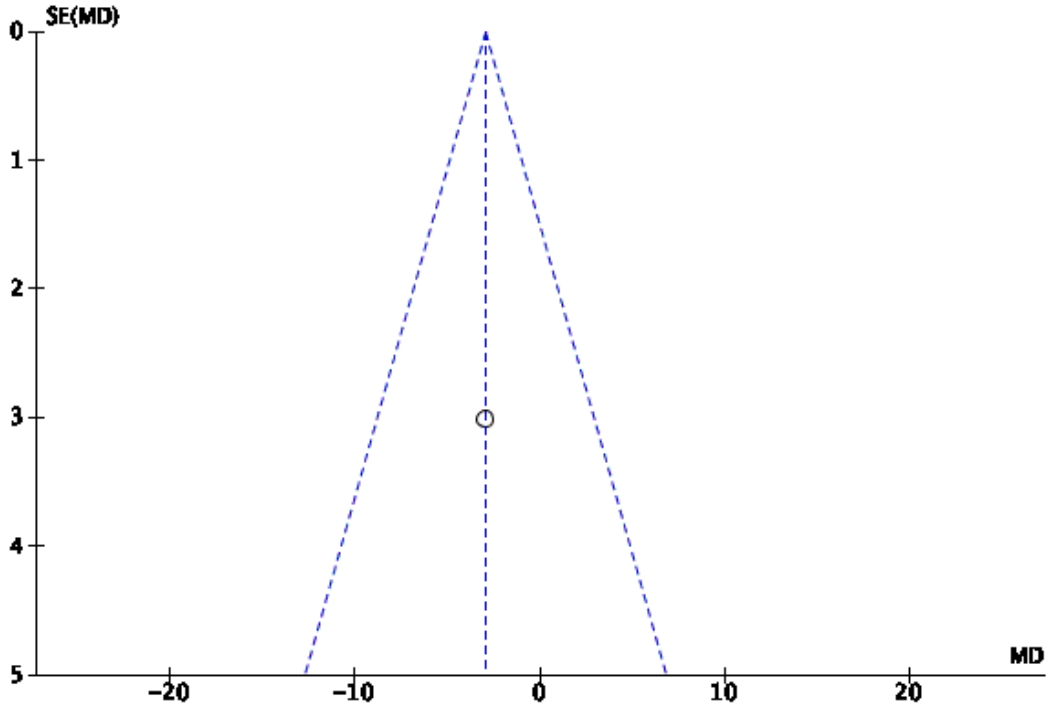

Figure 13. Funnel Plot Comparison of Self-Rating Depression Scale (SDS)

Confirmation of safety and side effects

Table 5 describes safety and side effects from 10 clinical trials. Based on this, there are no concerns about the safety and side effects of Acupuncture intervention for the patient who has Primary Dysmenorrhea.

Table 5: Descriptions on the Safety and/or Adverse Effect of Acupuncture Intervention to Primary Dysmenorrhea participants

Study	Quote
Caroline A. Smith 2011	There were no serious adverse effects reported
Cheng-Hao Tu 2021	No specific description
Cun-Zhi Liu 2011	One faintness after first treatment and no serious adverse events were documented
Cun-Zhi Liu 2014	Two small hematoma, one faintness, one needling pain. No serious adverse events were documented
Geetha B. Shetty 2018	None of the participants reported any adverse effects during the study period.
Haijun Wang 2019	7 adverse events including subcutaneous hemorrhage occurred during or after treatment. Such symptoms resolved properly within 7 days.
Intira Sriprasert 2015	15 local irritation or minor bleeding at acupuncture points, 4 headache or myalgia and 1 fever. All adverse events were minor in intensity and completely self-limited.
Shin-Lei Peng 2021	No specific description
Siyi Yu 2020	No specific description
Yanan Wang 2021	No specific description

IV. DISCUSSION

The systemic review and meta-analysis of 10 randomized control trials, including 1,047 participants indicated that the intervention group who received acupuncture and/or electro acupuncture therapy has larger beneficial effects than the control group who received no intervention, sham acupuncture and ibuprofen. In addition, many studies have shown that acupuncture and electroacupuncture are benefit for primary dysmenorrhea in alleviating pain. Overall, acupuncture and/or electroacupuncture therapy appears to be safe method for reducing pain in patients with primary dysmenorrhea, especially when the pharmaceutical drugs are not favorable choices.

The meta-analysis outcome measures for this review including VAS, RSS-COX1, RSS-COX2, SAS and SDS. The finding is supported by the existing evidence. There are 8 RCTs concluded that the VAS pain score was significant lower in the acupuncture groups than in the control group. In Caroline A. Smith et al., 2011, indicated that at Six months following trial entry, there was a significant reduction in the duration of menstrual pain in the acupuncture group (30 h) compared with the control group (39 h) and a reduced need for additional analgesia in the acupuncture (54%) compared with the control group (82%). However, there are 2 RTCs indicated that no significant interaction effect was found on VAS pain score between the acupuncture groups and the control group. In Intira Sriprasert et al., 2015, over the three treatment cycles, COC was more efficacious than acupuncture with respect to reduction in maximal dysmenorrhea pain scores, whereas the efficacy of both interventions was comparable with respect to reduction in the number of days per cycle suffering from dysmenorrhea, reduction in rescue analgesic used for relief of

dysmenorrhea, improvement in quality of life, and regression in VMSS score. Acupuncture had a lower rate of adherence to treatment than did COC.

None of other outcomes in this studied indicated significant difference between acupuncture group and control group including Cox retrospective symptom scale (RSS); a Total Frequency Ratings score (RSS-COX1) and an Average Severity Ratings score (RSS-COX2), and 1 trails of Self-Rating Anxiety Scale (SAS) and Self-Rating Anxiety Scale (SDS).

There are no reported serious adverse events for acupuncture. However, trials have shown that many patients may experience mild to moderate side effects of faintness, small hematoma, needling pain, subcutaneous hemorrhage, local irritation, headache, myalgia and fever.

Acupuncture points for Primary Dysmenorrhea that used in the 10 RCTs were the standard points included: 1) Primary points: SP6, SP4, ST29, Ren3, UB32, SP8, Ren6, Ren3, SP8, KD3, ST25, ST30, ST36, Ren4, UB62, HT7, LI4, PC6, UB54, ST28 2) Secondary points: used according to the individual diagnoses.

In the present systematic review and meta-analysis, only randomized controlled trials were included. This gives the review some strength. However, several limitations need to be taken into consideration. Many of the included RCTs had unclear risk bias. One study was not mention about allocation; two studies were not mention about blinding of participant and personnel; five studies were not mention about blinding of outcome assessment. The results of the analysis, though it is correct, may not represent the “true effect” of acupuncture. This may be primarily due to the low number of included studies. More controlled trials are needed with a larger sample size to provide

solid evidence that solves this debate. Heterogeneity is the most important limitation; a pooled homogeneous analysis of all trials was not possible.

V. CONCLUSION

According to the results of this meta-analysis, Acupuncture treatment showed significant improvement in VAS pain score [MD -1.00] associated with Primary Dysmenorrhea, however, RSS-COX1 [MD -1.33], RSS-COX2 [MD -0.74] and SAS [MD 1.41] and SDS [MD -2.97] did not show significance. As a conclusion, acupuncture is an alternative option for relieving dysmenorrhea, especially when the pharmaceutical drugs are not favorable choices. It is safe and effective treatment for patient with Primary Dysmenorrhea. However, we need more studies to evaluate the effectiveness of acupuncture on the quality of life of the Primary Dysmenorrhea patient.

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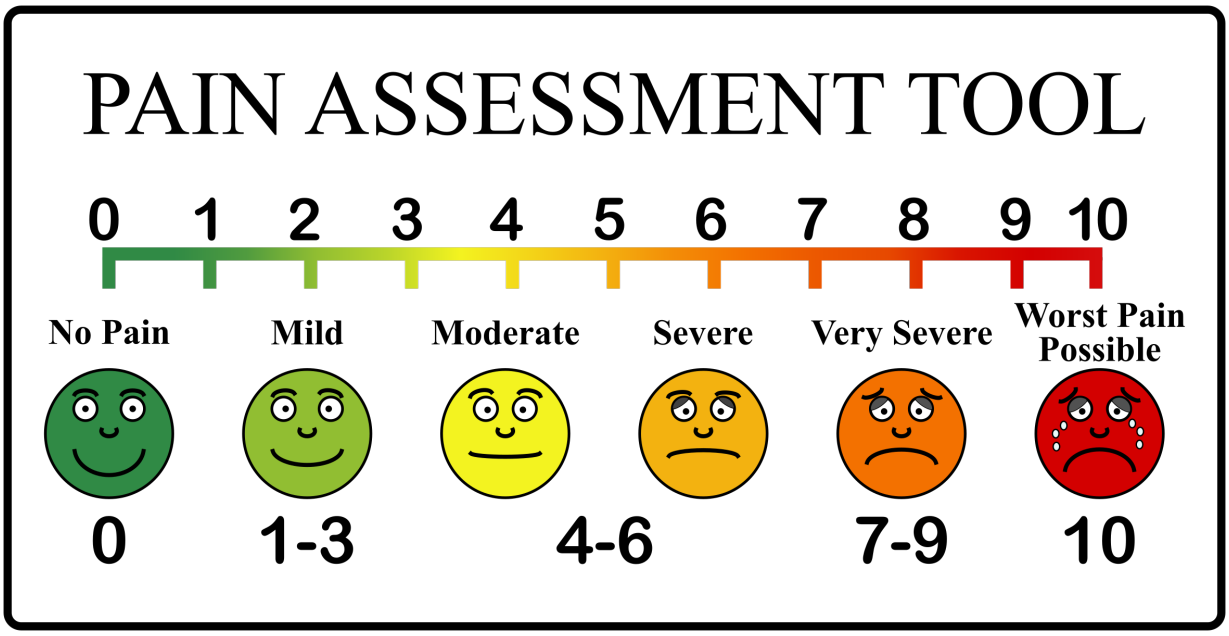
APPENDIX

Appendix 1: Visual Analogue Scale (VAS)



Appendix 2: Cox retrospective symptom scale (RSS) or Cox Menstrual Symptom Scale (CMSS)

The CMSS has been widely used for integrally evaluating patients' symptoms. The scale consists of 17 items or symptoms. In the severity evaluation, each symptom is scored via five levels: a score of 0 denotes that the symptom is not noticeable; one denotes it as slightly bothersome; two denotes it as moderately bothersome; three denotes it as severely bothersome; and four denotes it as very severely bothersome. In the duration evaluation, each symptom is scored in five grades: a score of 0 denotes that the symptom did not occur; one denotes that it lasted less than three hours; two denotes that it lasted between three and seven hours; three denotes that it lasted an entire day; and four denotes that it lasted several days (Jie Yang et al 2015).

Appendix 3: Zung Self-Rating Anxiety Scale (SAS)

NAME _____ DATE _____

Zung Anxiety Self-Assessment Scale

	None or a little of the time	Some of the time	Good part of the time	Most or all of the time
1. I feel more nervous and anxious than usual	☐ 1	☐ 2	☐ 3	☐ 4
2. I feel afraid for no reason at all	☐ 1	☐ 2	☐ 3	☐ 4
3. I get upset easily or feel panicky	☐ 1	☐ 2	☐ 3	☐ 4
4. I feel like I'm falling apart and going to pieces	☐ 1	☐ 2	☐ 3	☐ 4
5. I feel that everything is all right and nothing bad will happen	☐ 4	☐ 3	☐ 2	☐ 1
6. My arms and legs shake and tremble	☐ 1	☐ 2	☐ 3	☐ 4
7. I am bothered by headaches, neck and back pains	☐ 1	☐ 2	☐ 3	☐ 4
8. I feel weak and get tired easily	☐ 1	☐ 2	☐ 3	☐ 4
9. I feel calm and and can sit still easily	☐ 4	☐ 3	☐ 2	☐ 1
10. I can feel my heart beating fast	☐ 1	☐ 2	☐ 3	☐ 4
11. I am bothered by dizzy spells	☐ 1	☐ 2	☐ 3	☐ 4
12. I have fainting spells or feel faint	☐ 1	☐ 2	☐ 3	☐ 4
13. I can breath in and out easily	☐ 4	☐ 3	☐ 2	☐ 1
14. I get feelings of numbness and tingling in my fingers and toes	☐ 1	☐ 2	☐ 3	☐ 4
15. I am bothered by stomachaches or indigestion	☐ 1	☐ 2	☐ 3	☐ 4
16. I have to empty my bladder often	☐ 1	☐ 2	☐ 3	☐ 4
17. My hands are usually dry and warm	☐ 4	☐ 3	☐ 2	☐ 1
18. My face gets hot and blushes	☐ 1	☐ 2	☐ 3	☐ 4
19. I fall asleep easily and get a good night's rest	☐ 4	☐ 3	☐ 2	☐ 1
20. I have nightmares	☐ 1	☐ 2	☐ 3	☐ 4

Converting Raw Score Total to Anxiety Index

RAW SCORE	ANXIETY INDEX	RAW SCORE	ANXIETY INDEX	RAW SCORE	ANXIETY INDEX
20	25	40	50	60	75
21	26	41	51	61	76
22	28	42	53	62	78
23	29	43	54	63	79
24	30	44	55	64	80
25	31	45	56	65	81
26	33	46	58	66	83
27	34	47	59	67	84
28	35	48	60	68	85
29	36	49	61	69	86
30	38	50	63	70	88
31	39	51	64	71	89
32	40	52	65	72	90
33	41	53	66	73	91
34	43	54	68	74	92
35	44	55	69	75	94
36	45	56	70	76	95
37	46	57	71	77	96
38	48	58	73	78	98
39	49	59	74	79	99
				80	100

Raw Score Total ☐ Anxiety Index ☐

Interpreting the Anxiety Index

Anxiety Index	Clinical Interpretation
Below 45	Within normal range
45 – 59	Minimal to moderate anxiety
60 – 74	Marked to severe anxiety
75 and over	Most extreme anxiety

- Check that all statements have been answered
- Scoring values are printed next to the response
- Add up the Raw Total Score
- Convert the Raw Total to the Anxiety Index

Instruction for use: (Zung Anxiety Assessment Tool)

1. The same caregiver should administer this test each time.
2. Choose a quiet place, preferably the same location each time the test is administered.
3. The administration of this test should not be immediately after some mental trauma or unsteady period.
4. Speak in a soft, pleasant tone.
5. Answer all questions by placing a check in the box to the left of the number under the appropriate answer.
6. Add the Raw Score values (numbers to the right of the check) for all questions and record the total in the "RAW SCORE TOTAL" box.
7. Compare the raw score to the anxiety index on the conversion chart and record the corresponding anxiety index in the "ANXIETY INDEX" box.
8. Compare the anxiety index with the clinical interpretation chart.

Consult Pharm 1996; 11 (Suppl 4)

4-7

Appendix 4: Zung Self-Rating Depression Scale (SDS)

Zung Self-Rating Depression Scale

For each statement below, please circle the number in the column that best represents how you have been feeling or behaving in the last several days.

Statement	A little of the time	Some of the time	A Good part of the time	Most of the time
1. I feel down-hearted and blue	1	2	3	4
2. Morning is when I feel the best.	4	3	2	1
3. I have crying spells or feel like it.	1	2	3	4
4. I have trouble sleeping at night	1	2	3	4
5. I eat as much as I used to.	4	3	2	1
6. I still enjoy sex.	4	3	2	1
7. I notice that I am losing weight.	1	2	3	4
8. I have trouble with constipation.	1	2	3	4
9. My heart beats faster than usual.	1	2	3	4
10. I get tired for no reason.	1	2	3	4
11. My mind is as clear as it used to be.	4	3	2	1
12. I find it easy to do the things I used to.	4	3	2	1
13. I am restless and can't keep still.	1	2	3	4
14. I feel hopeful about the future.	4	3	2	1
15. I am more irritable than usual.	1	2	3	4
16. I find it easy to make decisions.	4	3	2	1
17. I feel that I am useful and needed.	4	3	2	1
18. My life is pretty full.	4	3	2	1
19. I feel that others would be better off if I were dead.	1	2	3	4
20. I still enjoy the things I used to do.	4	3	2	1

Zung WW. (1965). A self-rating depression scale. *Archives of General Psychiatry* 12: 63-70.

Add up all of the numbers that were circled and consult the scale provided below:

The scores range from 25-100.

- 25-49 Normal Range
- 50-59 Mildly Depressed
- 60-69 Moderately Depressed
- 70 and above Severely Depressed

Provided to you by Depression-Test.net for educational purposes only. If there is an indication that you might be depressed, please check out the site for additional information, tools and support.