Acupuncture in Treatment of Heroin Withdrawal Syndrome:

A Systematic Review and Meta-analysis

針刺療法治療海洛英依賴的整合性分析

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Abstract

Background and objectives: There are 13 million opiate addicts including 9 million heroin users throughout the world. Heroin abuse associates with a high risk of AIDS and other serious diseases, and social costs due to crime and poverty in this population may exceed those of most other drug abuses. Heroin dependence has been a priority of health and social problems in Hong Kong and many other areas. Acupuncture is a commonly used therapy for drug addiction. In recent years, a number of randomized controlled clinical trials have been conducted to identify the practice value of this therapy in heroin detoxification. This study aims to (1) assess the quality of trials, and measurement/category data in the trials, (2) evaluate the efficacy and safety of acupuncture in treatment of heroin withdrawal syndrome, and (3) analyze the most commonly used acupoints and manipulation methods in clinical application.

Methods: (1) Datum search: after preparation of a strict strategy, electronic databases and hand-search materials were widely searched for screening eligible trials. There was no language limitation in the paper collection. (2) Inclusive and exclusive criteria: randomized controlled trials to compare the efficacy and safety of acupuncture therapy (AT) with medication therapy (MT) for heroin detoxification were valid. (3) Datum analysis: the quality of eligible trials was assessed by Jadad's scale; the measurement data of trials were estimated by weight mean difference (WMD), the category data were estimated by odd ratio (OR) and 95% confidence interval (95% CI), in a meta-analysis. Datum extraction and assessment were performed by two reviewers independently.

Results: (1) 20 trials (1072 treated with acupuncture in total of 2134 patients) that

met the inclusive criteria were cited, and 6 trials in them were assessed as high-quality trials (scoring 3-5 marks), and the rest were low quality trials (scoring 1-2 marks) as poor description of randomization, blind-method and dropout reporting in study design. (2) Compared with MT, AT alone was more effective to diminish the withdrawal-symptom score (WSS) on the Day 2 to 10 (5 trials; WMD: -17.52 (-28.69, -6.35) to -4.83 (-8.13, -1.53); P<0.005) and HAMA score (1 trial; P<0.05), while there was no significant difference in patients' detoxicated number (PDN) after AT or MT treatment respectively (4 trials; OR: 1.04 (0.60, 1.82); P=0.88). (3) AT combined with MT showed higher efficacy than MT alone in reducing the WSS on the Day 1 to 10 (6 trials; WMD: -9.54 (-15.83, -3.25) to -2.50 (-4.48, -0.53); P<0.02) and HAMA score (3 trials; WMD: -4.85 (-8.12, -1.58); P=0.004), and a higher PDN after treatment (8 trials; OR: 4.31 (2.47, 7.52); P<0.00001). (4) The relapse rate after treatment by AT combined MT was significantly lower than MT alone in 6-month follow-up investigations (3 trials; OR: 0.30 (0.19, 0.46); P<0.00001). (5) The incidence of adverse effects caused by MT was significantly higher than AT. Only one trial in total 20 included trials reported a mild adverse effect that was local pain caused by needles. (6) The 10 most commonly used acupoints in total acupoints reported were *Neiguan* (PC 6, 75.4%), *Zusanli* (ST 36, 57.4%), *Hegu* (LI 4, 45.9%), *Sanyinjiao* (SP 6, 44.3%), *Shenmen* (HT 7, 26.2%), *Laogong* (PC 8, 23.0%), *Waiguan* (SJ 5, 21.3%), *Shuigou* (DU 26, 18.0%), *Yanglingquan* (GB 34, 13.1%) and *Shenshu* (BL 23, 11.4%). (7) The most commonly used manipulation method of acupoint stimulation of 20 included trials was electro-stimulation (70%). (8) A subgroup meta-analysis for heterogeneity indicated that the different manipulative methods and assessemet scales were key factors to interfere synthesis of measurement data in this study.

Conclusion: Our data suggest that AT is statistically more favorable than MT in relieving heroin withdrawal syndrome, and AT combined with MT may be more

effective in clinical application. Furthermore, AT is safe for treating patients clinically. AT therefore should be an effective and safe way for heroin detoxification. However, more trials with high quality of study design should be conducted to further verify the evidence in this study.

Keywords: Acupuncture; Heroin detoxification; Withdrawal syndrome; Meta-analysis

針刺療法治療海洛英依賴的整合性分析

摘要

背景與目的：在全球 1.3 千萬阿片類藥物濫用者中，濫用海洛因者佔了其中的 9 百萬，他們不僅帶來了愛滋病傳播等嚴重問題，因其而來的罪案及貧窮等社會開支亦較其他藥物爲高。海洛因濫用是香港及中國內地嚴重的健康及社會問題。近年來有不少隨機臨床試驗探討了針刺對海洛因戒斷的療效。本研究的目的爲：(1)對這些臨床試驗進行質量、計數及計量資料的評估；(2)評價針刺治療海洛因戒斷症狀的療效及安全性；(3)分析治療海洛因戒斷症狀最常用的穴位及針刺手法。

方法：(1)文獻檢索：通過電子資料庫、手工檢索和對入選文章的參考文獻進行引文檢索等方法收集相關臨床文獻，包括所有語種的文獻；(2) 篩選標準：選擇所有針刺治療海洛因戒斷綜合征的隨機對照臨床試驗（RCTs）；(3) 資料分析：對符合納入標準的臨床試驗採用 Jadad 計分定量評估其質量，在進行 Meta 分析時計量和計數資料分別用 WMD 或 Odd 比值及其 95% CI 表達；資料收集及評分由兩名分析人員獨立完成。

結果：(1) 按納入標準共篩選出 20 篇論文 (共報告 2134 例中 1072 例應用針刺治療)；評分結果提示 6 項臨床試驗的質量較高 (3-5 分)，其餘質量較低 (1-2 分)；主要原因包括隨機、盲法和報導失訪率等不達要求；(2) 單純針刺治療於第 2 至第 10 天在降低戒斷綜合積分上明顯優於藥物對照組 (5 trials, WMD: -17.52 (-28.69, -6.35) 至-4.83 (-8.13, -1.53); P<0.05)；HAMA 評分 (1 trial; P<0.05)；但單純針刺與藥物治療在戒斷人數上並無統計學差異 (4 trials; OR: 1.04 (0.60, 1.82); P=0.88)；(3) 針刺配合藥物治療於第 1 至第 10 天在降低戒斷綜合積分 (6 trials, WMD: -9.54 (-15.83, -3.25) 至 -2.50 (-4.48, -0.53); P<0.02) 和 HAMA 評分 (3 trials; WMD: -4.85 (-8.12, -1.58); P=0.004) 上明顯優於藥物對照組；而且在戒斷人數上也明顯優於藥物對照組 (8 trials; OR: 4.31 (2.47, 7.52); P<0.00001)；(4) 針刺配合藥物治療在復吸率方面(治療後六個月)明顯低於藥物對照組 (3 trials; OR: 0.30 (0.19, 0.46); P<0.00001)；(5) 藥物治療比針刺治療有更多不良反應；在 20 篇納入論文中，只有一篇提及針刺過程中可出現疼痛等輕微不適；(6) 分析提示臨床上最常用的 10 個穴位分別爲：內關 (75.4%)，足三裏 (57.4%)，合穀 (45.9%)，三陰交 (44.3%)，神門 (26.2%)，勞宮 (23.0%)，外關 (21.3%)，水溝 (18.0%)，陽陵泉 (13.1%)及腎俞 (11.4%)；(7) 分析提示在納入文獻中，最常用的針刺手法爲電刺激 (70%)；(8) 亞組 Meta 分析顯示，不同針刺手法和戒断症状评分量表是影響計量資料同質性的主要因素。

結論：本研究結果提示針刺治療海洛因戒斷綜合征的療效明顯優於藥物治療；而在臨床應用上又以針刺配合藥物治療爲優。針刺在海洛因戒斷治療上應爲一有效而安全的方法；然而本分析的結果尚需進一步驗證，開展高質量的臨床研究是很有必要的。

關鍵词：針刺療法，海洛因依賴，戒斷綜合征, Meta 分析

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Chapter 1. Literature review

1.1 Heroin dependence

1.1.1 General introduction

Heroin dependence is associated with significant morbidity and mortality[1, 2]. Epidemiological survey indicated that there are 13 million opiate addicts including 9 million heroin users throughout the world[3], and Eastern and Western Asia had the highest involved population[4]. Heroin dependence is a priority of health and social problems in Hong Kong. In 1998, 15,720 drug-dependent people were reported to the Central Registry of Drug Abuse. With types of drug provided, 86.3% of them were known to have abused heroin[5].

1.1.2 Impacts

1.1.2.1 Impacts on the health

Heroin depresses the activity of central nervous system (CNS) [6]. The effects may be cleared within six hours following heroin use and the subjective effects may last for four to five hours. As tolerance develops, the addicts would keep on taking the drug to avoid the withdrawal syndrome and a higher dose of heroin has to be taken for needs. Apart from the CNS, the digestive system of addicts is also upset. Constipation, hemorrhoids, peptic or duodenal ulcers would be common consequences. There is also an increased risk in heroin addicts for renal diseases and venereal diseases from contaminated needles or syringes.

The most dangerous problem of heroin abuse is the possibility of overdose or combined use of heroin with either alcohol or barbiturates. The additive effect of these components may depress respiration under life-threatening level. Both situations can be fatal. As addicts will inject the drug at sites such as the groin, temples or penis, there is a high risk of blood clots, gangrene, acquired immune deficiency syndrome (AIDS), hepatitis and venereal diseases for addicts who share contaminated needles and syringes without paying adequate attention on sterilization.

Moreover, heroin-dependent mothers will produce premature or low birth weight offspring. The babies born will also bear high risk of perinatal complications and a number of abnormalities. They may be overcome by neonatal narcotic withdrawal, hypoxia, hyperactivity or fetal death.

1.1.2.2 Impacts on the family

In a family, the harm of heroin may extend from an abuser to his/her spouse, parents, children or siblings. The relationships amongst the family members may be suffered from the drug-abusing habits of one or both partners, such as depletion of common financial resources, increased health costs, employment problems and emotional stress[7]. The sexual relationship may also be affected adversely, and affection between partners may degenerate into conflicts with possible disintegration of family unit. Parents who abuse drugs may unwittingly be setting a model, which their children will follow in the future. Children who are exposed to illicit drug consumption, production or distribution at an early age through adult contacts may be more likely to experiment themselves. Moreover, there is a serious risk of transmission of AIDS, sexually transmitted diseases (STDs) or other virus diseases to partners and children from abusers.

1.1.2.3 Impacts on the society

Heroin addicts may give burden to the society in many ways. It is costly in terms of addicts' extra expenses including losses of workplace or working time, inefficiency, and drug users are more likely than non-users to have occupational accidents, endangering themselves as well as those around them. Heroin addicts with lack of financial support may attempt to commit crime. The term "drug-related crime" is used to cover an extremely broad and complex range of offences. The first and most direct relationship is the drug law violation that includes unauthorized possession and consumption of controlled drugs, illicit cultivation and production of drugs, and sale drugs and laundering profits from these activities.

It is estimated that 80% of HIV infections seem to be related to drug injection[8]. The most common route for transmission of AIDS is through improper drug injection. It is

found that drug users by injection contribute to the highest percentage on patients who have AIDS globally. On the other hand, not only HIV, but also hepatitis, tuberculosis and STDs can be a consequence of heroin abuse that may have an even greater impact on society than HIV.

1.1.3 Withdrawal syndrome

Opioid abuse may be a milder and prodromal condition compared with that of opioid dependence. Patients that abuse opioid substances much less often than do those with dependence may do not show significant withdrawal syndrome[9]. Heroin dependence represents the higher level of drug abuse consisting of physical dependence and/or compulsive use[10].

Continuous administration of heroin leads to physical dependence and withdrawal syndrome during abstinence. Physical dependence is expected after 2-10 days of continuous use when the drug is stopped abruptly. Patients with heroin withdrawal syndrome may show: (1) Autonomic symptoms (diarrhea and rhinorrhea, nausea and emesis, etc.), (2) central nervous system arousal (sleeplessness, etc.), (3) pain (abdominal cramping, bone pains, and diffuse muscle aching, etc.), and (4) craving of drugs.

1.1.4 Treatment

Heroin withdrawal syndrome may persist to be experienced for 1-2 weeks after detoxification, but the recovery stage may last for months or years and may be depended on complex factors including medical treatment. In general, the treatment of heroin dependence is divided into two stages, a short-phase detoxification and longer-phase rehabilitation.

Heroin detoxification should be appropriately regarded as a process to achieve a safe and humane withdrawal from heroin dependence[11]. The process has been dominated by methadone in many areas including Hong Kong. In addition, there are a number of medications such as clonidine, buprenorphine, tramadol and estazolam that can relieve the withdrawal syndrome. In gerneral, commonly used Western medications

can be divided into substitutional medications (1.1.4.1) and symptomatolytic medications (1.1.4.2).

1.1.4.1 Substitutional medications

(1) Methadone

Methadone as a synthetic opioid drug occupies a prominent position in treatment of heroin dependence. Methadone possesses three properties making itself as benifit one among current medications: 1) Oral preparations are readily available that can prevent the drug injection; 2) its effect with long half-life (18-24 hours) may avoid the frequent withdrawal symptoms successfully by taking once per day only; 3) its stable effect and relative low-temptation may avoid an over-dose supply. In addition, Methadone Maintenance Treatment (MMT) may lead to some secondary benefits, for example, patients treated with MMT may reduce the activity of the illicit drug use; improve their general health, mood and personality. Methadone is commonly used to assist detoxification of heroin addicts in Hong Kong.

It was observed that MMT with a dose of more than 80 mg per day were necessary for heroin substitution. Thus, this dose was commonly used for a long term substitute in addicts with no intention to reduce. For some patients, the treatment procedure may be a gradual departure from the MMT. The term of “short term maintenance” or “maintenance-reduction treatment” is referred as the modification of MMT. On the other hand, a low-dose of methadone may reduce its side effects and particular addictive potential in patients.

However, MMT as a substitution approach is inherently controversial, in that it necessarily replaces one drug addiction with another new one and has no real equivalence for drug detoxification. There is a global trend to use lower dosage of methadone, which does not provide the “narcotic blockade”, therefore, in most cases, once a heroin addict becomes a methadone addict, they will remain so for life. The patients with MMT also contribute to a high relapse rate after detoxification. With a broader range of usage, the limitation and problems of methadone have become

increasingly apparent.

Although MMT appears to be quite safe for long term usage, methadone has significant adverse effects. The most serious direct risk of MMT is overdose, which is heightened by combined use with other drugs. Patients treated with MMT may show nausea, vomiting, dizziness, mental clouding, dysphoria, euphoria, constipation, respiratory depression, drying of respiratory secretions, sweating, biliary tract pressure increase, lymphocytosis, and increased plasma concentration of prolactin, albumin and globulins. Some adverse effects associated with methadone such as lethargy, heavy feelings in arms and legs, skin itching and other skin problems are possibly more significant than other opiates. Tolerance may develop more slowly with methadone than with morphine with respect to the depressant and sedative effects.

In summary, a prolonged use of high-dose methadone has hardly been accepted in current MMT. But the efficacy of a lower-dose “heroin-substitute” model is also far from our expectation. Alternative therapies and new medications are being sought for improvement of future clinical treatment.

(2) Buprenorphine

Buprenorphine can be seen as a substitutional medication, and it is a mix of opiate agonist-antagonist with effects to relieve withdrawal symptoms partially. It is suggested that brenorphine is safer, less addictive, and fewer interactions with other euphoriant drugs. Although buprenorphine earns strong theoretical support, it is still a rare choice in clinical practice. Clinical data indicated that buprenorphine had a lower treatment option in patients than methadone, and some patients would drop out at the maintenance phase with buprenorphine and request a return to methadone, and others continued to inject heroin or use additional benzodiazepines.

1.1.4.2 Symptomatolytic medications

(1) Clonidine

Clonidine can competitively combine with alpha-2 adrenergic receptors, and is currently approved for the treatment of hypertension officially. It is useful in the

treatment of heroin withdrawal because it acts on the noradrenergic system[12] by which some of the opiate withdrawal symptoms due to noradrenergic over-activity may be corrected. Specifically, it acts on pre-synaptic alpha-2 neurons to inhibit noradrenergic transmission. Thus, opiate withdrawal symptoms that are based on noradrenergic over-activity, such as watery eyes, running nose, sweating, diarrhea, chills and gooseflesh, can be relieved by clonidine. Although clonidine may be valuable in some inpatient treatments for the sedation and possible anti-anxiety, it is usually considered unsuitable for the treatment in community as its hypotensive and sedative effects.

(2) Tramadol

Drug addicts who cannot tolerate the side effects of anti-inflammatory drugs could sometimes take tramadol, a synthetic analgesic, to help relieving their pain. Side effects of tramadol may include dizziness, nausea, drowsiness, dry mouth, constipation, headache, or sweating[13]. In addition, chest pain, rapid heart rate, skin rash or itching, mental confusion, disorientation, seizures, tingling of the hands or feet, trouble breathing or allergic reaction may also occur in the patients after taking this medication.

(3) Estazolam

Heroin withdrawal disturbs the chemical constituents in brain, which then become unbalanced and cause insomnia or anxiety. Estazolam is a class of benzodiazepines, and is used to induce sleep and relaxation. However, it also causes side effects like drowsiness, dizziness, or clumsiness, depression, nausea, vomiting, diarrhea, or constipation, difficulty in urination, vivid dreams, headache, dry mouth, or changes in behavior[14].

In summary, although symptomatolytic medications used in treating drug withdrawals do not cause “new drug dependence”, they only relieve some of the withdrawal symptoms and do not treat the underlying pathology. Therefore, searching for safer and more effective therapies remains one of the most important research targets in this field.

1.1.4.3 Other therapies

Besides these medications, psychological therapy, etc., many clinical experiences of traditional Chinese medicine for heroin detoxification were accumulated by long term clinical practice. Based on Chinese medicine theory, acupuncture therapy (AT), Chinese herbal therapy and *Qigong* therapy could be applied for treating drug dependence at any stage. In recent years, more and more data of clinical trials, laboratory studies, review papers and patent files were published. The recent brief progress in the application of AT will be reviewed below.

1.2 Acupuncture therapy

Since early 1970's, Dr. H.L. Wen in Hong Kong at the first time treated heroin dependence with auricular-acupuncture successfully, AT has been widely used for drug detoxification in many countries. In recent years, more and more clinical studies have been conducted to examine the efficacy and safety of acupuncture for heroin addicts[15]. In our review, there are 81 papers (clinical trials and case reports) related to clinical application of acupuncture in the treatment of heroin dependence were published in Mainland China.

1.2.1 Clinical trials

There were 59 clinical trials published in Mainland China as well as in other countries from 1974 to 2005, and about 4526 cases that treated by acupuncture for heroin dependence were reported in the papers. The data showed that: (1) Acupuncture had a rapid and reliable therapeutic effect for heroin detoxicification[E1-E4], and acupuncture was effective with no-side effects and lower cost in treatment of patients[E5]; (2) acupuncture combined with methadone caused significantly reduce heroin withdrawal syndrome[E6]; (3) auricular acupuncture was also effective for heroin withdrawal[E7, E8]; (4) both acupuncture and Chinese medicine had therapeutic effects on heroin addiction and acupuncture showed a better effect than Chinese medicine[E9]; (5) acupuncture on acupoints of *Du Mai* had a significant therapeutic effect on heroin

withdrawal syndrome[E10]; (6) electro-stimulation was one of the effective methods in relieving the withdrawal syndrome in heroin addicts[E11-E14]; (7) acupuncture had the potentiality of preventing relapse and could be used for treating the protracted withdrawal syndrome and psychic dependence during the period of abstinence and rehabilitation[E13, E15-E18].

1.2.2 Case reports

There were 22 case reports published in Mainland China from 1974 to 2003, and about 1076 cases that were treated by acupuncture for heroin dependence were reported in the papers (Please see the Appendix 6B Non-clinical trials: case reports for more details). These case reports consist of the treatment of a group patients or treatment of a single patient. The data indicated that acupuncture had a therapeutic benefit for treating withdrawal syndrome and reducing relapse rate of heroin dependence similar to the clinical trials.

In summary, the data of clinical trials and case reports published indicated that acupuncture had a therapeutic benefit for treating withdrawal syndrome and reducing relapse rate of heroin dependence. However, these benefits were not well organized. According to the pyramid of evidence[16], in order to confirm efficacy and safety of acupuncture in clinical practice, the highest standard of clinical evidence from systematic review and meta-analysis is needed.

1.3 Evidence-based medicine

1.3.1 General introduction

Evidence-based medicine (EBM) can provide the highest standard evidence (current best evidence) for clinical application. EBM has been defined as: “an approach to practice medicine in which the clinician is aware of the evidence in support of clinical practice, and the strength of the evidence.” (Evidence Based Medicine Working Group). According to the Oxford center of evidence-based medicine, there are six levels of evidence that can be obtained from the data of clinical practice. (Please see the

Appendix 1 Level of evidence for more details). EBM is the practice of making medical decisions through the judicious identification, evaluation, and application of the most relevant information[17]. EBM is a process of life-long, problem-based learning. The process involves:

(1) Converting information needs into focused questions

(2) Efficiently tracking down the best evidence with which to answer the questions

(3) Critically appraising the evidence for validity and clinical usefulness

(4) Applying the results in clinical practice

(5) Evaluating performance of the evidence in clinical application

The EBM helps the health-care providers and consumers to keep up with the update literature and current best evidence. The primary research literatures can be synthesized, filtered and evaluated to generate current best evidence by systematic review and meta-analysis.

1.3.2 Systematic review and meta-analysis

Systematic review is an evidence-based qualitative process with thorough defining the questions, searching for literatures, assessing the quality of included clinical trials, applying eligible criteria, examining and comparing the included eligible trials, and conducting statistical synthesis of the data. Meta-analysis may be a part of systematic review when individual trials have similarity with each other and can be integrated for further estimate by which the data are combined statistically to yield a quantitative analysis on the size of the treatment effect and a test of homogeneity in the estimate of effect size.

According to the principles of EBM, systematic reviews are carried out to generate answers for clinical questions. It should be as carefully planned like any other research project as possible, with a detailed written protocol prepared in advance. The outcome of systematic review and meta-analysis is regarded as the most reliable clinical evidence currently. Its reliability can be higher than that of randomized controlled

clinical trials, cohort studies, controlled clinical trials, case reports, case series, editorial opinions, animal researches and *in-vitro* researches.

The concept and method of EBM have been popularly practiced in Western medicine. It is reported that the number of articles about systematic review and meta-analysis has grown exponentially, from one in 1992 to about 1000 in 1998[18]. Moreover, international interest has led to the development of six journals on EBM (up to six languages) that summarize many relevant data of clinical studies with systematic review and meta-analysis.

1.3.3 Systematic review on opioid detoxification

Growing et al. have conducted Cochrane reviews related to the management of opioid withdrawal in recent years. They analyzed the effectiveness of alpha-2 adrenergic agonists (clonidien, lofexidine, guanfacine, guanabenz acetate) in the management of opioid withdrawal, and concluded that (1) no significant difference in efficacy was detected between clonidine and lofexidine, (2) participants stayed in methadone treatment with longer retention and less adverse effects, (3) a lower incidence of hypotension in lofexidine treatment hinted it was more suitable than clonidine to be used in outpatients, (4) there were insufficient data available to support the efficacy of other alpha-2 adrenergic agonists[19]. In the second review, Gowing et al. reported that the use of opioid antagonists combined with alpha-2 adrenergic agonists might be feasible for patient detoxification[20].

In addition, meta-analysis has been done to assess the administration of opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal[21]. The results demonstrated that more research evidence would be needed before any conclusion could be drawn regarding the effectiveness of opioid antagonists under heavy sedation or anesthesia. The risk of vomiting during sedation, respiratory depression and cardiac irregularities might be the limitation of approach, and its risks and benefits remained uncertain. To assess the effectiveness of interventions involving the short term use of buprenorphine to manage the acute phase of opioid withdrawal, a meta-analysis was

demonstrated that buprenorphone was a potential medication to ameliorate the signs and symptoms of withdrawal from heroin[22].

1.3.4 EBM and acupuncture

Systematic review and meta-analysis can offer the highest standard and the most important information of clinical trials. To raise the power, it is valuable to identify the quality of trials with the principles and measurements of EBM. The outcome of systematical review and meta-analysis on clinical trials of Chinese medicine will be very helpful not only for designing high quality trials but also for making health policy. It is a bright future for developing the Evidence-based Chinese medicine[23].

Based on current databases including Cochrane Library, Medline, PubMed, CBMdisc etc., there are 25 systematic reviews and meta-analysis involving acupuncture that have been published so far. The distribution of these 25 systematic reviews and meta-analysis published showed that most of them were focused on pain-related management. One report reviewed auricular acupuncture for cocaine dependence and one report from the Cochrane Drug and Alcohol Abuse Group reviewed acupuncture for smoking cessation. However, there is no systematic review focused on acupuncture in treatment of heroin dependence. It is very valuable to fill this blank.

1.4 Aims of study

Heroin abuse associated with high risks of premature fetal death from drug overdose, violence and AIDS is a serious health and social problem in Hong Kong as well as other areas. So far MMT and other Western medications have significant limitations in clinical practice, and searching for alternative safe and effective therapies for abusers remains one of hot research targets in this field. Acupuncture has been used in the treatment of heroin dependence since 1972, and many clinical trials on acupuncture had been conducted during the last 30 years and claimed to be effective. In view of that there is no systematical review and meta-analysis on acupuncture treatment of heroin withdrawal syndrome, it is valuable for us to fill this blank by identifying the quality of

clinical trials, efficacy and safety of acupuncture based on the principles and measurement of EBM. This project at the first time aimed at:

(1) Assessing the quality of trials on acupuncture treatment for heroin dependence by reviewing all available research data,

(2) Evaluating the efficacy and safety of acupuncture by comparing acupuncture with other therapies, and

(3) Identifying the most commonly used acupoints and manipulation methods.

Chapter 2. Methods

2.1 Procedures

There are five steps[24] in performing a systematic review and meta-analysis:

Step 1: Framing questions

A structured approach to frame questions is to use the four components or factors including the population, intervention (or exposures), outcome (related to the problem posed in the review) and design. It is important to consider carefully the above four items for the framing process. Participants are a group of population among whom evidence is being sought in our review. Intervention is the action or alternative being considered for the population. Outcome is a measure of what the population wants to achieve from the intervention. Finally, our study will be designed to examine the effect of intervention.

Step 2: Identifying relevant literature

Thorough identification of the relevant literature is a crucial condition for a systematic review. It is driven by the desire to capture as many relevant studies as possible. A comprehensive literature search includes multistage and iterative processes. Relevant resources (e.g. electronic bibliographic databases, relevant journals, etc.) for primary and review articles will be screened, and full manuscripts of all potentially trials will be collected. Some papers will provide reference lists from which we may find more valuable citations, and the cycle of obtaining manuscripts and finding more references will go one more round. These processes will eventually lead to a set of inclusion/exclution criteria by which the review will be based on.

Step 3: Assessing study quality

The study quality may be defined as the levels to minimize bias and errors in its design, conduct and analysis. This approach helps to crudely define the weakest acceptable trials and to exclude some lower-quality trials. Once trials with a minimum acceptable quality can be selected, an in-depth critical appraisal will allow us to assess

the quality of the evidence in a more refined way.

Step 4: Summarizing the evidence

In a deeper exploration and analysis for which the findings need to be presented in a clear way, the effects of intervention and its consistence among the included trials will be evaluated. A meta-analysis may be performed to assess the combined individual effects if it is feasible and appropriate. These analyses allow us to generate meaningful conclusions from the reviews.

Step 5: Interpreting the findings

The validity of the main findings related to various populations, interventions and outcomes within the review should then be considered, and it will depend on the strength and weakness of the review such as:

(1) Are the searches adequate?

(2) Is there a risk of biases?

(3) Is the quality of included studies high enough?

(4) Are the observed clinical effects substantial, not just statistically significant?

The above steps will be conducted by following the standard format of systematic review and mata-analyisis recommended from the Cochrane Collaboration, by which we should be able to generate inferences and recommendations for clinical practitioners as well as researchers.

2.2 Inclusive and exclusive criteria

2.2.1 Types of studies

In this study, all randomized controlled trials (RCTs) and quasi-randomized controlled trials including controlled clinical trials (CCTs) were collected. But other clinical studies such as case reports were excluded. Only studies comparing the efficacy or safety of AT with medications were included. The studies for comparing the effect of acupuncture plus medicine versus medicine were also included.

In this project, AT is defined as stimulation on acupoints with any manipulation

methods. The acupoints and manipulations, drug types and doses and patients' characteristics in each included study were required in details. The nature of withdrawal signs and symptoms experienced was also required in details. In addition, the data of adverse effects were needed.

2.2.2 Types of participants

All inpatients and outpatients who were heroin addicts in the acute stage of abstinent symptom were considered as participants. No distinction was made between addicts dependent on heroin alone or on heroin plus other drugs. There was no restriction on age or gender.

2.2.3 Types of interventions

AT as the principle intervention for treatment group included any stimulation on any acupoint by any manipulation method to manage the signs and symptoms of opioid withdrawal syndrome. The control group was treated with any medication therapy (MT). Trials on AT in conjunction with MT (AT plus MT) versus MT alone will also be involved. Trials with Chinese herbal therapy were excluded as this project aims to study the effect of AT rather than Chinese herbal therapy, which may otherwise cause heterogeneity in datum synthesis of meta-analysis.

2.2.4 Types of outcome measures

The outcome included measures of efficacy and safety that was based on patients' withdrawal syndrome score (WSS, the abstinence syndrome intensity was assessed by special scale systems such as the Himmelbach's point system and the Clinical Institute Narcotic Assessment (CINA) system), HAMA score, patients' detoxicated number (PDN, the number of patients who were detoxicated successfully after treatment), relapse rate and incidence of adverse effects.

2.3 Search strategy

A search strategy was designed to retrieve all the literatures of relevant clinical trials by electronic searching, hand searching and additional searching regardless of language

and publication status (published, unpublished, in press, and in progress). The general structure of the search strategy was “heroin” and “acupuncture”, and their synonyms were applied as keywords. The following keywords as free-text search terms that involved combined terms such as heroin dependence, heroin addiction, heroin abuse, heroin detoxification, withdrawal syndrome, acupuncture therapy, electroacupuncture, auricular needle, auricular acupuncture, ear acupuncture, acupoint stimulation were used.

2.3.1 Electronic searching

The electronic databases including the Database of Chinese Science Journals, the Database of Chinese Journals of TCM, the Database of Chinese Biomedical Literatures (CBMdisc), the Database of Chinese New Medications, Cochrane Library, MEDLINE, EMBASE, BIOSIS, CINAHL, World Cat and Article first were searched from their date of commencement to 2005.

2.3.2 Hand searching

New papers in journals from January of 2005 to the latest copies, the reference lists of retrieved studies, reviews and conference abstracts were searched by hand in the Chinese Medicine Library of Hong Kong Baptist University and the universities in Mainland China.

2.3.3 Additional searching

The National Institute for Drug Addiction Website, the National Clearinghouse for Alcohol and Drug Information, the European Monitoring Center for Drugs and Drug Addiction, the Journal of the American Academy of Child and Adolescent Psychiatry were also searched. In addition, pharmaceutical industries, organizations (including WHO) and individual researchers working in this field will be contacted in order to obtain additional references such as unpublished trials, ongoing trials, confidential reports and raw data of published trials.

2.4 Datum analysis

2.4.1 Study selection

By being read the titles, abstracts or introduction of articles, each paper from the search strategy was assessed and extracted by two independent reviewers for eligible trials according to the inclusion and exclusion criteria stated in the section 2.2 Inclusive and exclusive criteria. For duplicated or doubled studies in different publications, only the latest versions were included. Missing information was sought by contacting study authors of the papers.

2.4.2 Data collection and quality assessment

Key information was extracted by one reviewer and confirmed by another reviewer. A data extraction form was used to summarize key information (Please see the Appendix 2. Data Extraction Form for the details). The methodological quality of the included trials that met the inclusion criteria was assessed using the guidelines for quality assessment of trials developed by the Cochrane Collaboration and the Jadad's scale. In summary, these regulations rate controlled trials as follows:

(1) The Cochrane Collaboration[25]:

1) Controlled clinical trials mentioned as "randomized allocation" (RCT)

2) Controlled clinical trials did not mention any "randomized allocation" (CCT)

(2) The Jadad's scale[26]:

1) Randomization (Is the trial randomized?)

2) Double-blinding (Is the trial double blinded?)

3) Description of withdrawal (Is there a description of withdrawals?)

4) Description of randomization (Is the randomization adequately described with random numbers generation or no description but random method mentioned?)

5) Description of blinding (Is the blindness adequately described?)

Adequate for participants and assessment of outcomes or unclear for participants or in outcome assessment

The Jadad's scale would award 1-5 points to a RCT or CCT. Trials with 1 or 2

points would be considered as low quality. While trials scored 3-5 points would be considered as high quality. Two independent reviewers assessed the methodological quality. Any disagreement was resolved by discussions of all reviewers.

2.4.3 Data synthesis and analysis (meta-analysis)

After the main results had been summarized, data from individual trials were combined for meta-analysis when the interventions were sufficiently similar. Category data (C-data) were presented as the odd ratio (OR) and 95% confidence interval (95% CI) and measurement data (M-data) were presented as the weight mean difference (WMD) and 95% CI. The analyses were carried out using Meta View 4.2 in Review Manager 4.2 provided by the Cochrane Collaboration.

Considering different manipulation methods and western medications in control groups might present, a fixed effect model would be firstly used. If heterogeneity presented, a random effect model would be used. If heterogeneity still presented, a subgroup analysis would be performed to investigate the relative factors of heterogeneity.

2.4.4 Statistical analysis

Other than combined effect size of C-data and/or M-data were compared between treatment group (AT alone or AT plus MT) and control group (MT), the statistical analysis on combine validity of included trials would be assessed by examining the homogeneity of outcomes from various trials using a Q-test (Mantel-Haenszel Chi-square test). Possible sources of heterogeneity would be assessed by sensitivity and subgroup analysis as described below. A graphical analysis (Forset plot) could be yielded by the Review Manager 4.2.

The outcome of meta-analysis should be represented and interpreted by the Forest plot. For unfavorable outcome like mortality or disability rate, the summary estimate point in the plot would trend towards treatment group. Vice versa, for favorable outcomes, the summary estimate point would trend towards control group. Thus, if

acupuncture was in superior in relief of withdrawal syndrome when compared with medications, the summary estimate point should favor the group treated by AT but trend towards control group. Therefore, readers were recommended to read the plot carefully in order to avoid wrong understanding[27].

2.4.5 Subgroup analysis

If a sufficient number of included trials can be identified, the following subgroup analysis would be performed to explore effect size differences: (1) Differences in control interventions (acupuncture versus different medications); (2) differences in treatment interventions (each acupoint or acupoint plus with different medications); (3) differences scoring in Jadad's scale (low-quality trials versus high-quality trials); etc.

2.4.6 Sensitivity analysis

A sensitivity analysis should be carried out to determine if the findings from the primary analysis are changed by incorporating different trials in the analysis. This would be done by varying the inclusion criteria and repeating the analysis with the new data set. If a sufficient number of randomized trials are identified, sensitivity analysis would be performed to explore the influence of trial quality on effect estimates.

We will perform sensitivity analysis in order to explore the influence of the following factors on effect size: (1) Repeating the analysis excluding unpublished studies (if there was any); (2) repeating the analysis taking account of study quality, as specified above; (3) repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding, etc.

2.4.7 Result presentation

The data in figures and tables obtained from systematic review and meta-analyses (Appendix 3. Characteristics of include trials and Appendix 5. Characteristics of excluded trials) would follow the reporting format recommended from the Cochrane Collaboration. Please note that there are two reference systems in this review: the references in Appendix 2. (References to studies included) and Appendix 6. (References to studies excluded).

Furthmore, please see following website for understanding the detail methodology of systematic review and meta-analysis including standard and procedure, estimation method, data management, statistical model and formula, etc. provided by the Cocrahne Library:

http://www.cochrane.org/resources/training.htm .

Chapter 3. Results

3.1 Description of studies

3.1.1 Collected papers

By literature searching process we collected 114 papers involving the use of acupuncture for treating heroin withdrawal syndrome. Most of the papers were published in Mainland China.

3.1.2 Excluded trials

94 trials did not meet the criteria for inclusion and thereby excluded in this review (Please see the section 2.2 Inclusive and exclusive criteria for more details). The reasons for exclusion were: (1) non-clinical reports and reviews (33 trials), (2) case reports (22 trials), (3) patients in the non-acute stage (9 trials), (4) insufficient outcome data (18 trials) and (5) non-medical control trials (12 trials).

3.1.3 Included trials

A total of 20 control trials matched the inclusion criteria were identified. 18 trials (90%) were undertaken in Mainland China and the rest 2 trials (10%), were undertaken in Malta (Jin Tao 2002 and Chen Li 2005).

(1) Participants

A total of 2134 participants were involved in 20 included trials. The group size of 20 included trials ranged from 20 to 111 participants. Sexual distribution was reported in 19 trials (95%), consisted of 77.8% male and 22.2% female participants. Participant's mean-age was reported by 14 trials (70%), which was 28.7 years old. Mean drug addiction period was mentioned by 12 trials (60%) which was 44.2 months. 12 trials (60%) reported the mode of heroin administration, with 42.6% of participants used heroin through snoring, 30.2% of participants by intravenous injection, 21.4% of participants by intramuscular injection and 5.8% of participants through smoke. In addition, about 9.4% participants used heroin by either intravenous or snoring, and some participants through more than two routes.

(2) Treatment

All treatments were provided on an inpatient basis. The treatment in 12 trials (60%) occurred in the hospitals, while treatment in 7 trials (35%) occurred in drug treatment centers. There was one trial conducted by Si Xiaoming in which the place of treatment was not mentioned. The use of electro-stimulation into acupoints was the most common form in patients' treatment. Other treatment forms include insertion of needles, moxibustion on acupoints, etc. The scheduled duration of treatment was 9 days or less in 3 trials (15%), more than 10 days in 13 trials (65%), and greater than 20 days in 2 trials (10%). Two trials (10%) did not mention the treatment duration of trials.

To compare AT with MT, most trials used methadone as controls (11 trials, 55%). Other control treatments include clonidine, diazepam, buprenorphine, lofexidine, and other symptomatolyic medications. No placebo control was applied in the 20 included trials.

3.2 Outcome measurement

1. Withdrawal-symptom score (WSS): 15 out of 20 included trials (75%) provided the WSS. 1072 participants (50.2%) were treated with acupuncture including 436 patients (40.7%) using acupuncture alone and 636 patients (59.3%) using acupuncture plus medications, while 1062 participants (49.8%) were treated with medications alone.

2. PDN: 12 out of 20 included trials (60%) provided the PDN. 614 participants (50.2%) were treated with acupuncture including 218 patients (35.5%) using acupuncture alone and 396 patients (64.5%) using acupuncture plus medications, while 608 participants (49.8%) were treated with medications alone.

3. Scores of anxiety (HAMA score): 4 trials (20%) reported the scores of anxiety including one trial applying acupuncture alone and 3 trials applying acupuncture plus medications.

4. Incidence of adverse effect: 2 trials (10%) reported the incidence of adverse

syndrome including one trial applying acupuncture alone and one trial applying acupuncture plus medications.

5. Long term follow-up (relapse rate): 3 trials (15%) reported the relapse rate in 6-month follow-up investigations.

3.3 Quality assessment

The assessment by Jadad's scale showed that 6 trials (Wu Liuzen 2001, Song Xiaoge 2002, Zeng Xiangling 2004, Zhang Pinggen 2004, Wen Tunqing 2005, He Jeling 2005) were classified as high-quality trials (3-5 points, 30%), and the other 14 trials (Liu Dinglu 1995, Liu Min 1997, Zhang Xiefang 1998, Wang Zetao 1999-1, Zhuang Yiqing 1999, Wang Zetao 1999-2, Tang Songying 2000, Zong Lei 2001, Yang Tao 2001, Jin Tao 2002, Si Xiaoming 2004, Rong Jun 2005, Wang Zetao 2005, Chen Li 2005) were low-quality trials (1-2 points, 70%)**.**

3.4 Efficacy and safety assessment

According to the study design of included trials, research data on efficacy and safety were subdivided into two parts reflecting the treatment strategies applied: (1) Comparison of AT with MT (3.4.1), and (2) comparison of AT plus MT with MT (3.4.2).

In 20 included trials all clinical outcomes were assessed and analyzed by doctors or researchers (not by patients themselves). In six trials (30%) the withdrawal severity was assessed by different self-developed assessment scales, and the withdrawal severity was assessed by using Clinical Institute Narcotic Assessment Scale (CINA Scale) by Si Xiaoming, Zeng Xiangling, Zhang Xiefang, Wen Tunqing and Liu Dinglu, or using Hamilton Anxiety Scale (HAMA Scale) by Wu Liuzhen, Wen Tunqing, Song xiaoge and Chen Li, or using Hamilton Depression Rating Scale (HAMD Scale) by Wu Liuzhen, or using others (Himmelsbach, OWS, etc.) by Zong Lei, Zhang Pinggen, Rongjun, Yang Tao and He Jieling.

3.4.1 AT vs. MT

Eight out of 20 included trials (40%) compared the therapeutic effects of AT alone with MT on heroin withdrawal syndrome. Five trials in them provided the WSS, and four trials provided the PDN after intervention. Only one trial which was done by Zhang Xuefang provided both WSS and PDN after intervention.

3.4.1.1 Abstinence symptoms (meta-analysis)

(1) WSS (M-data)

By using the random effect model, Fig. 1 showed a meta-analysis on the combined effects of 5 included trials that involved 5 to 7 comparisons and 198 to 528 patients at different timepoints from Day 1 to Day 10. On Day 1, the combined effects of 7 comparisons that involved 528 patients showed that AT efficacy was similar to that of MT (5 trials, WMD=-0.98, 95% CI: -2.93, 0.97, P=0.33). However, the AT efficacy was statistically significantly higher than that of MT on Day 2 to Day 10 (P<0.05).

On the Day 1, there was no heterogeneity presented statistically in the combined effects of 7 comparisons. However, on Day 2 to Day 10, a heterogeneity presented in the datum synthesis of comparisons (P<0.05). In the further subgroup analysis that 5 trials (Si Xiaoming 2004, Yang Tao 2001, Zhang Xuefang 1998, Zong Lei 2001 and Wen Tunqing 2005) or 4 trials (Si Xiaoming's trial was further excluded as its intervention did not include the insertion of needles into acupoints) or 3 trials (Yang Tao's trial was further excluded as auricular acupuncture was performed) or 2 trials (Zhang Xiefang's trial was further excluded as electric current was applied into the acupoints) were respectively combined on Day 2 to Day 10, the heterogeneity showed at different timepoints were gradually reduced as the combined trials that with different manipulations were reduced one by one. The results indicated that manipulation methods might play a key role in heterogeneity of combined data.

Furthermore, for testing the role of different assessment scales in heterogeneity occurrence of datum synthesis, a subgroup analysis involued above 5 trials (Si Xiaoming 2004, Yang Tao 2001, Zhang Xuefang 1998, Zong Lei 2001 and Wen

Tunqing 2005) was recombined by the scale types. The result of combining Yang Tao's data with Zong Lei's data (the Himmelsbach scale was used only in both trials) showed that the heterogeneity disappeared on the Day 1-4 or was reduced on other timepoints. It demonstrated that assessment scales might also be a key factor to cause heterogeneity of combined data.

(2) PDN (C-data)

By using the fixed effect model, Fig. 2 showed a meta-analysis on the combined effects of 4 included trials that 432 patients were involved. The result indicated that 194 out of 218 patients (89%) received AT showed a significant improvement in heroin withdrawal syndrome, while 186 out of 214 patients (87%) received MT also showed a significant improvement. There was not statistically significant difference between these two groups (4 trials, OR=-1.04, 95% CI: 0.60, 1.82, P=0.88). There was not heterogeneity (P>0.05) for the C-data synthesis in these 4 trials.

3.4.1.2 Anxiety

There was only one included trial to compare the efficacy of AT with MT by HAMA Scale (Wen Tunqing 2005). It reported that AT was more effective than MT after a 10-day treatment (P<0.05).

3.4.1.3 Adverse effects

Five trials (62.5%) did not report any adverse effect in participants treated by AT or MT (Yang Tao 2001, Liu Dinglu 1995, Zong Lei 2001, Si Xiaoming 2004 and Wen Tunqing 2005). In 3 included trials (37.5%), Liu Min, Zhang Xiefang and Tang Songying reported that there was no adverse effect in patients treated by acupuncture. However, one trial (12.5%) reported the side effects of clonidine treatment. The data showed that 37% patients experienced dizziness, nausea, vomiting, sweating, palpitation, dry mouth, poor sleeping quality and fatigue, and 7.1% patients showed abnormal ECG and 3.5% patients showed abnormal GPT after receiving clonidine treatment (Zhang Xiefang 1998).

3.4.1.4 Long term follow-up

In these 8 included trials there was no trial that reported long term effect of AT or MT treatment on heroin withdrawal syndrome.

3.4.2 AT plus MT vs. MT

Fourteen trials including 2 trials (Yang Tao 2001 and Zong Lei 2001) that were analyzed in the above section (3.4.1 AT vs. MT) out of the 20 included trials (70%) investigated therapeutic effects of AT plus MT on heroin withdrawal syndrome by a comparison between AT plus MT and MT alone. Seven trials in them could provide the WSS after intervention, and 8 trials could provide the PDN after intervention.

3.4.2.1 Abstinence symptoms (meta-analysis)

(1) WSS (M-data):

By using the random effect model, Fig. 3 showed a meta-analysis on the combined effects of 7 included trials that involved 5 to 7 comparisons and 249 to 405 patients at different timepoints from Day 1 to Day 10.

On the Day 1, 3, 5, 7, 9 and 10, combined data of 5 comparisons that 249 to 271 patients were involved showed that the AT plus MT was significantly more effective than that of MT alone (WMD=-6.91, 95% CI: -12.88, -0.95, P=0.02 on the Day 1; WMD=-7.32, 95% CI: -12.76, -1.87, P=0.008 on the Day 3; WMD=-8.73, 95% CI: -15.18, -2.28, P=0.008 on the Day 5; WMD=-9.54, 95% CI: -15.83, -3.25, P=0.003 on the Day 7; WMD=-8.32, 95% CI: -13.91, -2.73, P=0.004 on the Day 9; and WMD=-7.12, 95% CI: -10.60, -3.64, P<0.0001).

On the Day 2, 4, 6 and 8, combined data of 7 comparisons (from 6 trials) that 405 patients were involved also showed that the AT plus MT was significantly more effective than that of MT alone (WMD=-2.50, 95% CI: -4.48, -0.53, P=0.01 on the Day 2; WMD=-3.23, 95% CI: -5.56, -0.91, P=0.006 on the Day 4; WMD=-5.83, 95% CI: -8.79, -2.87, P=0.0001 on the Day 6; WMD=-5.70, 95% CI: -8.60, -2.80, P=0.0001 on the Day 8).

Because an obvious heterogeneity presented in all above analysis from the Day 1 to

Day 10, the significancy of different medication catogeries as controls in included trials was assessed by a subgroup meta-analysis. The data indicated a significant heterogeneity that presented in all analysis when 6 trials (Zong Lei 2001, Yang Tao 2001, Zhang Pinggen 2004, Zeng Xiangling 2004, Rong Jun 2005 and He Jieling 2005) were combined from the Day 1 to 10. Thus, in a further subgroup analysis only 4 included trials that used methadone as a control (Yang Tao and Zong Lei's trials were excluded as other medications were used) were combined on the Day 1 to 10, but a significant heterogeneity still presented in the results. It demonstrated that different medication types used as controls in the trials would not be a major factor for causing heterogeneity in our datum synthesis.

(2) PDN (C-data):

By using the fixed effect model, Fig. 4 showed a mata-analysis on the combined effect of 8 included trials that 790 patients were involved. The result indicated that 378 out of 396 patients (95.5%) received AT plus MT showed a significant improvement in heroin withdrawal syndrome, while 332 out of 394 patients (84.3%) received MT showed a significant improvement. There was a statistically significant difference between these two groups (8 trials, OR=4.31, 95% CI: 2.47, 7.52, P<0.00001). There was not heterogeneity (P>0.05) for the C-data synthesis in these 8 trials.

3.4.2.2 Anxiety (meta-analysis)

By using the random effect model, Fig. 5 showed a meta-analysis of 3 included trials (Wu Liuzen 2001, Song Xiaoge 2002 and Chen Li 2005) that involved 165 participants indicated that AT plus MT was more effective in relieving anxiety than MT statistically (3 trials; WMD: -4.85, 95% CI: -8.12, -1.58; P=0.004). However, a heterogeneity (P=0.002) presented in the result.

3.4.2.3 Adverse effects

Ten out of twelve trials (83.3%) did not report any adverse effect in participants treated by AT plus MT or MT alone. Zhuang Yiqing (8.3%) reported that there was no adverse effect caused by AT plus MT in participants. Zhang Pingen (8.3%) reported that

some patients receiving electroacupuncture might experience local muscle spasm and pain that might disappear by adjusting intensity of electroacupuncture, while methadone might cause nausea and vomitting in 8 patients (18.6%), sweating, dilated pupils and burred vision in 6 paients (14.0%), breathing inhibition (10 breaths/min) in 5 patients (11.6%), and hallucination in 2 patients (4.7%).

3.4.2.4 Long term follow-up (meta-analysis)

Three trials (23.1%) reported long term effects of treatments on heroin withdrawal syndrome (Wang Zetao 1999-1, Wang Zetao 1999-2, Wang Zetao 2005). By using the fixed effect model, Fig. 6 showed a meta-analysis on the combined effects of 3 included trials that 380 patients were involved. The result indicated in a 6-month follow-up investigation after treatment, the relapse rate was 28.1% (62 patients) in 220 patients treated by AT plus MT, while was 56.9% (91 patients) in 160 patients treated by MT alone. The difference between the two groups was statistically significant (3 trials, OR=0.30, 95% CI: 0.19, 0.46, P<0.00001). The test for the data synthesis did not show any heterogeneity (P>0.05). It indicated that AT might be more benefitial than MT in avoiding relapse of heroin dependence after detoxification.

3.5 Acupuncture analysis

3.5.1 Acupoints

3.5.1.1 Commonly used channels

In the 20 included trials, where 34 body acupoints were used, 4 acupoints (11.8%) were extraordinary points. The remaining 30 acupoints were distributed in the 14 channels except on the Lung Channel and the Small Intestine Channel. The three channels from which most of the acupoints come from were *Du Mai* (*Du* Channel, 23.5%), Urinary Bladder Channel (14.7%) and *Ren Mai* (*Ren* Channel, 8.8%).

3.5.1.2 Distribution of acupoints

In the 20 included trials, body acupuncture was used in 17 trials (85.0%), auricular acupuncture was used in 5 trials (25.0%) and, scalp and head acupuncture were used in

7 trials (35.0%). Scalp and head acupuncture were used together with body acupuncture by Wang Zetao 1999-1, 2, Zong Lei, Zhang Pinggen, Zeng Xiangling and Rong Jun (6 trials, 30%). Body acupuncture and auricular acupuncture were used together in 3 trials (15.0%) by Yang Tao, Chen Li and Zhuang Yi Qing. Only one trial of Yang Tao (5%) used body acupuncture, auricular acupuncture and scalp and head acupuncture together. While auricular acupuncture was used alone in 3 trials (15%) by Jin Tao, Wang Zetao 2005 and He Jieling and body acupuncture was used alone in 8 trials (40%).

A total of 64 acupoints were used in the 20 included trials. There were 34 body acupoints (53.1%), 18 auricular acupoints (28.1%) and 12 head and scalp acupoints (18.8%).

3.5.1.3 Commonly used body acupoints

In the 20 included trials, a total of 34 total acupoints were used by 17 trials. The 10 most commonly used acupoints in total acupoints reported were *Neiguan* (PC 6, 75%), *Zusanli* (ST 36, 60%), *Hegu* (LI 4, 55%), *Sanyinjiao* (SP 6, 50%), *Laogong* (PC 8, 30%), *Shenmen* (HT 7, 25%), *Waiguan* (SJ 5, 25%), *Shenshu* (BL 23, 20%), *Baihui* (DU 20, 15%), and *Dazhui* (DU 14, 15%).

Commonly used body acupoints were further analysed from both the included and excluded trials in a larger sample size. Thus, acupoints from 60 published clinical trials were analysed and the 10 most commonly used acupoints were *Neiguan* (PC 6, 75.4%), *Zusanli* (ST 36, 57.4%), *Hegu* (LI 4, 45.9%), *Sanyinjiao* (SP 6, 44.3%), *Shenmen* (HT 7, 26.2%), *Laogong* (PC 8, 23.0%), *Waiguan* (SJ 5, 21.3%), *Shuigou* (DU 26, 18.0%), *Yanglingquan* (GB 34, 13.1%) and *Shenshu* (BL 23, 11.4%).

3.5.1.4 Commonly used auricular acupoints

Auricular acupuncture was used in 6 the included trials (30%) with stimulation on auricular points such as Liver, Kidney, Endocrine, Lung, Heart, Brainstem, *Shenmen*, Small Intestine, Stomach, Spleen, Sympathetic, Urinary Bladder, Sacral Spine and Opccipital. In two trials, Zhuang Yiqing and He Jieling applied electricity to stimulate the auricular acupoints (33.3%), Wang Zetao and Chen Li appled auricular plaster (王不

留行籽) on auricular points (33.3%), Yang Tao embedded 0.3 cm soft-needles into auricular points (16.7%) and Jin Tao vertically inserted 0.5 inch needles (needles of the No. 32) into selected auricular points for stimulation (16.7%).

3.5.2 Manipulation methods

3.5.2.1 Duration of stimulation

For acupuncture stimulation in the 20 included trials, needles were retained in the body for 15 to 60 minutes, with the most of trials (7 trials, 35%) retained needles in body for 30 minutes. One trial (5%) did not mention clearly the stimulation time (Wu Liuzhen 2001).

The time course for treatment program in the 20 included trials was ranged from 7 days to one month, with the most of trials (9 trials, 45%) kept treatment and observation for 10 days. Two trials (10%) did not mention clearly the time course of treatmrnt program (Liu Dinglu 1995 and Chen Li 2005).

3.5.2.2 Electro-stimulation

Electro-stimulation was used in 12 out of 20 included trials (60%). Eight trials (40%) reported that the frequency (in Hz) from 2 to 100 Hz was used for stimulation during treatment. Five trials (25%) applied 2/100 Hz (Zhang Xiefang 1998, Wu Liuzhen 2001, Yang Tao 2001, Si Xiaoming 2004 and Rong Jun 2005). Four trials (20%) reported that the electric current 10 to 30 mA was used during treatment (Liu Dinglu 1995, Liu Min 1997, Wu Liuzen 2001 and Si Xiaoming 2004). Intermittent wave was used in 3 trials (15.0%, Liu Min 1997, Zhang Xiefang 1998 and Rong Jun 2005), while continuous wave was used in 2 trials (10%, Liu Min 1997 and Chen Li 2005). Two trials (10%) did not mention clearly the details of the electro-stimulation applied (Zhuang Yiqing 1999 and Zhang Pinggen 2004).

3.5.2.3 Moxibustion

Moxibustion was used in 2 out of the 20 included trials (10%, Yang Tao 2001 and Chen Li 2005). Yang Tao performed moxibustion stimulation on acupoints *Shuigou* and *Baihui* for 20 minutes twice a day, but the moxibustion materials used was not

mentioned clearly, while Chen Li performed moxibustion stimulation on acupoint *Guanyuan* for 5 minutes twice a day by using stick of Chinese Muhwort. In both trials, moxibustion was used together with acupuncture.

3.5.2.4 Others

Puncturing to release blood (點刺放血) was also one of the methods used in treating heroin withdrawal syndrome. Acupoint *Zhiyang* was chosen in two trials (Wang Xiaozhong 1996 and Wu Junmei 2002).

Chapter 4. Discussions

4.1 Efficacy of acupuncture

All 436 participants from 8 included trials treated with AT alone had been detoxified successfully from heroin dependence. Furthermore, 1072 participants in all 20 included trials treated with either AT or AT plus MT had also been detoxified successfully. It suggested that AT should be an effective way for heroin detoxification. Meanwhile, our analysis also suggested that the efficacy of AT plus MT should be better than AT alone.

C-data of AT alone versus MT showed that AT alone had similar effect as MT in PDN (4 trials; OR: 1.04 (0.60, 1.82); P=0.88), while C-data of AT plus MT versus MT showed that AT plus MT had a higher PDN after treatment (8 trials; OR: 4.31 (2.47, 7.52); P<0.00001). The results from meta-analysis of PND reported by 20 included trials indicated that AT plus MT might be more efficacious than MT alone or AT alone in relieving heroin withdrawal syndrome as AT plus MT showed a higher efficacy in improving PDN than MT, while AT alone only showed a similar efficacy as MT. The treatment results of combined therapy seems better than any single one, although so far any datum from direct comparison between AT plus MT and AT alone has not been available. The results from PND analysis hint that AT plus MT should be the first choice for heroin detoxification clinically.

M-data including WSS and HAMA score showed that AT alone was more effective to diminish the WSS on the Day 2 to 10 (5 trials; WMD: -17.52 (-28.69, -6.35) to -4.83 (-8.13, -1.53); P<0.05) and to diminish HAMA score (1 trial; P<0.05), and AT plus MT showed a higher efficacy than MT alone in reducing the WSS on the Day 1 to 10 (6 trials; WMD: -9.54 (-15.83, -3.25) to -2.50 (-4.48, -0.53); P<0.05) and reducing HAMA score (3 trials; WMD: -4.85 (-8.12, -1.58); P=0.004). Although both AT and AT plus MT had a higher efficacy on reducing patients' abstinence symptoms and anxiety symptoms than MT statistically, AT plus MT would have a quicker response in diminishing the WSS because the statistical difference compared to MT presented on the first treatment

day. AT plus MT should be one of the most reliable approaches for heroin detoxification.

More valuable data have been obtained from a long term observation by followed up treatments. 3 trials reported long term effects of AT plus MT and MT on relapse of heroin dependence, and the relapse rate in patients treated by AT plus MT (28.1%, 62 out of 220 patients) was significantly lower than that in patients treated by MT alone (56.9%, 91 out of 160 patients). Current result suggested that AT may provide more benefits than MT alone in long term rehabilitation of heroin detoxification.

4.2 Safety of acupuncture

Western medications for treating heroin withdrawal syndromes have undesirable adverse effects. For example, a report from USA showed that mortality related to methadone was increased from 0.16 to 0.98 per 100,000 during 1997 to 2001; and the major cause might be 4-fold increase of methadone application in the population during the corresponding time period (Ballesteros et al, 2003)[28]. In another case, the Adverse Drug Reactions Advisory Committee (ADRAC, 2003)[29] of Australia reported that considerable cases with adverse reactions were recorded in 4 years after tramadol was available in Australia. Those adverse reactions caused by tramadol included confusion, hallucination, convulsions, etc. In addition, neuropsychiatric syndromes such as lightheadedness, drowsiness or even seizures were also reported in some cases with overuse of clonidine or other western medications.

Some properties of medications may account for the occurrences of side effects. The methadone can keep its half-life in plasma up to 72 hours, but its clinical effect may not last for 12 hours. Thus, frequent repeat of taking methadone for maintaining its effects may result in significant side effects. Tramadol can stimulate opioid receptors, inhibit noradrenaline and serotonin, lower seizure threshold, decrease prothrombin activity and cause its own withdrawal symptoms. Adverse effects were frequently found after high-dose tramadol usage or in combination with other reagents with synergistic

effects. It is also dangerous to apply clonidine for its acts on alpha-2 receptors and noradrenergic system.

It is well known that acupuncture may treat disorders of patients by its regulatory roles on the function and metabolism in human body. Obviously, its regulatory roles to the bodies are not a supplement or replacement of bioactive substances from outside of the bodies. Acupuncture which may make it readily to prevent the presence of side effects induced by medications exerts its effectiveness to human bodies possibly via different mechanisms from those of medications.

In clinical reports, adverse effects were uncommon in patients treated by acupuncture, and only a few cases were occasionally suffered infections from poor aseptic techniques or damaged surrounding structures by inappropriate needle stimulation. These kinds of so-called side effects are caused by improper practice rather than the inherent property of therapy. Therefore, they should not be counted as side effects of acupuncture. Some possible accidents may also happen in acupuncture treatments such as fainting, hematoma, bending, needle sticking, breaking and so on. Most of these accidents result from poor knowledge, unfamiliar technique, improper location, etc. They should be different from side effects of medications. In recent years, more and more new types of stimulations have been involved in acupuncture treatments such as electrical stimulation and acupoint injection, etc. These additional stimulations may not be safe. Theoretically, acupuncture may not cause any side effect as long as qualified practitioners apply it in traditional way.

In current study, most included trials did not find any adverse effect related to acupuncture during treatment, except only 1 trial reported some patients treated by electroacupuncture that might cause local muscle spasm and pain which could disappear soon after adjusting electroacupuncture intensity. However, several kinds of adverse effects in the patients treated by Western medications were reported in these included trials. For example, in an included trial 37% patients treated by clonidine had dizziness, nausea, vomiting, etc, 7.1% patients showed abnormal ECG and 3.5%

patients showed abnormal GPT. The research data strongly support that acupuncture should be much safer than Western medications in treatment of heroin withdrawal syndrome.

Moreover, in another included trial methadone caused nausea and vomiting in 8 patients (18.6%), sweating, dilated pupils and burred vision in 6 patients (14.0%), breathing inhibition (10 breaths/min) in 5 patients (11.6%), and hallucination in 2 patients (4.7%). But in the same trial the patients treated by both methadone and acupuncture did not show similar adverse effects mentioned above. It hinted that acupuncture not only rarely caused adverse effect but also might diminish adverse effects caused by Western medications. Further researches should be performed to illustrate the interactions and mechanisms between acupuncture and medication treatment.

4.3 Mechanisms of acupuncture

4.3.1 Regulation effects of acupuncture

It has been generally accepted that in patients with heroin dependence a high concentration of exogenous opiate may inhibit the biosynthesis and function of endogenous opioid peptides and receptors in bodies. Once exogenous opiates are abstinent, the endogenous opioid system can not adapt the needs of body homeostasis. It may result in dysfunctions and withdrawal symptoms that naturally generate a motivation for seeking exogenous opiates to maintain the pathological homeostasis[31].

Recent researches have confirmed that acupuncture has a wide and significant effect in regulation of body functions. Although its mechanisms in treatment of dysfunctions may be complex, its regulatory effects on nervous system should play a key role for controlling heroin withdrawal syndrome. For example, AT can increase the release of endogenous opioid in the body, interact with μ and δ opioid receptors, excite the dopaminergic neurons in ventral tegmental area that promote the release of dopamine in nucleus accumbens (NAc); thus AT may prevent the drug-seeking behavior. On the

other hand, AT may activate the dynorphinergic neurons at spinal level, increase biosynthesis and release of dynorphin, interact with κ opioid receptor to reduce the dopamine in NAc; thus AT may attenuate the reward effect and drug-craving due to exogenous opiates. In addition, AT may also widely activate neurotransmitter systems other than the endogenous opioid system, such as dopamine norepinephrine, 5-hydrixytryptamine, glutamic acid and many others. These transmitter systems may involve in the opioid addiction and tolerance.

In summary, there are at least two suggested mechanisms to be involved in the regulation of acupuncture on heroin withdrawal syndromes:

(1) Endorphin mechanism: acupuncture stimulation on appropriate acupoints may significantly increase the release of endogenous opiate-like substances (such as endorphin, enkephalin, dynorphin, etc.) in brain and spinal cord. Since the shortage of endogenous opioid peptides play important roles in heroin withdraw, the increased release of opiate-like substances after acupuncture stimulation may help to ameliorate the deficient due to exogenous opiates limitation.

(2) 5-hydrixytryptamine mechanism: many dependent drugs can bring euphoria felling and therefore, abusers pursuing euphoria felling are driven into drug-seeking behavior. Deficient of dopamine in limbic system of brain may lead to euphoria decrease of abusers, and these can be regulated by 5-hydrixytryptamine pathway in hypothalamus. When appropriate acupoints are stimulated, 5-hydrixytryptamine pathway will be activated, dopamine will be increased via the cascade reaction of transmitter system in limbic system (for example, nucleus accumbens and amygdale), and euphoria felling will be eventually obtained. These results may ameliorate heroin withdrawal syndromes.

Traditional Chinese medicine (TCM) has unique theory to describe and explain the pathology of heroin dependence and withdrawal syndromes. According to the TCM theory, opiates including heroin are toxic substances with pungent taste and hot property. They can stimulate the *Qi* (energy or function) of human body, and induce

extraordinary excitement with incomparable happiness. However, drug-users have to take these toxins constantly for the desire of special feeling and extraordinary activity status. Thus they have to rely on the opiates in their daily lives. For long term dependence, the toxicity of opiates may damage internal organs and disturb human mind[30] that may cause addicts to occur deficient-syndrome and lose their ability to work even to live. Without opiate supplement, they will suffer from the withdrawal syndrome because of their *Qi* disorder and organ dysfunction (Zeng Xiangling 2005).

By stimulating certain acupoints, it can promote the circulation of *Qi* and blood throughout the body, rectify and improve organ functions, refresh and calm mind, nourish and restore the balance of metabolism. Therefore, acupuncture has a therapeutic effect for treatment heroin withdrawal syndrome.

4.3.2 Properties of channels

The selection of channels for detoxification was extensive. The three channels of which most of acupoints came from were the *Du Mai* (23.5%), Urinary Bladder Channel (14.7%) and *Ren Mai* (8.8%) without high percentages. The specificity, function and significance of these commonly used channels for heroin detoxification should be valuable to be analyzed.

4.3.2.1 Specificity of channels

(1) *Du Mai*: This Channel arises from the lower abdomen and emerges on perineum, runs posteriorly along interior of spinal column to acupoint *Fengfu* (DU 16) at nape where it enters the brain. It further ascends to the vertex and winds along forehead to nasal column, and its branches run downward to the kidneys. This pathway of *Du Mai* is coincidently the same as the route of corticobrainstem pathway (皮質腦幹束) and corticospinal tract, which is regulated consciously by cerebral cortex, responsible for voluntary action (visual, verbal, audio and locomotion) of bodies[32].

In the Twelve Ordinary Channels and Eight Extraordinary Channels, *Du Mai* has the closest connection to brain. Physiologically and pathologically, there is close relationship between *Du Mai* and brain by their pathway[33]. Zhang Xichun (張錫純), a

doctor of ancient China suggested that the place of *Du Mai* circulation had nerves and filled by cerebral spinal fluid. It was suggested that *Du Mai* joined the nerves system and trophectoderm of skin.

(2) The Urinary Bladder Channel: This Channel starts from the inner canthus, ascends to forehead and joins the *Du Mai* at an acupoint *Baihui* on vertex, where its branch goes to the temple. The straight portion of the Channel enters and communicates with brain from vertex. It then emerges and bifurcates to descend along the posterior aspect of neck, runs downward alongside medial aspect of scapula region and parallel to vertebral column, reaches lumbar region, then enters body cavity via paravertebral muscle to connect with Kidney and joins its pertaining organ Urinary Bladder.

(3) *Ren Mai*: This Channel starts from the inside of lower abdomen and emerges from perineum. It goes anteriorly to the pubic region and ascends along interior of abdomen, passing along median line to throat. By further ascending, it curves around the lips, passes through cheek and enters infraorbital region.

4.3.2.2 Function of channels

The *Du Mai* and *Ren Mai*, as two important Extraordinary Channels, can govern, connect and regulate all of Twelve Ordinary Channels, although their circulation courses are not as regular as Twelve Ordinary Channels so as to be called “Extraordinary Channels”. The Urinary Bladder Channel, as the most complicated Ordinary Channel pertains to and connects with Urinary Bladder and Kidney. From the *Zang-Fu* theory in TCM, Urinary Bladder and Kidney is a couple of interior-exterior organs. Their functions are linked with each other closely.

4.3.2.3 Significance of channels

(1) *Du Mai*: The principal roles are treatment of mental diseases, febrile diseases, local diseases of limbo-sacral region, back, head and neck, and corresponding splanchnopathies. Clinical observations showed that the acupoint-stimulation on *Du Mai* can effectively alleviate the abstinence symptoms, particularly treat symptoms such as pain in the muscle and bone, perspiration and anxiety (Zeng Xiangling). Acupuncture

in points of the *Du Mai* can tonify the *Qi.* When the *Qi* in the *Du Mai* is full, the *Qi* of the whole body will also be plentiful, thus normal functional activities of the body can be promoted and maintained.

(2) The Urinary Bladder Channel: The principal roles are treatment of diseases in head, nape, eye, lumbar region, lower extremities and mental diseases. The Back-*Shu* Points on this channel are corresponding points on the back area where the *Qi* of the respective *Zang-fu* systems is infused. They are commonly used to treat diseases of their relevant organs and tissues respectively. Most of them are situated close to their related *Zang-fu* systems and they present abnormal reactions, such as tenderness, to the dysfunction of their corresponding *Zang-fu* systems.

(3) *Ren Mai*: The principal roles include stopping pain in epigastric region, lower abdomen, and genital area, leucorrhea, urine retention, etc. According to the theory of TCM, *Ren Mai* is like a sea of *Yin* (essentials of metabolisms) and blood in human bodies. It could govern and connect six channels including Lung, Pericardium, Heart, Liver, Spleen and Kidney channels.

4.3.3 Properties of acupoints

4.3.3.1 Specificity of acupoints and Specific Acupoints

Acupoints are the sites through which the *Qi* of the *Zang-fu* systems and channels is transported to the body surface. Therapeutic action could be achieved only when stimulation was done on acupoints because the physiology of acupoints differs from that of non-acupoints. It has been reported[34] that blood vessels react greatlier when blood passes through acupoints than non-acupoints. In addition to the difference in efficacy between acupoints and non-acupoints, the action of acupoints also shows difference. Compared acupoints with non-acupoints, stimulating acupoints would get different results from doing non-acupoints. The former would get needle sensation and achieve therapeutic function but non-acupoints would not. An acupoint by definition is a microcirculation unit, which can regularly expand and contract. This explains the special effect of an acupoint[35].

Specific Acupoints refer to those of the Twelve Ordinary Channels, *Du Mai* and *Ren Mai* that have special therapeutic effects and special names. There are ten categories of Specific Acupoints and can be classified as Five-*Shu* Points, *Yuan*-Primary Points, *Luo*-Connecting Points, Eight Confluent Points, Back-*Shu* Points, Crossing Points, etc. For example, the *Five-Shu Points* were situated from the ends of extremities to the elbow or knee with the sequence of *Jing*-*Well, Xing*-Spring, *Shu*-Stream, *Jing*-River and *He*-Sea. Five-*Shu* Points, they had been described in classic TCM books that the flow of *Qi* as the flow of water that was flourishing gradually. This expression fits in that of blood circulation system which capillaries are abundant and intricate at four extremities; the location of main blood vessels normally is closer to body trunks and far from limbs.

Acupoints from 60 clinical trials were analyzed and the top 10 most commonly used acupoints were *Neiguan* (PC 6, 75.4%), *Zusanli* (ST 36, 57.4%), *Hegu* (LI 4, 45.9%), *Sanyinjiao* (SP 6, 44.3%), *Shenmen* (HT 7, 26.2%), *Laogong* (PC 8, 23.0%), *Waiguan* (SJ 5, 21.3%), *Shuigou* (DU 26, 18.0%), *Yanglingquan* (GB 34, 13.1%) and *Shenshu* (BL 23, 11.4%). They all belong to Specific Acupoints. Among the 20 included trials, the selection of all acupoints is from Specific Acupoints as well. Specific Acupoints are more commonly applied in practice than other acupoints. The research results show some evidence to identify the specificity of acupoints and Specific Acupoints but they are insufficient to demonstrate essence of channels and acupoints.

4.3.3.2 Function and significance of acupoints

The top 10 most commonly used acupoints are all from 8 Ordinary Channels and *Du Mai*. These channels are Pericardium, Stomach, Large Intestine, Spleen, Heart, *Sanjiao*, Gallbladder, Urinary Bladder and *Du Mai*. The former 8 Ordinary Channels have functions on pertain to and connect with the relevant *Zang-fu* systems and *Du Mai* has functions of governing these *Zang-fu* systems.

Neiguan (PC 6), the *Luo*-Connecting Point of the Pericardium Channel which links its exterior-interior Channel – Heart, and one of the Eight Confluent points joining the *Yinwei* Channel (one extra channel mixed with *Ren Mai* at the end of its course in the

front neck area), can calm mind and treat angina, palpitation, stomachache, etc. These indications of *Neiguan* exactly express those of the above three Channels - Percardium, Heart and *Ren Mai*. Experimental results[36] showed that *Neiguan* could regulate heart rate, improve function of blood vessels and regulate *Neiguan* autonomic nervous system[36]. It has been reported that acupuncture on this point may regulate the coronary circulation and prolong the ejection period of the left ventricle, hence increasing the myocardial contraction force and cardiac output of patients with angina pectoris, decreasing the preload, improving the compliance of the left ventricle and lowering its end diastolic pressure.

Zusanli (ST 36), the *He*-Sea Point of the Stomach Channel in Five-*Shu* Points, can improve digestive system and has tonificative effects. It has been reported that acupuncture on this point of children with simple indigestion or toxic indigestion enables low-level free acid and total gastric acidity, and activities of pepsin and gastric lipase to increase rapidly. Song Xiaoge observed that stimulation on *Zusanli* could decrease blood morphine concentration of morphine-withdrawing mice, and increase the concentration of IL-2 and B-EP (Song Xiaoge, 2002). Experimental results have shown that *Zusanli* is marked for its pain relieving effect[38].

Hegu (LI 4), the *Yuan*-Primary Point of the Large Intestine Channel, which is close to the wrist or ankle joint where *Qi* of *Zang-fu* systems is retained, can relieve pain remarkably in the neck area and can achieve the same goal in the chest, abdomen and extremities. The research showed that puncturing this point could regulate the central nervous system, produce inhibition on the cerebral cortical motor area with strong stimulation, and excitation with light stimulation; its regulation of the autonomic nerve could mainly adjust vasomotor activity, heart rate, rheoencephalogram and blood pressure.

Sanyinjiao (SP 6), the *Yuan*-Primary Point of the Spleen Channel, the Crossing Point of the channels of Spleen, Liver and Kidney, can nourish and supplement Liver-*Yin*, Spleen-*Yin*, and Kidney-*Yin* together with reinforcing manipulation which is

one of the basic needle manipulations for regulating the state of *Qi* deficiency.

Shenmen (HT 7) is the *Yuan*-Primary Point of the Heart Channel. Its functions mainly focus on treating insomnia, palpitation, depression and epilepsy. Experimental research showed that acupuncture in this point could lower blood pressure and might likely regulate the electroencephalogram of the patients with grand mal epilepsy or lower the electric potential of their pathologic brain waves. Wang et al[39] reported that puncturing *Sanyinjiao* (SP 6) (main point) and *Shenmen* (HT 7) (additive point) can treat insomnia successfully. Qiao[40] used *Shenmen* (HT 7) as the main point to treat anxiety. These data indicated that *Sanyinjiao* (SP 6) and *Shenmen* (HT 7) have functions of inhibiting excitement of adrenergic nerves and adjusting the working procedure of cerebral cortex.

Laogong (PC 8), the *Xing*-Spring Point of the Pericardium Channel, is to treat angina, vomiting and loss of consciousness. The *Xing*-Spring Point is where *Qi* in the channels starts to gush and its function is focused on cardiovascular and digestive system. It can be used in an emergency to recover consciousness. It had been reported that puncturing this point could treat stomach spasm and breathlessness very successfully[41, 42].

Waiguan (SJ 5), the *Luo*-Connecting Point of the *Sanjiao* Channel, one of the Eight Confluent Points connecting with the *Yangwei* channel, indicates to treat headache and relieve pain. As described earlier, the *Luo*-Connecting Point links its exterior-interior channels which are the *Sanjiao* and Pericardium Channel at this case. Experimental study demonstrated that strong manipulation of electroacupuncture in this point increased pain threshold for 140% in rabbits.

Shuigou (DU 26), the Crossing Point of the *Du Mai*, Large Intestine Channel and Stomach Channel, can regulate the *Qi* in *Du Mai*, which governs *Qi* for the whole body, hence its main indication is to wake patients from unconsciousness. It was reported that acupuncture on *Shuigou* could regulate the central nervous system and hence the overactive neurons of the CNS could be inhibited[43]. Experimental studies[44] showed that

electrical stimulation of *Shuigou* or terminal nucleus of trigemini (TNT) shortened the duration of apnea and evoked rhythmic breathing. It indicated that *Shuigou* and sensorius superior system of trigemini had certain specificity in the improvement of respiratory disorder. Another experimental study[45] showed that electroacupuncture at *Shuigou* could increase Regional Cerebral Blood Flow (rCBF) so as to reduce the damage of the ultrastructure in hippocampus of rats from ischemic injury.

Yanglingquan (GB 34), the *He*-Sea Point of the Gallbladder Channel in Five-*Shu* Points, can promote the flow of *Qi* to relieve pain. Experimental results have shown that *Yanglingquan* is remarked for its pain relieving effect[34]. Chan et al[46] reported that puncturing on *Yanglingquan* could relieve colic pain of bile cyst effectively.

Shenshu (BL 23) is a point of the Urinary Bladder Channel and Back-*Shu* Point of Kidney channel. This point is remarkable for its tonification. As described earlier, Back-*Shu* Points are significantly relevant to their connective *Zang-fu* systems and can treat related diseases of those systems. It therefore can nourish essence and tonify Kidney-*Yang*. Animal studies showed that puncturing on *Shenshu* has functions of diuresis, activating pituitarium – adrenal cortex system and increasing 5-HT in brain tissue.

Generally, selection of acupoints for heroin detoxification has been involved mainly in some Specific Acupoints. The research results showed that the functions of the selected acupoints are closely related to those of nervous system, cardiovascular system, digestive system and endocrine system. It may be one of the therapeutic mechanisms of AT for treatment of heroin withdrawal syndrome.

4.3.4 Manipulation methods

4.3.4.1 Electroacupuncture

Our data showed that electro-stimulation was the most commonly used manipulation method in 20 included trials (12 trials, 60%). Results of experimental researches supported the efficacy of electroacupuncture in treating drug withdrawal syndrome clinically. Research data[47] indicated that using 100 Hz electroacupuncture could promote the release of dynorphin, so as to relieve pain. An animal study[48]

observed the effect of using different frequency in electroacupuncture on tachycardia of rats undergoing detoxification, and found that 15 and 100 Hz electroacupuncture had suppressive effects on tachycardia, on avoiding tolerance and on providing higher excitement which might improve blood circulation, metabolism and provision of nutrient. In a human study[49], 2/100 Hz intermittent wave could promote the release of enkephalins and dynorphin simultaneously to achieve synergetic effect. During drug detoxification, enkephalin and dynorphin could still be released by the central nervous system when stopping using opiate-kind substance.

4.3.4.2 Stimulation by needle puncturing

The manipulation of needle puncturing was the second choice in included trials of this analysis. The fundamental principles of acupuncture treatment are needles insertion and acupoint stimulation and induction of *Qi* (a special feeling after acupuncture stimulation such as expansion, ache, numbness, etc.). As for the selection of manipulations, it depends on many factors such as feature of diseases, methods of treatment, location of acupoints, etc. In addition, moxibustion was used in 2 included trials.

Due to the property of drug dependence, the deficiency syndrome was commonly diagnosed in patients according to TCM theory; therefore, “reinforcing manipulation” has been applied mostly rather than reducing manipulation in clinical treatment. The manipulation of acupuncture treatment is a benifit stimulation which caauses direct and indirect effect[38]. In treating heroin dependence, it mainly achieves its efficacy indirectly, which involves stimulating the pressure, temperature or pain receptors on or below the superficial layer of the skin physically, as these sensory receptors are connected to the brain or internal organs, where self regulation could be achieved.

4.4 Heterogeneity analysis

In a meta-analysis, combined results from homogenous trials are more reliable than those from heterogeneous ones. Meanwhile, finding the reasons of heterogeneity

occurrence in datum synthesis of individual trials is an important result of meta-analysis that will be valuable for further clinical trials. For measurement datum synthesis in this study, a significant heterogeneity presented in the results of WSS. By subgroup analysis we found that different manipulation methods (electro-stimulation, moxibustion, body acupuncture, auricular acupuncture, etc.) and assessment scales (CINA, Himmelsbach, OWS, etc.) should be key factors and contribute more than control medications (methadone, clonidine, etc.) in introducing heterogeneity of the datum synthesis.

4.5 Study design and quality

4.5.1 Study duration

The heroin withdrawal syndrome is characterized by various symptoms and signs including lacrimation, running nose, yawning, and sweating, which occur 8-12 hours after the last dose of heroin, followed by increasing restlessness, dilated pupils, piloerection, tremor, irritability, anorexia, bone and joint pain and stomach cramps. As symptoms peak at 48-72 hours, the dependent user will experience an intensification of symptoms such as insomnia, more pronounced lack of appetite, violent, yawning and sneezing, severe lacrimation, and profuse nasal discharge. The duration for treatment and observationin in 20 included trials in this analysis was ranged from 7 days to one month. In view of that the acute abstinence and anxiety symptoms will naturally occur during 10 days and disappear or significantly lighten over 10 days, our analysis in this study was focused on the measurement data (WSS and HAMA score) and category data (PDN) of trials from Day 1 to Day 10.

Following acute phase of heroin detoxication, there seems to be a longer-term secondary or protracted abstinence syndrome in patients consisting of general malaise, fatigue, decreased well-being, poor tolerance of stress, and a craving for heroin, which may last some months or years, when there is a high rate of relapse to regular heroin users. A treatment strategy to help patients during their rehabilitation after heroin detoxification should be urgent needed. Although our analysis in this study showed that

AT or AT plus MT may effect to reduce relapse rate after detoxification, further clinical trials should be conducted to systematically examine the long-term effects of acupuncture.

4.5.2 Outcome mesurement

There were many different self-developed assessment scales that were used as scoring system in included trials. Our data showed that difference of assessment scales might be one of the key factors associated with heterogeneity occurrence in datum synthesis of meta-analysis. It hints that non-standardized way of measuring outcome resulted in difficulties when presenting the results in individual trials and meta-analysis. It is therefore suggested to use the uniform or similar scoring system in the future trials.

In view of that the measurement data (WSS and HAMA score) and category data (PDN, incidence of adverse effect and relapse rate) have been assessed by this meta-analysis, further meta-analysis should be conducted to evaluat other outcomes. We propose to investigate effects of AT by other research data which may be commonly concerned by clinical practitioners. The assessment may include intensity of withdrawal by time-course of withdrawal or duration of treatment, predominant signs and symptoms, drug positive results in urine samples and so on.

4.5.3 Quality assessment

Among the 20 included trials, 18 of them (90%) claimed to use randomization in study design; 3 of them (15%) claimed to use single-binding method and 7 of them (75%) reported dropout number. However, the results of quality assessment by the Jadad’s scale demonstrated that 14 out of 20 included trials (70%) were ranked as low-quality trials due to poor descriptions of the process of randomization and details of binding method. Some trials did not mention the methodology for quality control of the trials. The poor quality of these trials may baffle to analyze and document the results, and further trials with high quality of study design should be conducted to verify the evidence from this study.

Chapter 5. Conclusions and further researches

5.1 Conclusions

In this study, 20 RCTs or CCTs were included and a systematic review and meta-analysis was firstly used to assess their quality, M-data and C-data; evaluate the efficacy and safety of acupuncture treatment including AT along and AT plus MT for heroin detoxification; and analyze the most commonly used acupoints and manipulation methods in clinical application. In summary, our data indicated the current evidence as follows:

(1) All 436 participants treated with AT alone had been detoxified successfully from heroin dependence, and the effects of AT alone were statistically more favorable than MT alone. Therefore, AT should be an effective therapy in relieving heroin withdrawal syndrome.

(2) AT plus MT not only had statistically higher effects than MT alone, but might be better than AT alone. Thus, AT plus MT may be the first choice in clinical application.

(3) AT or AT plus MT may have effects to reduce relapse rate after detoxification. Further researches should be done to examine the long term effects of acupuncture.

(4) Adverse effects were commonly reported in patients treated by MT. Compared with MT, AT should be a safe way for both short term and long term treatments.

(5) AT plus MT rarely caused some adverse effects that commonly presented in MT treatments. AT may have a benefit for patients to diminish adverse effects caused by MT. The interaction between AT and MT may raise a new topic for further researches.

(6) The top 10 commonly used acupoints reported should be *Neiguan, Zusanli, Hegu, Sanyinjiao, Shenmen, Laogong, Waiguan, Shuigou, Yanglingquan* and *Shenshu*. Further clinical trials and experimental studies will be needed to explore their different roles and mechanisms.

(7) The most commonly used manipulation method for acupoint stimulation should be electro-stimulation. Further clinical trials and experimental studies will be needed to

compare this manipulation with other stimulations on the effects and mechanisms.

(8) A subgroup meta-analysis for heterogeneity indicated that the different manipulative methods and assessment scales were key factors to interfere synthesis of measurement data in this study.

(9) However, more trials with high quality of study design should be conducted to further verify the evidence in this study, since 70% trials included for this review and analysis were evaluated as low quality.

5.2 Suggestions

(1) The systematic review should be updated once every 3~5 years thus new published data of clinical trials can be added to give a more powerful combined estimate on the efficacy and safety.

(2) Other than acupuncture, systematic review and mata-analysis on the alternative treatments and regimens including traditional herbal therapy and *Qigong* therapy for treatment of drug withdrawal syndrome should be recommended.

(3) As this study investigates the overall effect of AT in relieving heroin withdrawal syndrome, further investigation on specific symptoms and signs should be followed afterwards.

(4) Future clinical trials need to be improved in the quality of study design, in terms of randomization, double blindness, and dropout rate being completely described.

(5) Further research should provide more wide and standardized outcome measurements such as criminal activities, urine or blood sample analysis, etc.

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Forest plots

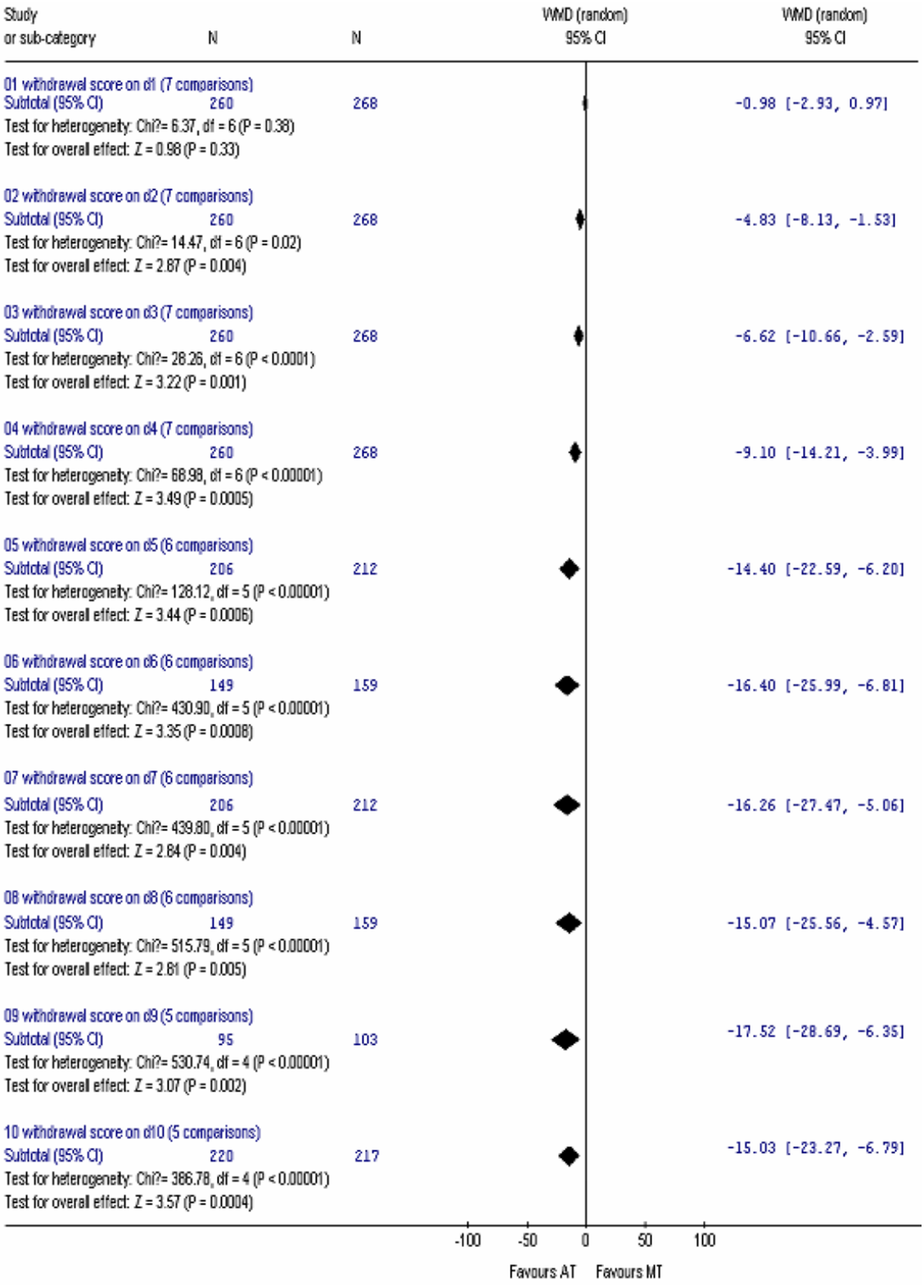

Figure 1. Meta-analysis on WSS: AT vs. MT

(The original data on each timepoint please see Figure 7 to 16)

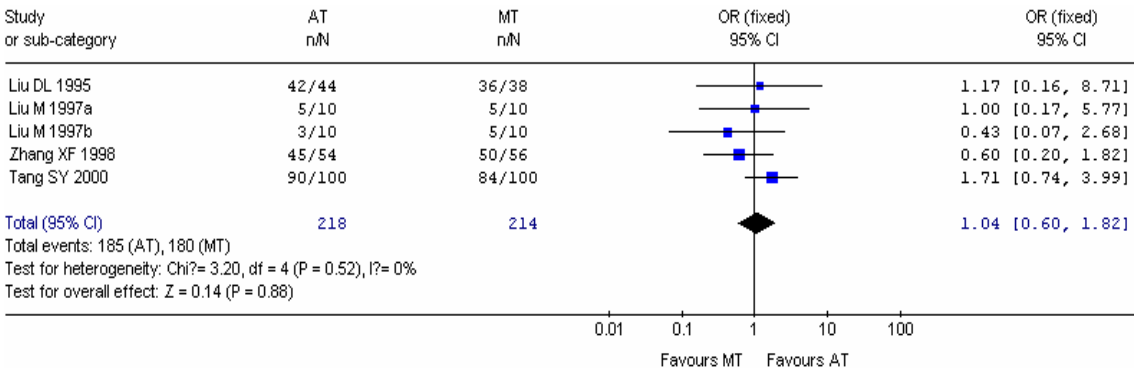

Figure 2. Meta-analysis on PDN: AT vs. MT

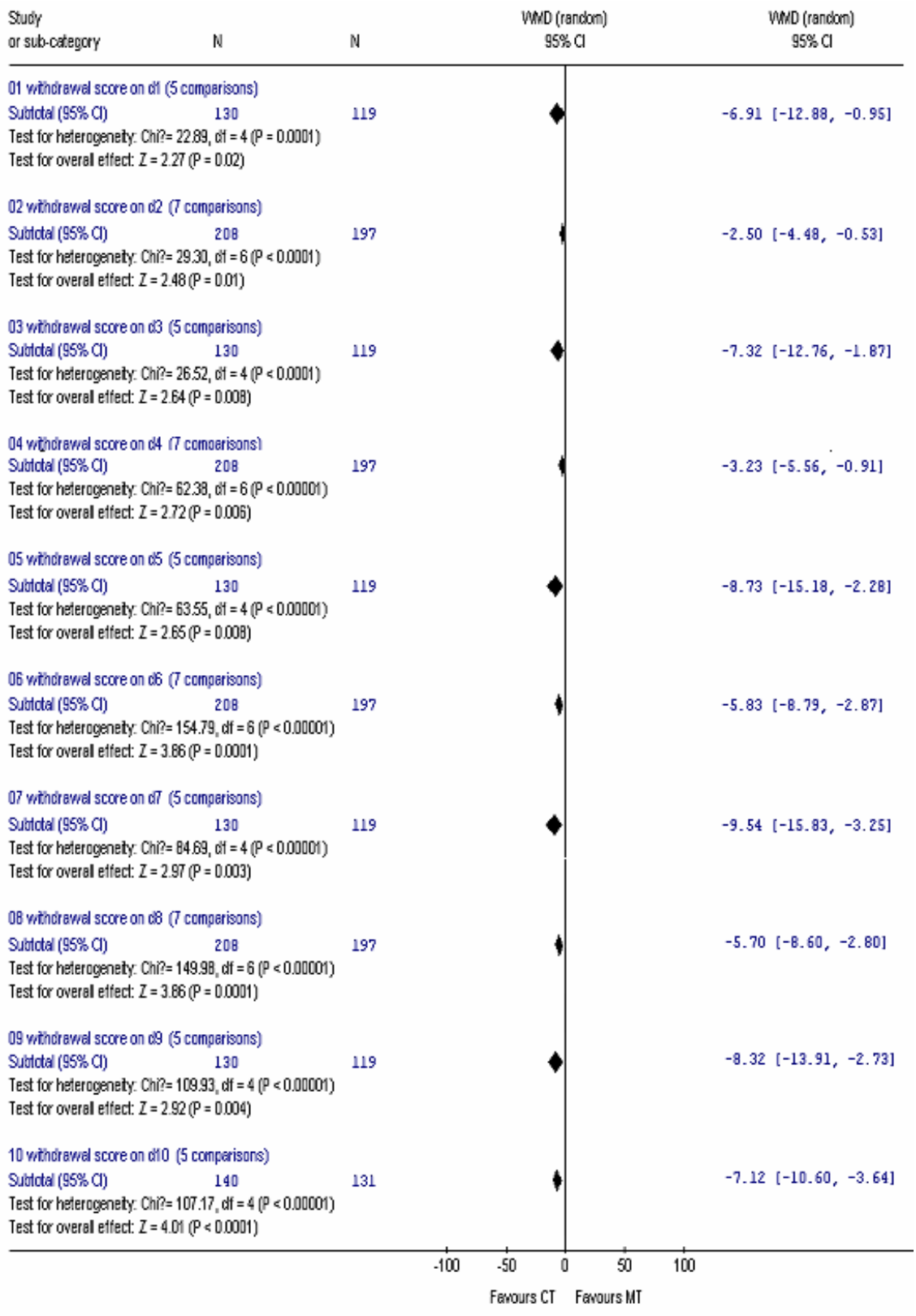

Figure 3. Meta-analysis on WSS: AT plus MT vs. MT
(The original data on each timepoint please see Figure 17 to 26)

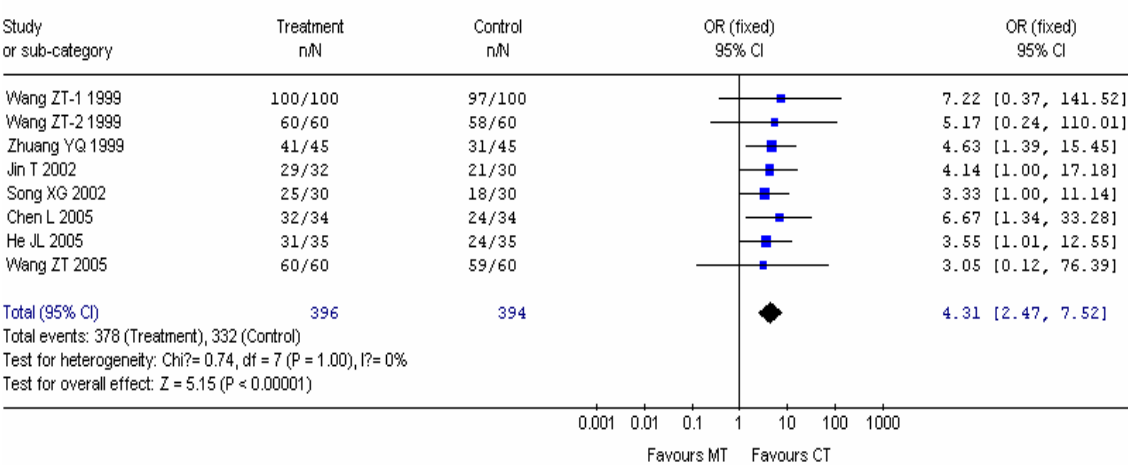

Figure 4. Meta-analysis on PDN: AT plus MT vs. MT

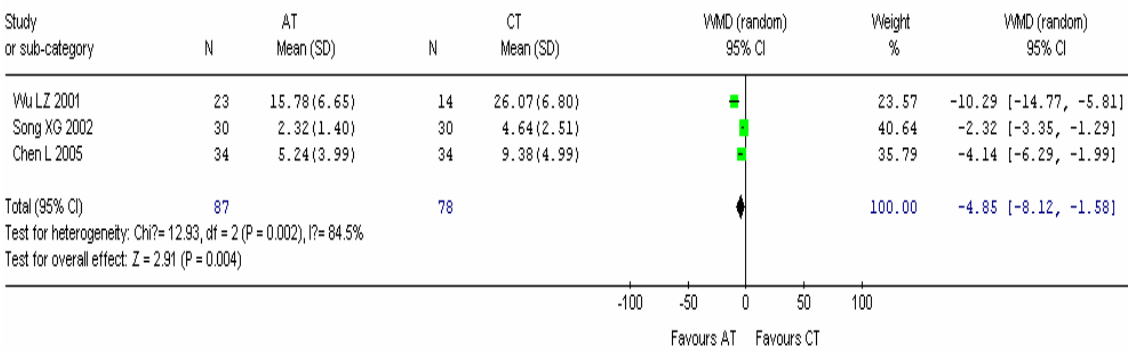

Figure 5. Meta-analysis on anxiety (HAMA scores): AT plus MT vs. MT

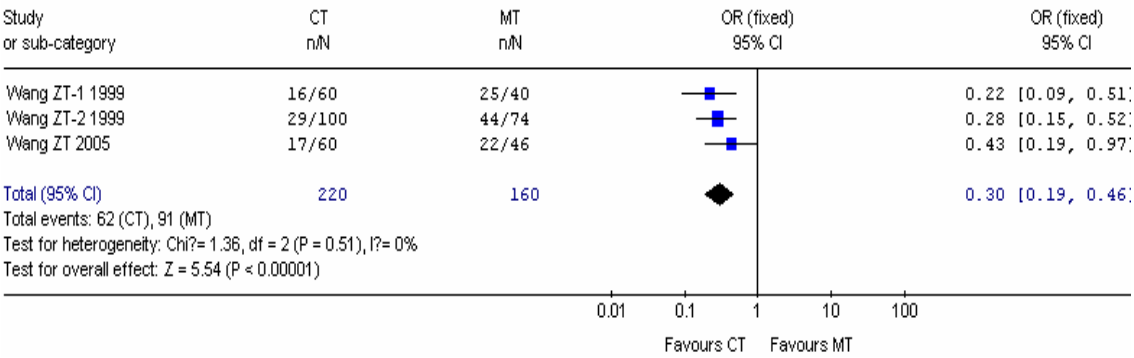

Figure 6. Meta-analysis on relapse rate: AT plus MT vs. MT

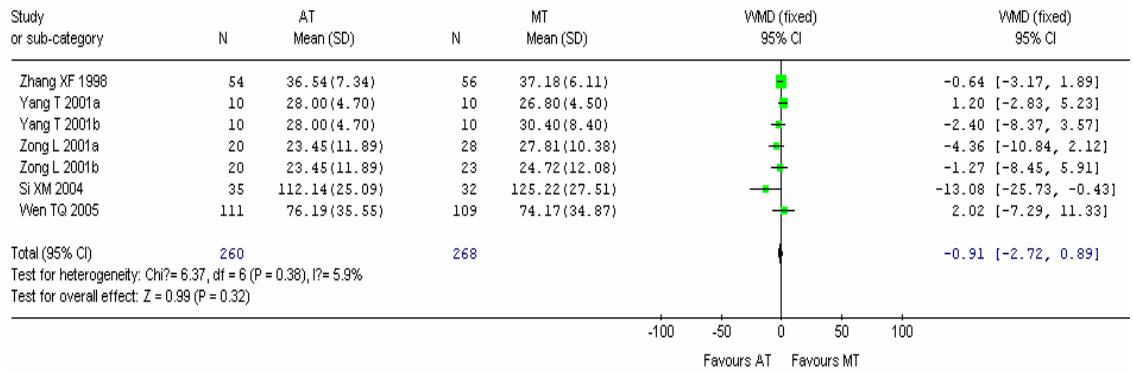

Figure 7. Meta-analysis on WSS: AT vs. MT on the Day 1

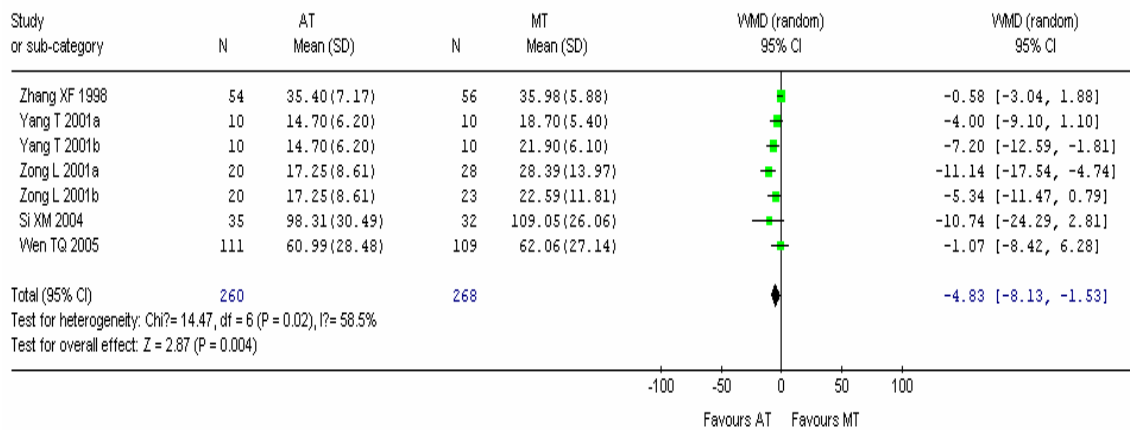

Figure 8. Meta-analysis on WSS: AT vs. MT on the Day 2

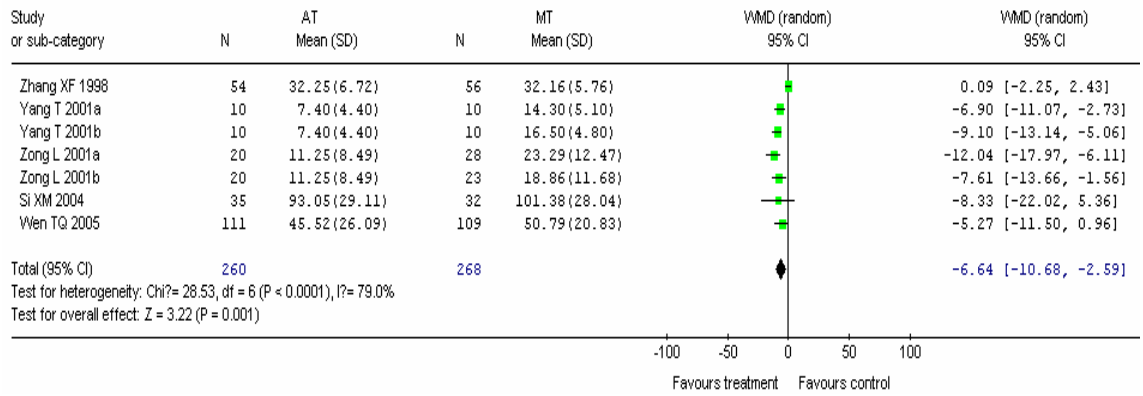

Figure 9. Meta-analysis on WSS: AT vs. MT on the Day 3

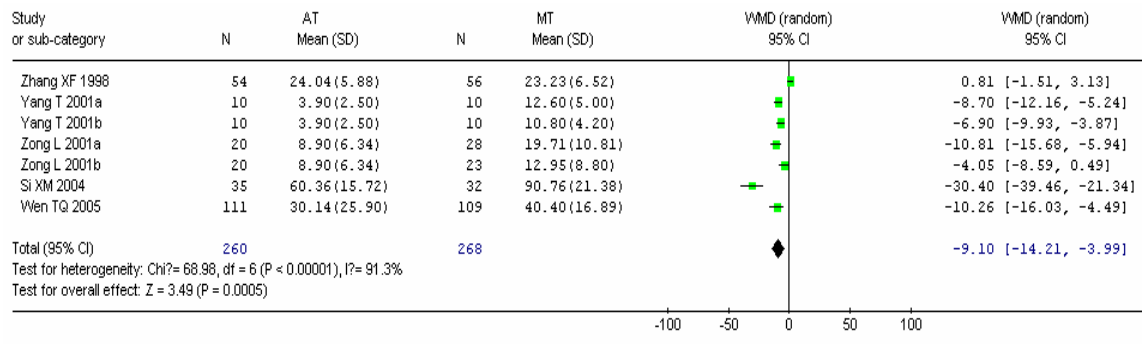

Figure 10. Meta-analysis on WSS: AT vs. MT on the Day 4

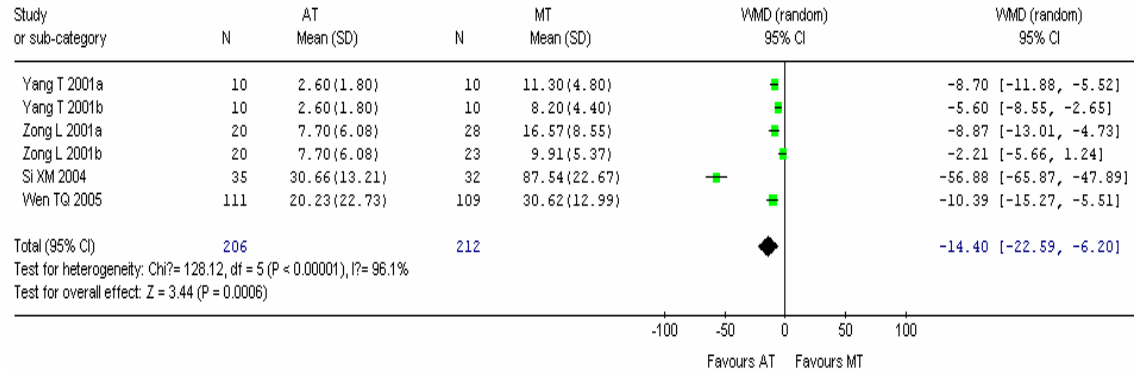

Figure 11. Meta-analysis on WSS: AT vs. MT on the Day 5

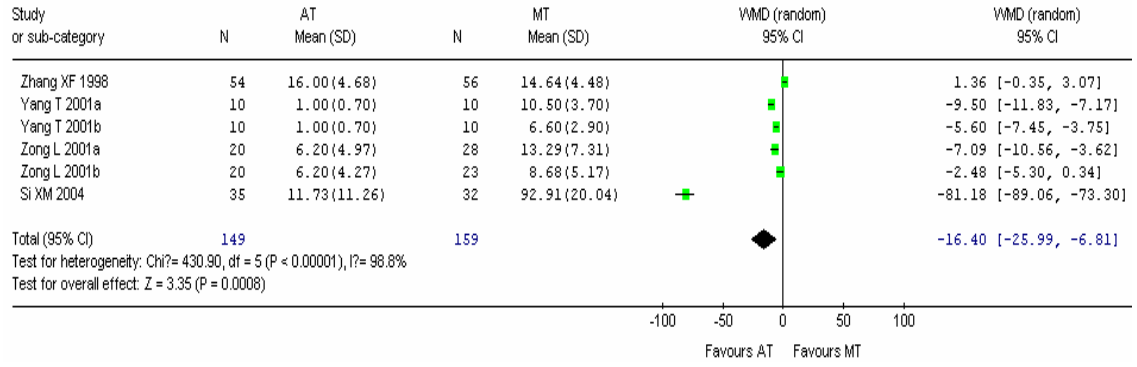

Figure 12. Meta-analysis on WSS: AT vs. MT on the Day 6

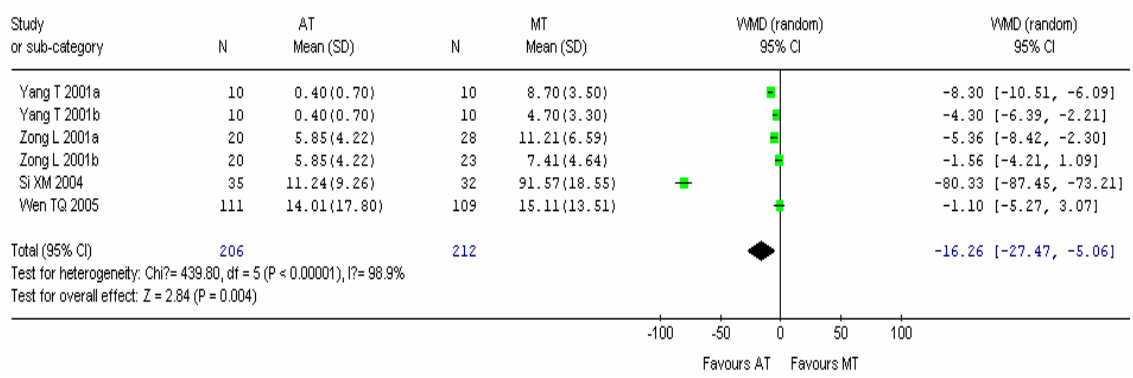

Figure 13. Meta-analysis on WSS: AT vs. MT on the Day 7

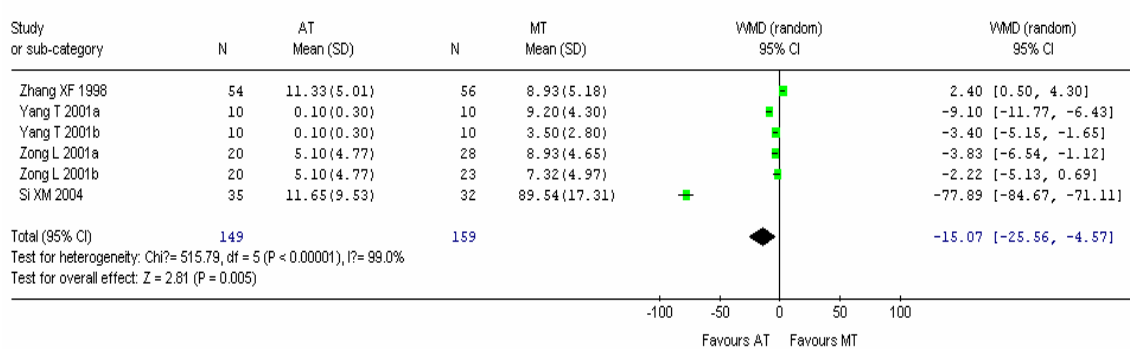

Figure 14. Meta-analysis on WSS: AT vs. MT on the Day 8

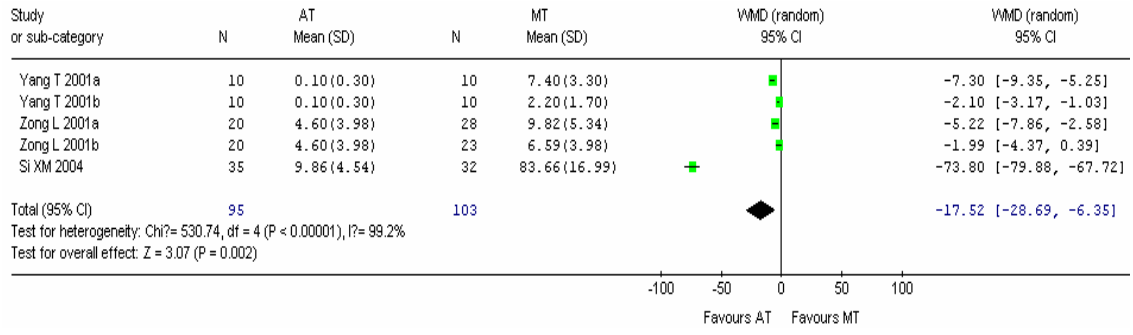

Figure 15. Meta-analysis on WSS: AT vs. MT on the Day 9

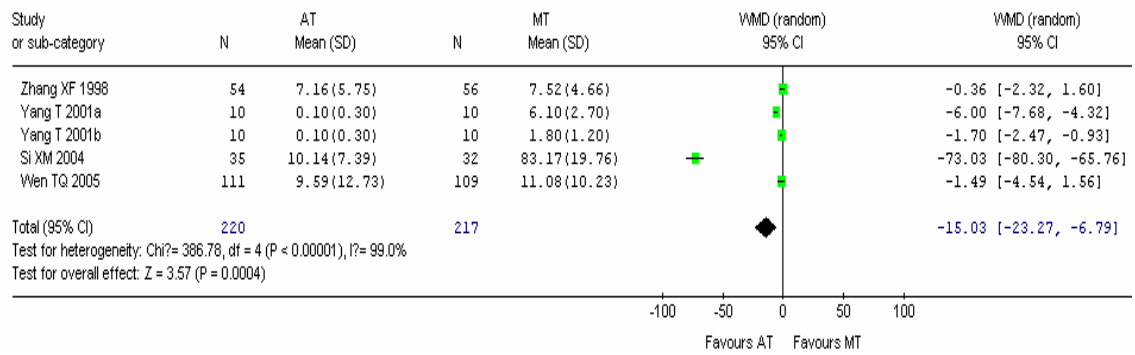

Figure 16. Meta-analysis on WSS: AT vs. MT on the Day 10

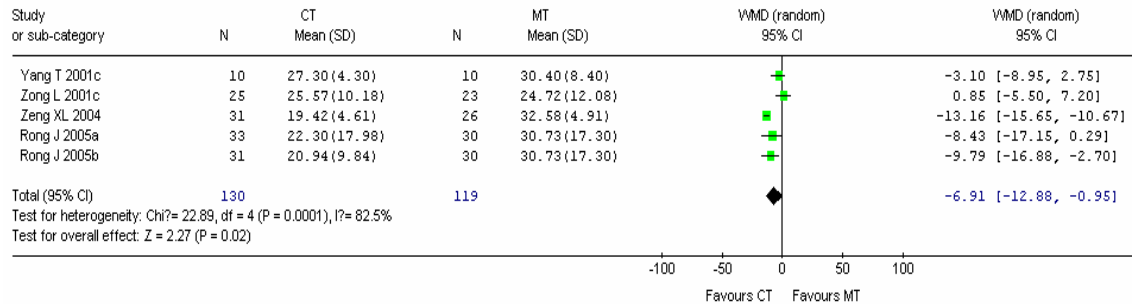

Figure 17. Meta-analysis on WSS: AT plus MT vs. MT on the Day 1

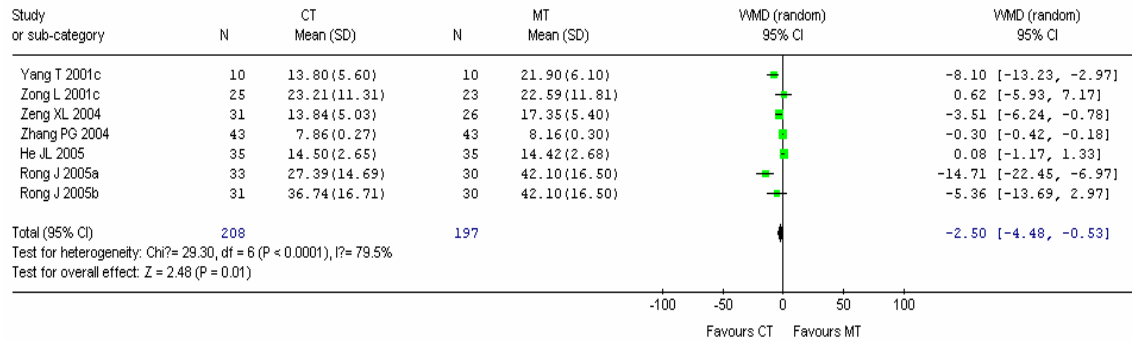

Figure 18. Meta-analysis on WSS: AT plus MT vs. MT on the Day 2

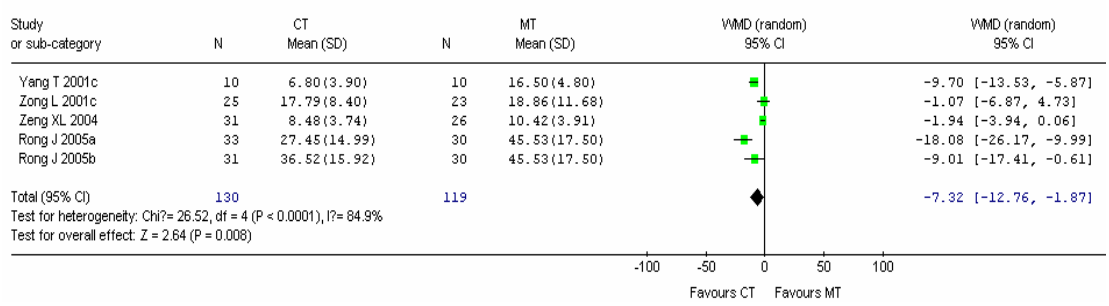

Figure 19. Meta-analysis on WSS: AT plus MT vs. MT on the Day 3

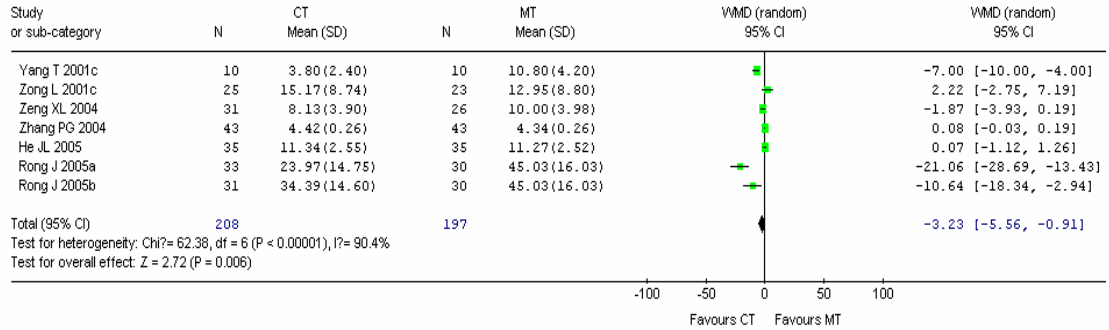

Figure 20. Meta-analysis on WSS: AT plus MT vs. MT on the Day 4

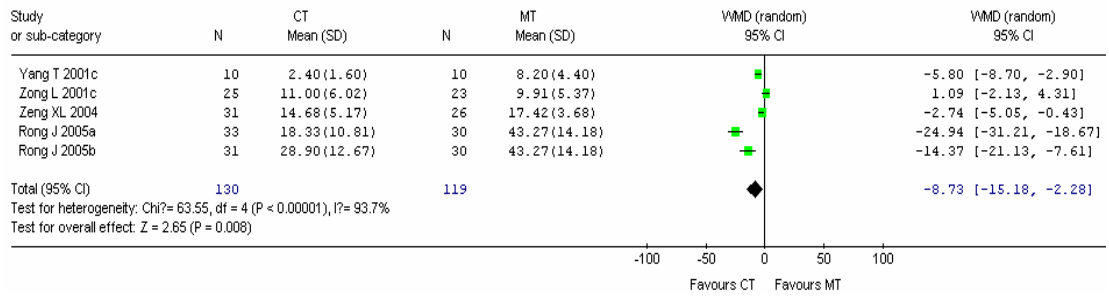

Figure 21. Meta-analysis on WSS: AT plus MT vs. MT on the Day 5

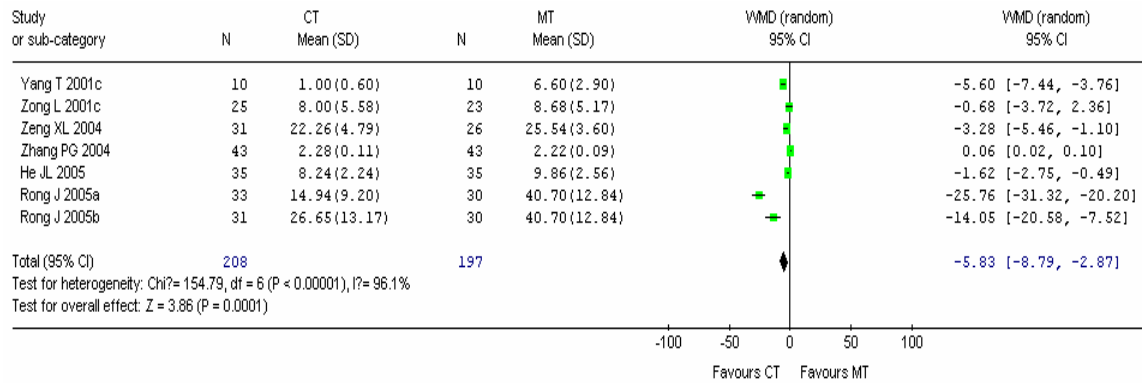

Figure 22. Meta-analysis on WSS: AT plus MT vs. MT on the Day 6

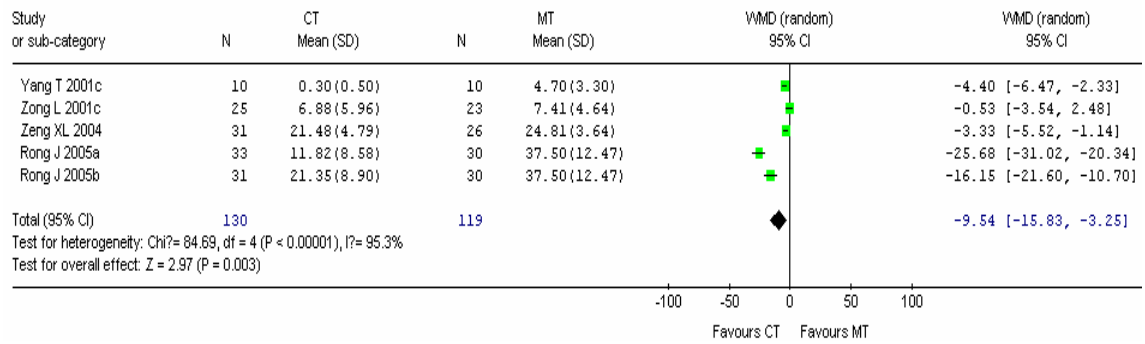

Figure 23. Meta-analysis on WSS: AT plus MT vs. MT on the Day 7

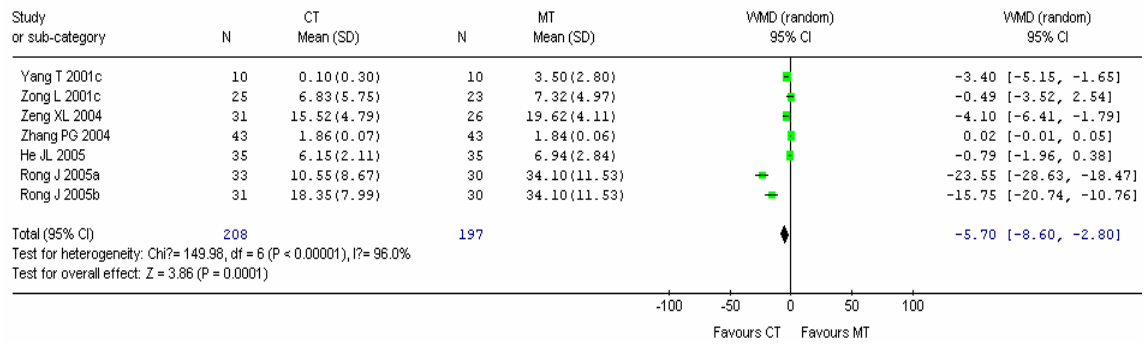

Figure 24. Meta-analysis on WSS: AT plus MT vs. MT on the Day 8

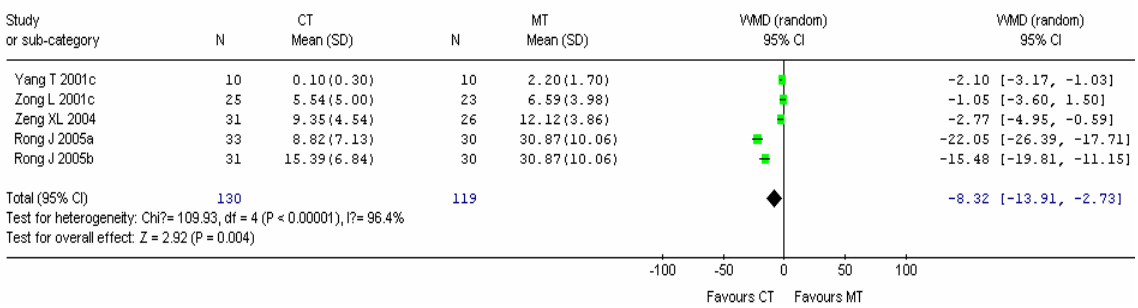

Figure 25. Meta-analysis on WSS: AT plus MT vs. MT on the Day 9

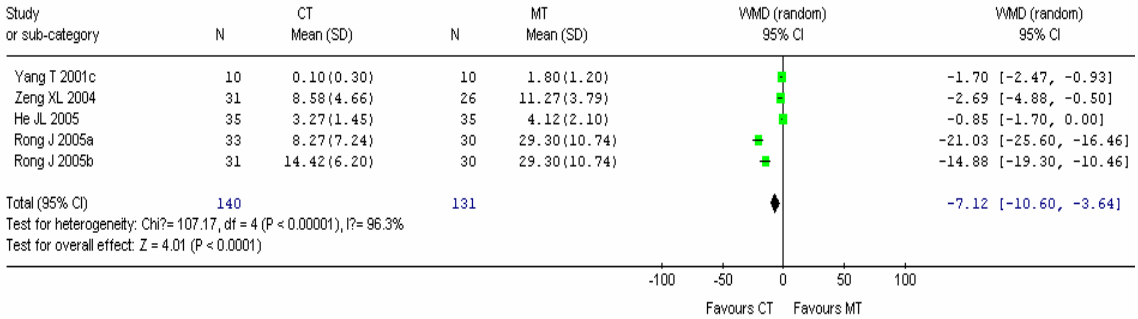

Figure 26. Meta-analysis on WSS: AT plus MT vs. MT on the Day 10

Appendixes

Appendix 1. Level of evidence rated by the Oxford Center (May 2001)

Level	Therapy/Prevention, Aetiology/Harm
1a	Meta-analysis of RCTs
1b	Individual RCT (with narrow Confidence Interval)
1c	All or none
2a	SR (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
2c	“Outcomes” Research; Ecological studies
3a	SR (with homogeneity) of individual Case-Control Study
3b	Individual Case-Control Study
4	Case-series (and poor-qua;ity cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or base on physiology, bench research or “first principles”

Appendix 2. Identification of RCTs and CCTs in systematic review by the Cochrane Collabaoration

Trials eligible for inclusion are classified according to the reader's degree of certainty that random allocation was used to form the comparison groups in the trial. If the author(s) state explicitly (usually by some variant of the term ‘random’ to describe the allocation procedure used) that the groups compared in the trial were established by random allocation, then the trial is classified as an "RCT" (randomised controlled trial). If an eligible trial has not been explicitly described by the author as randomised, then there is less certainty that it is, in fact, an RCT. This uncertainty is reflected in a different classification: "CCT" (controlled clinical trial). The classification "CCT" is also applied to quasi-randomised studies where the method of allocation is known but is not considered strictly random. Examples of quasi-random methods of assignment include alteration, date of birth, and medical record number.

The classification is based solely on what the author has written, not on the reader's interpretation; thus, it is not meant to reflect an assessment of the true nature or quality of the allocation procedure. For example, although double-blind trials are nearly always randomized, many trial reports fail to mention random allocation explicitly and should therefore be classified as ‘CCT’.

Website: http://www.cochrane.org/resources/hsmpt1.htm

Appendix 3. Data abstraction form (20 trials)

Appendix 3.1 Sample

Checklist	
No:	
Study:	
Year:	
(n):	
Mean age:	
Sex (% in male):	
Sex (% in female):	
Treatment:	
Acupoints and manipulations:	
Treatment (n):	
Control:	
Control (n):	
Duration:	
Follow-up:	
Diagnosis criteria:	
Observation scale:	
Primary outcomes:	
Jadad's scale	
1) Is the study randomized?	
2) Is the study doubled-blinded?	
3) Is there a description of withdrawals?	
4) Is the randomization adequately described?	
5) Is the blindness adequately described?	
Score:	/5
Cochrane Collaboration:	
1) Mentioned any "randomized allocation"/ "隨機分配受試者" (RCT)	
2) Did not mention andy "randomized allocation"/ "隨機分配受試者" (CCT)	

Appendix 3.2 Data abstraction of 20 trials

Trial 1	Liu Dinglu 1995
Study Eligibility	This study explored the effectiveness of CMZ-II electroacupuncture device during heroin-withdrawal stage.
Method	82 heroin addicts were enrolled into the treatment group and control group. By using the CINA, symptom score were recorded.
Participant	44 participants were treated by electroacupuncture. In the control group, 18 participants were treated by BUP and 20 participants were treated by DHZ. The mean age was 26.6 years old and considered of 71% males and 29% females. The mean drug-dosage was 1.33 g/d but mean drug-addiction period was not mentioned.
Intervention	Treatment: CMZ-II electroacupuncture probes were placed on the skin exactly at the location of bilateral Neiguahn (PC 6), Zusanli (ST 36) and Dazhui (DU 14) that were stimulated by 10 Hz for 20-30 min. Treatment frequency was not mentioned. Control: BUP and DHZ were used, but the dosage and duration were not mentioned.
Outcome	CINA score, improved patient number, time to show therapy effectiveness, relationship between efficacy and drug-addiction period
Trial duration	N/A
Note	CMZ-II electroacupuncture had similar effects as BUP and DHZ. No adverse effect was reported during treatment with CMZ-II electroacupuncture.

Trial 2	Liu Min 1997
Study Eligibility	This study used electroacupuncture to treat heroin addicts under a randomized controlled setting.
Method	30 patients were randomly allocated into electroacupuncture treatment with intermittent-wave group or with continuous-wave group or a medication-control group (10 cases in each group). By using a self-developed scale, the symptom score, urine-morphine positive result, improved patient number and safety observation were recorded on Day 3, 6, 9 and 14.
Participant	Participants were 86.7% males and 13.3% females. Mean age of patients was 27.3 (+/-4.0) years old with mean drug addicted period of 20.3 (+/-17.7) months and mean drug dosage of 99.3 (+/-60.1) g/d.
Intervention	Treatment: bilateral Neiguan (PC 6), Laogong (PC 8) or Zusanli (ST 36) were stimulated by electroacupuncture with intermittent or continuous wave respectively for 15-20 min. Control: the medication dosage and duration were not mentioned.
Outcome	Symptom score, variation of withdrawal symptoms, improved patient number
Trial duration	14 days
Note	Electroacupuncture had siminlar effects as control medications. No adverse effect was reported during treatments.

Trial 3	Zhang Xuefang 1998
Study Eligibility	Electroacupuncture with specific frequency and amplitude on specific acupoints was tested for its efficacy in controlling late withdrawal symptoms.
Methods	112 patients were randomly allocated into treatment and control group. By using CINA scoring system, the efficacy of intervention was measured.
Participants	112 participants (67.0% males and 33.0% females) were involved and divided into the treatment or control group respectively. Mean age of patients was 28.6 (+/-6.96) years old and mean drug addicted period was 12.46 (+/-18.64) months. Mean drug dosage was not mentioned.
Interventions	Treatment: LH201 treatment device was applied on unilateral Neiguan (PC 6), Hegu (LI 4) and Laogong (PC8) on the other side for 30 min with intermittent electric wave (12 - 20 mA, 2/100 frequency), q.id. or t.i.d. until Day 10. Control: clonidine (0.075 - 0.1 mg, t.i.d.) were used from the Day 1 to 3, and dosage was decreased (1/4 -1/6) gradually from Day 4 to 10.
Outcomes	CINA score, adverse effect
Trial duration	10 days
Notes	Electroacupuncture had better therapeutic effects and fewer adverse effects than that of clonidine.

Trial 4	Wang Zetao 1999-1
Study Eligibility	This study compared the effects of electroacupuncture plus methadone with methadone alone in heroin deoxification.
Methods	Heroin addicts were randomly allocated into treatment and control groups. The Himmelsbach scale was used for assessment, and improved patient number was recorded.
Participants	120 heroin addicts were enrolled with 85.8% males and 14.2% females. 60 patients were divided into treatment or control group respectively. Mean age of patients, mean drug addicted period and mean drug dosage were not mentioned.
Interventions	Treatment: based on methadone 10-day decrescendo therapy, electroacupuncture stimulation on Taichong (LR 3), Taixi (KI 3), Sanyinjiao (SP 6), Yanglingquan (GB 34), Hegu (LI 4), Quchi (LI 11), Jiaji (T5-7), Zhongwan (Ex-B 1), Tianshu (RN 12), Zusanli (ST 36), Shangjuxu (ST 25), Shenmen (HT 7), Neiguan (PC 6), Yintang (Ex-HN 3), Shenshu (BL 23) was done by using 1.5-2 inch needles and G6805 electroacupuncture device for 20 min per day until the Day 10. Control: Methadone 10-day decrescendo therapy was conducted, but dosage was not mentioned.
Outcomes	Himmelsbach score, improved patient number, relapse rate
Trial duration	10 days
Notes	Electroacupuncture therapy plus methadone provided higher effects than that of methadone alone.

Trial 5	Zhuang Yiqing1999
Study Eligibility	This study compared the effects of SLD multi-purposed therapeutic device plus medicine with medicine alone in heroin deoxification.
Methods	Heroin addicts were allocated into a treatment group and a control group. By using self-developed scale, the symptom scores and improved patient number were recorded.
Participants	90 male heroin addicts were enrolled. Treatment and control group consisted of 45 patients respectively with mean age of 22.35 years old. Mean drug addicted period and mean drug dosage were not mentioned.
Interventions	Treatment: In addition to the administration of medications as control group, SLD multi-purposed therapeutic device was applied on bilateral Laogong (PC 8), Yongquan (KI 1) and Shenque (RN 8), and a ground electrode was plasced on Dazhui (DU 14) for 20 min. For serious cases, the electrode was used to stimulate anathesia point of ear and Shuigou (DU 26) for 1-3 min per day. When acute symptoms were relieved, Sanyinjiao (SP 6), Qihao, Shenmen (HT 7) was used instead. When symptoms were absented, Zusanli (ST 36), Sanyinjiao (SP 6), Shenmen (HT 7) ware used with 12 – 20 mA electric current, intermittent wave of 2/100 frequency for 30 min, q.i.d. or t.i.d. until the Day 10. Control: Symptomatolytic medications were used. APC and atropine were given to treat headache and abdominal pain until Day 9. Dosage was not mentioned.
Outcomes	Symptom score, improved patient number
Trial duration	9 days
Notes	Electroacupuncture plus medicines provided higher efficacy than that of medicines alone. No adverse effect was reported during treatment.

Trial 6	Wang Zetao 1999-2
Study Eligibility	This study explored the effects of acupuncture therapy on heroin detoxification under a randomized controlled setting.
Methods	Heroin addicts were randomly allocated into acupuncture plus medicine group or medicine group. By using self-developed scale, improved patient number was recorded.
Participants	200 heroin addicts were enrolled with 86.5% males and 13.5% females. 100 patients were divided into treatment and control groups respectively. Mean age of patients, mean drug addicted period and mean drug dosage were not mentioned.
Interventions	Treatment: based on methadone treatment (methadone 10-day decrescendo therapy), acupuncture on Taichong (LR 3), Taixi (KI 3), Sanyinjiao (SP 6), Yanglingquan (GB 34), Hegu (LI 4,) Jiaji (T5-7) (Ex-B 1), Zhongwan (RN 12), Tianshu (ST 25), Zusanli (ST 36), Shenmen (HT 7), Neiguan (PC 6), Yintang (Ex-HN 3), Shenshu (BL 23), Zhishi was done by using 1.5-2 inch needles for 30 min per day until day 10. Control: methadone 10-day decrescendo therapy was performed. Dosage was not mentioned.
Outcomes	Detoxified patient number
Trial duration	10 days
Notes	Acupuncture plus methadone provided better therapeutic effects and lower relapse rate than that of methadone alone.

Trial 7	Tang Shunying 2000
Study Eligibility	This study explored the effects of acupuncture for heroin detoxification under a randomized control setting.
Methods	Heroin addicts were randomly allocated into acupuncture group or medicine group. By using self-developed scale, improved patient number was recorded.
Participants	200 heroin addicts were enrolled with 73.0% males and 27.0% females. 100 patients were divided into treatment and control groups respectively. Mean age of patients, mean drug addicted period and mean drug dosage were not mentioned.
Interventions	Treatment: acupuncture on 3-4 acupoints of Hegu (LI 4), Zusanli (ST 36), Neiguan (PC 6), Waiguan (SJ 5), Xingjian, Xiaxi, Feishu, Weishu, Shenshu (BL 23), Zhishi was done for 20 min per day until the Day 7. Control: *Kuai Su Wu Yin Jie Du Pian* (快速無癮戒毒片) was used (0.3 mg, t.i.d.).
Outcomes	Detoxified patient number
Trial duration	7 days
Notes	Acupuncture treatment provided similar therapeutic effects as that of medicine treatment. No adverse effect was reported during treatment.

Trial 8	Wu Liuzhen 2001
Study Eligibility	2/100 Hz cross-skin electro-stimulation affected the dosage of methadone used, depression and anxiety during early heroin-withdrawal stage under a randomized controlled setting.
Methods	Heroin addicts were randomly allocated into treatment and control group. By using self-developed scale and HAMD scale and HAMA scale, depression, anxiety and methadone dosage were recorded.
Participants	37 heroin addicts (100% males) were enrolled. 23 and 14 patients were divided into treatment and control group respectively. Patients' mean age was 33.57+/-6.3 years old, mean drug-addicted period was 2.96+/-1.06 years and mean drug dosage was 1.89+/-0.38 g/d.
Interventions	Treatment: based on methadone 14-day decrescendo therapy, 2/100 Hz cross-skin electro-stimulation on Hegu (LI 4), Laogong (PC8), Neiguan (PC 6), Waiguan (SJ 5), Xingjian and Sanyinjiao (SP 6) was done by using 10-15 mA on the Day 1, 15-25 mA on Day 2, and 15-30 mA on Day 3-14. Control: methadone 14-day decrescendo therapy was performed. Dosage was not mentioned.
Outcomes	HAMA score, HAMD score, methadone dosage
Trial duration	14 days
Notes	Electroacupuncture might reduce the dosage of methadone. Electroacupuncture plus methadone provided better effects on ameliorating melancholy and anxiety than that of methadone alone.

Trial 9	Zong Lei 2001
Study Eligibility	This study investigated clinical effects of acupuncture with or without Western medicine on heroin addiction under randomized setting.
Methods	Heroin addicts were randomly allocated into acupuncture group, Chinese medicine group, acupuncture plus Chinese medicine group and control group. By using Himmelsbach scale, the symptom score was recorded.
Participants	96 heroin addicts (100% males) were enrolled. 20, 23, 25 and 28 patients were divided into acupuncture group, Chinese medicine, acupuncture plus Chinese medicine group and control group respectively with mean age of 30.5 years, mean drug addicted period of 29.5 months and mean drug dosage of 1.16 g/d.
Interventions	Acupuncture group: acupuncture on Zhongwan (RN 12), Yintang (Ex-HN 3), Zusanli (ST 36), Sanyinjiao (SP 6), Neiguan (PC 6), Shenshu (BL 23), bilateral Jiaji (T5-7), Zusanli (ST 36) and Sanyinjiao (SP 6) was done with G6805-2 electroacupuncture device, 3-5 Hz, third degree of stimulation for 20 min until Day 20. Control: diazepam (10mg, p.o.) and 654-2 (10 mg/d i.m.) were used from the Day 1 to 3. Acupuncture with medicine group: combined interventions of acupuncture and control group.
Outcomes	Himmelsbach score, patients' body weight, urine morphine test
Trial duration	20 days
Notes	Acupuncture treatment provided better therapeutic effects than other treatments.

Trial 10	Yang Tao 2001
Study Eligibility	This study observed therapeutic effects of acupuncture, Chinese medicine and Western medicine on heroin withdrawal syndrome under a randomized control setting.
Methods	Heroin addicts were randomly allocated into acupuncture group, Chinese medicine group, Western medicine group, acupuncture plus Chinese medicine group and blank-control group. By CINA, Himmelstach and OWS, symptom scores were recorded and urine morphine was tested.
Participants	250 heroin addicts were enrolled. 50 patients were divided into 5 groups respectively. Genders, mean age of patients, mean drug addicted period and mean drug dosage were not mentioned.
Interventions	Acupuncture: 0.3 cm needles were embedded into ear points Endocrine, Lung, Heart and Shenmen, and replaced every 3 days. Acupuncture and moxibustion on Shuigou (DU 26), Neiguan (PC 6), Baihui (DU 20), Zusanli (ST 36), Sanyinjiao (SP 6) and Hegu (LI 4), Stimulation on Shuigou (DU 26) and Baihui (DU 20) were done by using G6805-3 multifunction electroacupuncture device with 2/100 Hz after needle insertion for 20 to 30min, twice a day until the Day 10. Chinese medicine: nine herbs including *Rhizoma Coptidis, Rhizoma Atractylodis Macrocephalae, Fructus Aurantii, Fructus Aurantii,* etc, were prepared and taken (150 ml q.i.d., on the Day 1-3, and t.i.d. on the Day 5-10). Western medicine: diazepam was used. Dosage was not mentioned. Acupuncture plus Chinese medicine: combined intervention of acupuncture group and Chinese medicine group. Blank control: non medicine was given, and other management might be applied depending on symptoms.
Outcomes	CINA score, OWS score, average time of withdrawal
Trial duration	10 days
Notes	Acupuncture treatment provided better effects on controling craving, anorexia, vomiting, stomachache, courbature, etc. than that of other treatments.

Trial 11	Song Xiaoge 2002
Study Eligibility	This study observed therapeutic effects of acupuncture plus methadone on heroin withdrawal syndrome under a randomized control setting.
Methods	Heroin addicts were randomly allocated into treatment and control group. By HAMA scale, symptom score and improved patient number were recorded.
Participants	60 heroin addicts with 61.7% males and 38.3% females were enrolled. 30 patients were divided into treatment and control group respectively with mean age of 27.48+/-5.25 years old, mean drug addicted period of 36.59+/-9.24 months, and mean drug dosage of 1.25+/-0.43 g/d.
Interventions	Treatment: based on methadone treatment (methadone 7-days decrescendo therapy), acupuncture on Neiguan (PC 6), Hegu (LI 4) and Sanyinjiao (SP 6) was done by using 1.5 inch needles, retaining for 60 min, and manipulating 1 min for every 30 min until Day 7. Control: Methadone 7-days decrescendo therapy was performed. Dosage was not mentioned.
Outcomes	HAMA score, improved patient number, blood test of immunoglobulins
Trial duration	7 days
Notes	Acupuncture plus methadone provided better therapeutic effects than that of methadone alone.

Trial 12	Jin Tao 2002
Study Eligibility	This study investigated the effects of auricular-acupuncture and methadone on heroin withdrawal symptoms under a randomized control setting.
Methods	Heroin addicts were randomly allocated into a treatment and a control group. By self-developed scale, of improved patient number was recorded.
Participants	62 participants (79.0% males and 21.0% females) were enrolled. 32 and 30 patients were divided into treatment and control groups respectively with mean age of 26.6 years old, mean drug addicted period of 5.25 years, and mean drug dosage of 1.23 g/d.
Interventions	Treatment: in addition to the same medicine used as control group, auricular-acupuncture on Shenmen, Lung, Liver, Heart, Kidney and Spleen was done for 30 min, twice per week, until 1 month. Control: methadone 1-month decrescendo therapy was performed. Dosage was not mentioned.
Outcomes	Improved patient number
Trial duration	1 month
Notes	Acupuncture plus methadone provided better therapeutic effects than that of methadone alone.

Trial 13	Zhang Pinggen 2004
Study Eligibility	This study investigated the synergic effect of electroacupuncture and methadone on heroin withdrawal symptoms under a randomized control setting.
Methods	Heroin addicts were randomly allocated into treatment or control group. By Himmelsbach scale, symptom score and adverse effects were recorded.
Participants	86 participants (91.9% males and 8.1% females) were enrolled. 43 patients were divided into treatment or control groups respectively with mean age of 27.3 years old, mean drug addicted period of 8.08 years, and mean drug dosage of 1.69 g/d.
Interventions	Treatment: using half dose of the methadone decrescendo therapy as control group, acupuncture on Baihui (DU 20), Houding (DU 19), Taiyang (Ex-Hn 5), Quchi (LI 11), Neiguan (PC 6), Zusanli (ST 36), Yanglingquan (GB 34) and Shenmen (HT 7) was done by using a 8050-II electroacupuncture device for 30 min, twice per day until the Day 10. Control: methadone 10-day decrescendo therapy was performed. Initial dose on the Day 1 to 3 and reduced 5 to 10 mg every 2 to 3 days.
Outcomes	Himmelsbach score, adverse effect
Trial duration	10 days
Notes	Electroacupuncture plus methadone provided similar therapeutic effects as that of methadone alone. Compared with methadone alone, adverse effects were reduced by treatment with methadone plus electroacupuncture.

Trial 14	Si Xiaoming 2004
Study Eligibility	This study used a low-frequency electric current to treat heroin addiction under a randomized controlled setting
Methods	Heroin addicts were randomly allocated into treatment or control group. By using CINA scale, symptom score was recorded.
Participants	67 patients (55.2% males and 52.6% females) were enrolle. 35 and 32 patients were divided into treatment and control groups respectively. Mean age of patients, mean drug addicted period and mean drug dosage were not mentioned.
Interventions	Treatment: acupuncture on Hegu (LI 4), Laogong (PC 8), Neiguan (PC 6) and Waiguan (SJ 5) was done by using LH203 low frequency electric treatment device with 9 V, 2/100 Hz intermittent, 10 mA for 30 min, repeated every 4-6 h on the Day 1-3, 6-8 h on Day 4-7, and 10-12 h on Day 8-15. Control: Methadone (50 mg p.o.) was used on the Day 1, decreased each day to 5 mg until on Day 15.
Outcomes	CINA score
Trial duration	15 days
Notes	Electroacupuncture treatment provided better effects than that of methadone treatment.

Trial 15	Zeng Xiangling, 2004
Study Eligibility	This study investigated the effects of acupuncture on points of the Governor Vessel for heroin detoxification under a randomized control setting.
Methods	Heroin addicts were randomly allocated into treatment and control group. By CINA, symptom score was recorded.
Participants	70 participants were enrolled, but only 57 participants with 82.5% males and 17.5% females completed the investigation. 13 patients were dropped out. 31 and 26 patients were divided into treatment and control groups respectively with mean age of 33.65+/-5.20 years old, mean drug addicted period of 6.10+/-2.87 years, and mean drug dosage of 1.31+/-0.72 g/d.
Interventions	Acupuncture plus methadone group: in addition to use the same medicine as control group, acupuncture on Baihui (DU 20), Dazhui (DU 14), Shendao (DU 11), Lingtai (Du 10), Zhiyang (DU 9) and Mingmen (DU 4) was done by using 1.0-1.5 inch needles for 30 min per day until the Day 10. Control: methadone 10-day decrescendo therapy was performed. Dosage was not mentioned.
Outcomes	CINA score, improved patient number
Trial duration	10 days
Notes	Acupuncture plus methadone provided better therapeutic effects than that of methadone alone.

Trial 16	Wen Tunqing 2005
Study Eligibility	This study explored effects of acupuncture treatment for heroin withdrawal syndrome under a randomized control setting.
Methods	Heroin addicts were randomly allocated into treatment or control group. By using the HAMA and CINA scale, symptom scores were recorded.
Participants	220 patients (77.7% males and 22.3% females) were enrolled. 111 and 109 patients were divided into acupuncture and control groups respectively with mean age of 33.80+/-6.94 years old, mean drug addicted period of 20.13+/-8.35 years, and mean drug dosage of 0.83+/-0.35 g/d.
Interventions	Treatment: acupuncture on bilateral Hegu (LI 4), Zusanli (ST 36) Neiguan (PC 6), Waiguan (SJ 5), Shenmen (HT 7) and Sanyinjiao (SP 6) was done for 30min per day until the Day 10. Control: 1-2 pieces of lofexidine, b.i.d., on the Day 1; while 3-4 pieces b.i.d., on the Day 3-5; 2-3 pieces, t.i.d., on the Day 6-7; 1-2 pieces t.i.d., on the Day 8-9; 1 piece, t.i.d., on the Day 10.
Outcomes	HAMA score, CINA score, blood test, liver and kidney function tests
Trial duration	10 days
Notes	Acupuncture provided better therapeutic effects than that of methadone. No adverse effect was reported during treatments.

Trial 17	Rong Jun 2005
Study Eligibility	This study compared the effects of scalp acupuncture plus methadone and body acupuncture plus methadone with methadone alone for heroin detoxification under a randomized control setting.
Methods	Heroin addicts were randomly allocated into scalp acupuncture plus methadone, body acupuncture plus methadone, and methadone alone group. By using a Himmelsbach scale, symptom scores were recorded.
Participants	94 heroin addicts (85.1% males and 14.9% females) were enrolled. 33, 31 and 30 patients were divided into scalp acupuncture plus methadone, body acupuncture plus methadone or methadone groups respectively with mean age of 31.00+/-5.90 years old, mean drug addicted period of 7.19+/-3.98 years and mean drug dosage of 0.98+/-0.44 g/d.
Interventions	Scalp acupuncture plus methadone: in addition to the same medicine used as control group, scalp acupuncture on the lines of scalp was conducted by using a G6805-3 electroacupuncture device with 2/100 Hz frequency for 20 min per day. Body acupuncture plus methadone: in addition to tha same medicine used as control group, acupuncture on Sishencong (Ex-HN 1), bilateral Neiguan (PC 6), Hegu (LI 4), Zusanli (ST 36) and Sanyinjiao (SP 6) was done by using a G6805-3 electroacupuncture device with 2/100 Hz frequency for 20 min per day. Control group: methadone 10-day decrescendo therapy was performed. Dosage, mode and frequency of administration were not mentioned.
Outcomes	Symptom score
Trial duration	10 days
Notes	Scalp acupuncture and body acupuncture plus methadone provided better therapeutic effects than that of methadone alone.

Trial 18	Wang Zetao 2005
Study Eligibility	This study explored the efficacy of auricular-plaster therapy plus medicine for heroin detoxification under a randomized control setting.
Methods	Heroin addicts were randomly allocated into treatment plus medicine or medicine alone group. By using a self-developed scale, the improved patient number was recorded.
Participants	120 patients (83.3% males and 16.7% females) were enrolled. 60 patients were divided into treatment and control groups respectively. Mean age of patients, mean drug addicted period and mean drug dosage were not mentioned.
Interventions	Treatment: base on methadone 10-day decrescendo therapy, auricular plaster were placed on auricular points of Liver, Kidney, Lung, Endocrine, Brainstem, Shenmen, Heart, Small Intestine, Stomach, Spleen, Large Intestine, Sympathetic, Urinary Bladder and Sacral spines. Patients were required to press the auricular points 1-2 min, q.i.d. Control: methadone 10-day decrescendo therapy was perfomed. Dosage was not mentioned.
Outcomes	Improved patient number, relapse rate
Trial duration	10 days
Notes	Auricular plaster plus methadone provided better therapeutic effects than that of methadone alone.

Trial 19	He Jeling 2005
Study Eligibility	This study explored the effects of electroacupuncture therapy for heroin detoxification under a randomized control setting.
Methods	Heroin addicts were randomly allocated into treatment and control groups according to the admitting sequence. By using the OWS, symptom scores were recorded.
Participants	70 heroin addicts (84.3% males and 15.7% females) were enrolled. Treatment and control group consisted of 35 patients respectively with mean age of 28.21+/-6.36 years old, mean drug addicted period of 3.32+/-0.66 years and mean drug dosage of 0.48+/-0.28 g/d.
Interventions	Treatment: by using electroacupuncture device, acupoints were selected depending on the symptoms of patients. Electric stimulation was applied on specially-defined auricular points for 30 min. Methadone decrescendo therapy was used by starting at 50 mg, reducing 5 mg/day until the Day 5, reducing 10 mg/day on Day 6-8, and stopping on Day 9. Control: methadone decrescendo therapy was conducted as mentioned above.
Outcomes	OWS score
Trial duration	14 days
Notes	Electroacupuncture plus methadone provided better therapeutic effects than that of methadone alone.

Trial 20	Chen Li 2005
Study Eligibility	This study explored the effects of electroacupuncture plus medications for heroin detoxification under a randomized control setting.
Methods	Heroin addicts were randomly allocated into treatment and control group according to the admitting sequence. By using a HAMA scale, symptom scores were recorded.
Participants	68 heroin addicts (67.6% males and 32.4% females) were enrolled. Treatment and control group consisted of 34 patients respectively with mean age of 25 years old and mean drug addicted period of 8 years. Mean drug dosages was not mentioned.
Interventions	Treatment: by using 6805-C electroacupuncture device, acupoints of Laogong, Sanjinjiao, Zusanli, Neiguan and Hegu were stimulated. Electricity was applied for 30 min, with 2 Hz, continuous wave. Auricular acupuncture with auricular plaster on points of Shenmen, Liver, Stomach and Endocrine. Medication was also given at the same setting as control group. Control: methadone was orally taken once per day. Dosage of methadone was not mentioned.
Outcomes	HAMA score, improved patient number
Trial duration	1 month
Notes	Electroacupuncture therapy plus methadone provided better therapeutic effects than that of methadone alone.

Appendix 4. Characteristics of included trials

No	Study	Jadad Score	Primary Outcomes	Treatment Group	Control Group
1.	Liu Dinglu 1995	1	CINA; PDN	Electroacupuncture on Neiguan, Zusanli and Dazhui	BUP or DHZ
2.	Liu Min 1997	1	PDN; Self-developed withdrawal scale scores	Electroacupuncture on Neiguan, Zusanli and Laogong	Symptomatolyic medications
3.	Zhang Xiefang 1998	1	Adverse effect; CINA;	Electroacupuncture on Neiguan, Waiguan, Hegu and Laogong	Clonidine
4.	Wang Zetao 1999-1	1	PDN; Himmmelsbach; Relapse rate	Electroacupuncture on Taichong, Taixi, Sanyinjiao, Yanglinquan, Hegu, Quchi, Jiaji, Zhongwan, Tianshu, Zusanli, Shangjuxu, Shenmen, Neiguan, An Mian, Yingtang, Shenshu and Zhishi	Methadone
5.	Zhuang YiOing 1999	1	PDN	Electroacupuncture on Laogong, Yongquan, Shenque, Shuigou, Dazhui, Sanyinjiao, Oihai, Shenmen, Zusanli and analgesia point on the ear	Symptomatolyic medications
6.	Wang Zetao 1999-2	1	PDN; Relapse rate	Acupuncture on Taichong, Taixi, Sanyinjiao, Yanglinquan, Hegu, Quchi, Jiaji, Zhongwan, Tianshu, Zusanli, Shangjuxu, Shenmen, Neiguan, An Mian, Yingtang,	Methaone

				Shenshu and Zhishi	
7.	Tang Songying 2000	1	PDN	Acupuncture on Hegu, Zusanli, Neiguan, Waiguan, Xingjian, Feishu, Weishu, Shenshu, Zhishi and Xiaxi.	Kuai Su Wu Yin Jie Du Pian (快速無癮戒毒片)
8.	Wu Liuzhen 2001	3	PDN; HAMA score; HAMD score	Electroacupuncture on Hegu, Laogong, Neiguan, Waiguan, Xingjian and Sanjinjiao	Methadone
9.	Zong Lei 2001	1	Himmelsbach; PDN	Electroacupuncture on Zhongwan, Yingtang, Zusanli, Sanyinjiao, Neiguan, Shenshu and Jiaji	Diazepam
10.	Yang Tao 2001	1	OWS	Electroacupuncture on Shuigou, Neiguan, Baihui, Zusanli, Sanyinjiao and Hegu, and auricular AT on Endocrine, Lung, Heart and Shenmen.	Diazepam, opiate subsitutional drugs
11.	Song Xiaoge 2002	3	HAMA score	Acupuncture on Neiguan, Hegu and Sanyinjiao	Methadone
12.	Jin Tao 2002	1	PDN	Auricular AT on Shenmen, Lung, Heart, Kidney and Spleen	Methadone
13.	Zhang Pinggen 2004	3	Adverse effect; Himmelsbach	Electroacupuncture on Baihui, Houding, Taiyang, Quchi, Neiguan, Zusanli, Yanglingquan and Shenmen	Methadone
14.	Si Xiaoming 2004	1	CINA;	Electroacupuncture on Hegu, Laogong, Neiguan and Waiguan	Methadone
15.	Zeng	3	CINA;	Acupuncture on	Methadone

	Xiangling 2004			Baihui, Dazhui, Shendao, Lingtai, Zhiyang and Mingmen	
16.	Wen TunOing 2005	3	CINA; HAMA score;	Acupuncture on Hegu, Zusanli, Neiguan, Waiguan, Shenmen and Sanyinjiao	Lofexidine
17.	Rong Jun 2005	1	Himmelsbach;	Electroacupuncture on scalp and Sishencong, Neiguan, Hegu, Zusanli and Sanyinjiao	Methadone
18.	Wang Zetao 2005	1	PDN; Relapse rate	Auricular AT on Liver, Kidney, Endocine, Brainstem, Shenmen, Heart, Small Intestine, Stomach, Spleen, Large Intestine, Sympathetic, Urinary Bladder and Sacral spines.	Methadone
19.	He Jeling 2005	3	OWS;	Electroacupuncture on specially-defined auricular points	Methadone
20.	Chen Li 2005	1	HAMA score; PDN	Electroacupuncture on Laogong, Sanjinjiao, Zusanli, Neiguan and Hegu, and auricular AT on Shenmen, Liver, Stomach and Endocine	Methadone

Appendix 5. References of included trials

1. **Liu Dinglu 1995**

   劉鼎祿，劉春希，劉靜飛，等，CMZ-II 型多功能電子針罐控制海洛因依賴戒斷症狀 44 例即時療效觀察，中國針灸, 1995; 增刊:69-71.

2. **Liu Min 1997**

   劉敏，蘇同生，畢宇峰，等，電針戒毒對海洛因成癮的脫癮效能觀察，針灸臨床雜誌, 1997; 13(4-5):40-42.

3. **Zhang Xiefang 1998**

   張學芳，李翔，馮春霞，電針治療阿片類依賴稽延性戒斷症狀的臨床研究，中國藥物依賴性雜誌, 1998; 7(3):152-155.

4. **Wang Zetao 1999-1**

   王澤濤，袁宜勤，王軍，等，電針配合藥物治療海洛因依賴臨床療效觀察，中國中醫藥信息雜誌, 1999; 6(9):35-35.

5. **Zhuang YiOing 1999**

   莊義青，劉國華，生理電治療儀對海洛因成癮的治療作用，中國療養醫學, 1999; 8(1):25-27.

6. **Wang Zetao 1999-2**

   王澤濤，袁宜勤，王軍，等，針刺配合藥物治療海洛因依賴臨床療效觀察，中國針灸, 1999; 11:657-658.

7. **Tang Songying 2000**

   唐順英，海洛因成癮的針刺治療與調護，中國民間療法, 2000; 8(3):11-12.

8. **Wu Liuzhen 2001**

   吳鎏楨，崔彩蓮，韓濟生, 2/100 Hz 電刺激可降低脫毒期美沙酮用量和脫期毒後期抑鬱及焦慮情緒，中國藥物依賴性雜誌, 2001; 10(2):124-126.

9. **Zong Lei 2001**

   宗蕾，胡軍，李煜，等，針刺、中藥、針藥結合戒毒的療效對比，上海針灸雜誌,

2001; 20(2):1-3.

10. Yang Tao 2001

楊濤，針灸戒毒的臨床研究，貴陽中醫學院學報, 2001; 23(4):56-59.

11. Song Xiaoge 2002

宋小鴿，張浩，王振華，等，針刺配合美沙酮改善海洛因戒斷綜合征臨床觀察，中國針灸, 2002; 12(12):795-797.

12. Jin Tao 2002

金濤，針刺耳穴配合美沙酮聯合戒毒 32 例，南京中醫藥大學學報, 2002; 18(5).

13. Zhang Pinggen 2004

張平根，康波，鐘旗，電針與美沙酮治療海洛因戒斷症狀的協同作用研究，上海針灸雜誌, 2004; 23(2):5-6.

14. Si Xiaoming 2004

司曉明，劉軍，低頻電流治療海洛因依據戒斷症狀，中華物理學與康復雜誌，2004; 26(5):303-304.

15. Zeng Xiangling 2004

曾湘玲，雷龍鳴，盧永紅，等，針刺督脈穴用於海洛因依賴脫毒治療的臨床對照觀察，中國針灸, 2004; 24(6):385-387.

16. Wen TunOing 2005

溫屯清，陽召軍，雷希齡，等，針刺治療海洛因戒斷綜合征的臨床應用，中國針灸, 2005; 25(7):449-453.

17. Rong Jun 2005

戎軍，陳俊逾，劉智豔，頭針改善海洛因依賴者脫毒期戒斷症狀的臨床研究，2005; 28(7):615-617.

18. Wang Zetao 2005

王澤濤，袁宜勤，王軍，等，耳穴貼壓配合藥物治療海洛因依賴療效觀察，上海針灸雜誌, 2005; 24(12):6-7.

19. He Jeking 2005

賀捷靈，李玉蘭，電針在戒毒治療中的應用，中國藥物濫用防治雜誌，2005;

11(3):169-170.

20. Chen Li 2005

陳理，針灸加美沙酮治療海洛因戒斷症狀 34 例臨床觀察，江蘇中醫藥，2005; 26(9):32-33.

Appendix 6. Characteristics of excluded papers

Appendix 6A: Non-clinical trials: reviews

No.	Sudy	Year	Title
1	Alling FA	1990	Cranial electrostimulation (CES) use in the detoxification of opiate-dependent patients
2	Brewington V	1994	Acupuncture as a detoxification treatment: an analysis of controlled research
3	Brumbaugh, Alex G	1993	Acupuncture complements addiction treatment
4	Chen GS	1977	Enkephalin, drug addiction and acupuncture
5	Chevlen E	2003	Opioids: A Review
6	Culliton PD	1996	Overview of Substance abuse acupuncture treatment research
7	Dean AJ	2005	Natural and complementary therapies for substance use disorders
8	Ernst E	2002	Complementary therapies for addictions: not an alternative
9	Grossman A	1985	Endorphins: “opiates for the masses”
10	Janssen PA	2005	Acupuncture for substance abuse treatment in the downtown Eastside of Vancouver
11	Kleber HD	1982	The treatment of nacrotic withdrawal: a historical review
12	Linde K	2001	Systematic reviews of complementay therapies – an annoted bibliography. Part 1: Acupuncture
13	Lu PK	2004	Managing acute withdrawal syndrome on patients with heroin and morphine addiction by acupuncture therapy
14	Margolin	1998	Investigation Alternative Medicine Therapies in Randomized Controlled Trials
15	Margolin A	2003	Acupuncture for Substance Abuse
16	Martin J	1993	Addressing treatment needs of Southeast Asian Mien Opium users in Califormia
17	McLellan AT	1993	Acupuncture treatment for drug abuse: a technical review
18	Moon	1994	Drug Treatment in Adult Probation: An Evaluation of an Outpatient and Acupuncture Program
19	O’Brein	1994	Overview: The treatment of drug dependence
20	Oleson	2002	Auricilotherapy stimulation for neuro-rehabilitation
21	Otto	2003	Acupuncture and Substance Abuse: A synopsis, with Indications for Further Research
22	Rogora GA	1997	A biochemical hypothesis for the effectiveness of acupuncture in the treatment of substance abuse:

			acupuncture and the reward cascade
23	Scott S	1997	A biochemical hypothesis for the effectiveness of acupuncture in the treatment of substance abuse: acupuncture and the reward cascade
24	Smith MO	1998	An acupuncture programme for the treatment of drug-addicted persons
25	Spencer CP	1980	Traditional therapies and the treatment of drug dependence in Southeast Asia
26	Susan Moner	1996	Acupuncture and Addiction Treatment
27	Ter Riet G	1990	A meta-analysis of studies into the effect of acupuncture on addiction
28	Unknown	1997	NIH panel validates role of acupuncture in addiction treatment
29	Vaughn	2003	Evaluating a prison-based drug treatment program in Taiwan
30	錢志雲	1998	針刺戒毒點滴體會

Appendix 6B: Non-clinical trials: case reports

No.	Sudy	Year	Title
1	Cocchi R	1979	Experience with detoxification and weaning of heroin addicts by means of acupuncture, gabergic drugs and psychopharmacologic agents in low doses
2	Kroening RJ	1985	Rapid narcotic detoxification in chronic pain patients treated with auricular electroacupuncture and naloxone
3	Kinsook S	2000	The experience of Acupuncture for treatment of Substance Dependence
4	Lorini G	1979	Acupuncture as a part of a program of detoxification and weaning from opiates: 25 cases
5	Lorini G	1982	Supression of the opiate withdrawal syndrome with GABA analogs, low-dose psychotrophic drugs and acupuncture
6	Rusell LC	2000	Acupuncture for addicted patients with chronic histories of arrest
7	Sainsbury MJ	1974	Acupuncture in heroin withdrawal
8	Shuaib BM	1976	Acupuncture treatment of drug dependence in Pakistan
9	Uwe Verthein	2002	Auricular Acupuncture As a Treatment of Cocaine, Heroin and Alcohol Addiction
10	Wen HL	1977	Fast Detoxification of heroin addicts by acupuncture and

			electrical stimulation (AES) in combination with naloxone
11	陳寶珠	1995	電耳針戒毒及其機理鎮江醫學院學報
12	沈餘生	1998	針刺戒毒驗方
13	範紅	1998	針刺治療海洛因戒斷綜合征 20 例
14	方勇飛	2001	針灸與藥物相結合救治海洛因中毒後昏迷 15 天 1 例報告
15	李峰	1998	針刺治療海洛因戒斷反應 27 例
16	王金漢	2003	針灸在美沙酮替代遞減戒斷療法中的運用
17	王曉中	1996	至陽穴在海洛因戒斷治療中的效應
18	王忠全	1997	山莨菪堿及針刺治療海洛因依賴者的療效觀察
19	韋勇	1997	耳穴電刺激配合體針治療吸毒者睡眠障礙
20	溫屯清	1997	針刺治療戒毒者頑固性失眠 156 例
21	溫屯清	1999-1	針刺內關治療戒毒者癲癇 78 例
22	溫屯清	1999-2	針刺治療海洛因成癮 200 例

Appendix 6C: Non-clinical trials: letters, editorials

No.	Sudy	Year	Title
1	Low SA	1974	Letter: Acupuncture and heroin withdrawal
2	Sainsbury MJ	1974	Letter: Heroin Withdrawal using ear acupuncture
3	Unknown	1974	Editorial: Acupuncture in heroin withdrawal

Appendix 6D: Insufficient outcome data

No.	Sudy	Year	Title
1	Johnson SH	1983	Treatment of drug abusers in Malaysia: a comparison
2	Montazeri K	2002	The effect of acupuncture on the acute withdrawal symptoms from opioid detoxification
3	Newmeyer JA	1984	Acupuncture as a detoxification modality
4	Timofeev MF	1999	Effects of acupuncture and an agonist of opiate receptors on heroin dependent patients
5	Washburn AM	1993	Acupuncture heroin detoxification: a single-blind clinical trial
6	Wells EA	1995	Acupuncture as an adjunct to methadone treatment services
7	Wen HL	1975	Experience in the treatment of drug addiction by electro-acupuncture
8	Wen HL	1980-1	Clinical experience and mechanism of acupuncture and

			electrical stimulation (AES) in the treatment of drug abuse
9	Wen HL	1980-2	Immunoassayable Beta-Endorphon Level in the Plasma and CSF of Heroin Addicted and Normal Sujects Before and After Electroacupuncture
10	劉輝	2001	針刺合美沙酮對 20 例海洛因戒斷綜合征胃電圖影響
11	羅永芬	2001	針刺對海洛因依賴者血 IL-2 的影響
12	王華	2001-1	穴位電刺激治療海洛因依賴者稽延性綜合征臨床研究
13	王華	2001-2	胃電穴位刺激聯合多慮平治療脫毒後戒斷征
14	吳俊梅	2002	針刺改善海洛因依賴者心理渴求的研究
15	吳俊梅	2005	針刺對海洛因依賴者脫毒末期 90 項症狀清單各因數的影響
16	張本國	2000	單獨應用韓氏戒毒儀治療海洛因成癮 121 例報告
17	趙長根	1997	阿片類成癮慢性戒斷症狀電針治療的對照研究

Appendix 6E: Non-medicinal control

No.	Sudy	Year	Title
1	Berman AH	2004	Treating drug using prison inmates with auricular acupuncture: A randomized controlled trial
2	Gurevich MI	1996	Is auricular acupuncture beneficial in the inpatient treatment of substance-abusing patients?
3	Severson L	1977	Heroin detoxification with acupuncture and electrical stimulation
4	Wen HL	1979	Acupuncture in heroin addicts: changes in met-enkephalin and β-endorphin in blood and cerebrospinal fluid
5	Wu JM	2003	Clinic research on heroin de-addiction effects of acupuncture and its potentiality of preventing relapse
6	吳俊梅	2003	針刺對海洛因依賴的脫毒療效及其防複吸潛力的臨床研究
7	吳鑒楨	1992	韓氏穴位神經刺激儀（HANS）對 75 例海洛因戒斷者心率的影響
8	吳鑒楨	1995	韓氏穴位神經刺激儀治療阿片戒斷綜合征的臨床研究
9	吳慶民	1999	電戒療法用於阿片類藥物依賴脫毒治療的臨床觀察
10	張桂芝	2004	針刺治療海洛因依賴者的閉經
11	莊禮興	1995	針灸結合中藥治療吸服海洛因成病 25 例療效觀察
12	莊禮興	1995	針灸結合中藥治療吸服海洛因 25 例療效觀察

Appendix 6F: Patients in non-acute stage

No.	Sudy	Year	Title
1	蔡植	1998	戒毒後期的針灸治療
2	曹長安	1997	韓氏穴位神經刺激儀與丁丙諾啡聯合應用應用治療 72 例海洛因依賴者的臨床觀察
3	賀捷靈	2005	電針與藥物療法治療阿片類物質依賴患者的療效對比
4	聶慧明	2001	耳穴壓迫法治療吸毒者繼發性閉經及稽延性戒斷症狀療效分析
5	牛文民	2000	耳針在阿片類毒品戒斷綜合征治療中的運用
6	舒榮	2003	經絡導平治療海洛因戒斷後期稽延性綜合征
7	萬萍	1997	耳穴貼壓爲主治療海洛因依賴慢性戒斷症狀 89 例療效觀察
8	文玫	2004	耳穴貼壓法治療海洛因依賴者稽延性戒斷症狀臨床觀察
9	朱忠春	2005	電針治療海洛因依賴者戒斷後睡眠障礙的臨床觀察

Appendix 7: References of excluded papers

Appendix 7A: Non-clinical trials: reviews (English papers: 29; Chinese paper: 1)

Appendix 7A1. English:

1. **Alling FA 1990**

   Alling FA. Cranial electrostimulation (CES) use in the detoxification of opiate-dependent patients. J Subst Abuse Treat, 1990; Vol. 7 (3), pp.173-80.

2. **Brewington V 1994**

   Brewington V. Acupuncture as a detoxification treatment: an analysis of controlled research. J Subst Abuse Treat, 1994 Jul-Aug; Vol. 11 (4), pp.289-307.

3. **Brumbaugh 1993**

   Brumbaugh, Alex G. Acupuncture complements addiction treatment. Addiction Letter, 1993 Oct, Vol. 9 (10), pp.3, 1/3p.

4. **Chen GS 1977**

   Chen GS. Enkephalin, drug addiction and acupuncture. Am J Chin Med (Gard City N Y), 1977 Spring; Vol. 5 (1), pp.25-30.

5. **Chevlen E 2003**

   Chevlen E. Opioids: A Review. Current Pain and Headache Reports. 2003; Vol. 7, pp.15-23.

6. **Culliton PD 1996**

   Culliton PD, Kiresuk TJ. Overview of Substance abuse acupuncture treatment research. J Altern Complement Med, 1996 Spring; Vol. 2(1), pp.149-59, discussion 161-5.

7. **Dean AJ 2005**

   Dean AJ. Natural and complementary therapies for substance use disorders. Current opinion in Psychiatry, 2005; Vol. 18 (3), pp.271-276.

8. **Ernst E 2002**

   Ernst E. Complementary therapies for addictions: not an alternative. Addiction,

2002 Dec; Vol. 97 (12), pp.1491, 2p.

9. **Grossman A 1985**

Grossman A. Endorphins: “opiates for the masses”. Med Sci Sports Exerc, 1985 Feb; Vol. 17(1), pp. 101-5.

10. **Janssen PA 2005**

Janssen PA, Demorest LC, Whynot EM. Acupuncture for substance abuse treatment in the downtown Eastside of Vancouver. Journal of Urban Health-Bulletin of the New York Academy of Medicine, 2005 Jun, Vol. 82 (2), pp.285-295.

11. **Kleber HD 1982**

Kleber HD. The treatment of nacrotic withdrawal: a historical review. J Clin Psychiatry, 1982 Jun; Vol. 43 (6.2), pp. 30-34.

12. **Linde K 2001**

Linde K, Vickers A, Hondras M, ter Riet G et al. Systematic reviews of complementay therapies – an annoted bibliography. Part 1: Acupuncture. BMC Complementary and Alternative Medicine, 2001; Vol. 1, pp.3.

13. **LU PK 2004**

Lu PK. Managing acute withdrawal syndrome on patients with heroin and morphine addiction by acupuncture therapy. Acupunct Electrother Res, 2004; Vol. 29(3-4), pp. 187-195.

14. **Margolin 1998**

Margolin, Arthur, Avants, S. Kelly. Investigation Alternative Medicine Therapies in Randomized Controlled Trials. Journal of the American Medical Association, 1998; Vol. 280 (18), pp. 1626, 3p.

15. **Margolin A 2003**

Margolin A. Acupuncture for Substance Abuse. Current Psychiatry Reports, 2003; Vol. 5, pp.333-339.

16. **Martin J 1993**

Martin J. Addressing treatment needs of Southeast Asian Mien Opium users in Californiа. J Psychoactive Drugs, 1993 Jan-Mar; Vol. 25 (1), pp. 73-76.

17. **McLellan AT 1993**

McLellan AT. Acupuncture treatment for drug abuse: a technical review. J Sunst Abuse Treat, 1993 Nov-Dec; Vol. 10 (6), pp.569-76.

18. **Moon 1994**

Moon, Melissa M, Laressa, Edward J. Drug Treatment in Adult Probation: An Evaluation of an Outpatient and Acupuncture Program. Evaluation and Program Planning, 1994 Apr-Jun; Vol. 17(2), pp.217-36.

19. **O'Brien 1994**

O'Brein, Charles P. Overview: The treatment of drug dependence. Addiction, 1994 Nov; Vol. 89 (11), pp.1565-1569, 5p.

20. **Oleson 2002**

Oleson, Terry. Auricilotherapy stimulation for neuro-rehabilitation. NeuroRehabilitation, 2002; Vol. 17 (1), pp.49, 14p.

21. **Otto 2003**

Otto, Katherine C. Acupuncture and Substance Abuse: A synopsis, with Indications for Further Research. American Journal on Addiction, 2003 Jan/Feb; Vol. 12(1), pp.43-51, 9p.

22. **Rogora GA 1981**

Rogora GA. Critical considerations on the use of acupuncture in a group of heroin addicts. Minerva Med, 1981 Sep 15; Vol. 72 (33), pp. 2223-5.

23. **Scott S 1997**

Scott S. A biochemical hypothesis for the effectiveness of acupuncture in the treatment of substance abuse: acupuncture and the reward cascade. American Journal of Acupuncture, 1997 Jan 1; 25(1), pp.33-8.

24. **Smith MO 1998**

Smith MO. An acupuncture programme for the treatment of drug-addicted persons.

Bull Narc, 1998; Vol. 40(1), pp. 35-41.

25. **Spencer CP 1980**

Spencer CP. Traditional therapies and the treatment of drug dependence in Southeast Asia. Am J Chin Med, 1980 Autumn; Vol. 8 (3), pp.230-8.

26. **Susan Moner 1996**

Susan Moner. Acupuncture and Addiction Treatment. Journal of Addictive Diseases, 1996, Vol. 15 (3), pp.79.

27. **Ter Riet G 1990**

Ter Riet G. A meta-analysis of studies into the effect of acupuncture on addiction. Br J Gen Pract, 1990 Sep; Vol. 40 (338), pp.379-382.

28. **Unknown 1997**

Unknown. NIH panel validates role of acupuncture in addiction treatment. Alcoholism & Drug Abuse Weekly, 1997, Vol. 9(45), pp.7, 1/2p.

29. **Vaughn 2003**

Vaughn, Michael S, Deng et al. Evaluating a prison-based drug treatment program in Taiwan. Journal of Drug Issues, 2003 Spring; Vol. 33(2), pp.357, 28p.

Appendix 7A2. Chinese:

30. **Oian Zhiyun 1998**

錢志雲. 針刺戒毒點滴體會. 中國針灸, 1997; 12(17):735-736.

Appendix 7B: Non-clinical trials: case reports

(English papers: 10; Chinese papers: 12)

Appendix 7B1: English:

1. **Cocchi R 1979**

Cocchi R. Experience with detoxification and weaning of heroin addicts by means of acupuncture, gabergic drugs and psychopharmacologic agents in low doses. Minerva Med, 1979 May 19; Vol. 70 (24), pp. 1735-44.

2. **Kroening RJ 1985**

Kroening RJ. Rapid narcotic detoxification in chronic pain patients treated with auricular electroacupuncture and naloxone. Int J Addict, 1985 Sep; Vol. 20(9), pp. 1347-60.

3. **Kunsook Song 2000**

Kinsook S. The experience of Acupuncture for treatment of Substance Dependence. Journal of Nursing Scholarship, 2000, Vol. 32(3), pp.267.

4. **Lorini G 1979**

Lorini G. Acupuncture as a part of a program of detoxification and weaning from opiates: 25 cases. Minerva Med, 1979 Dec 15; Vol. 70 (56), pp.3831-6.

5. **Lorini G 1982**

Lorini G. Supression of the opiate withdrawal syndrome with GABA analogs, low-dose psychotrophic drugs and acupuncture. Minerva Med, 1982 Mar 31; Vol. 73 (13), pp.707-10.

6. **Russell LC 2000**

Rusell LC. Acupuncture for addicted patients with chronic histories of arrest. A pilot study of the Construction Treatment Center. J Subst Abuse Treat, 2000 Sep; Vol. 19 (2), pp. 199-205.

7. **Sainsbury MJ 1974**

Sainsbury MJ. Acupuncture in heroin withdrawal. Med J Aust, 1974 Jul 20; Vol. 2(3), pp.102-5.

8. **Shuaib BM 1976**

Shuaib BM. Acupuncture treatment of drug dependence in Pakistan. Am J Chin Med (Grad City N Y), 1976 Winter; Vol. 4(4), pp.403-7.

9. **Uwe Verthein 2002**

Uwe Verthein. Auricular Acupuncture As a Treatment of Cocaine, Heroin and Alcohol Addiction. Addictive Disorders & Their Treatment, 2002; Vol.1(1), pp.11.

10. **Wen HL 1977**

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Appendix 7B2: Chinese:

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陳寶珠. 電耳針戒毒及其機理鎮江醫學院學報, 1995; 5(3):252-253.

12. Chen Yu Sheng 1998

沈餘生. 針刺戒毒驗方. 浙江中醫雜誌, 1998: 33(10): 468-468.

13. Fan Hom 1998

範紅. 針刺治療海洛因戒斷綜合征 20 例. 上海針灸雜誌, 1998; 17(1):11-12.

14. Fang Yongfei 2001

方勇飛, 鄒曉陽, 王勇. 針灸與藥物相結合救治海洛因中毒後昏迷 15 天 1 例報告. 中國藥物濫用防治雜誌, 2001; 6:45-46.

15. Li Feng 1998

李峰, 何小平, 成玉蘭, 等. 針刺治療海洛因戒斷反應 27 例. 福建中醫藥, 1998; 29(5):30-30.

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王曉中, 馬素蘭, 馬毅鈞. 至陽穴在海洛因戒斷治療中的效應. 1996; 10:19-20.

18. Wang Zhongquan 1997

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19. Wei Yong 1997

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溫屯清. 針刺治療戒毒者頑固性失眠 156 例, 中國針灸. 1999; 19(1):17-17.

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溫屯清. 針刺治療海洛因成癮 200 例. 浙江中醫雜誌, 1999; 21:416-417.

Appendix 7C: Not-clinical trials: letters, editorials (English papers: 3)

1. Low SA 1974

Low SA. Letter: Acupuncture and heroin withdrawal. Med J Aust, 1974 Aug 31; Vol. 2 (9), pp.899.

2. Sainsbury MJ 1974

Sainsbury MJ. Letter: Heroin Withdrawal using ear acupuncture. Med J Aust, 1974 Jun 1; Vol. 1 (22), pp.899.

3. Unknown 1974

Unknown. Editorial: Acupuncture in heroin withdrawal. Med J Aust, 1974 Jul 20; Vol. 2 (3), pp.82.

Appendix 7D: Insufficient outcome data (English papers: 10; Chinese papers: 8)

Appendix 7D1. English:

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Johnson SH. Treatment of drug abusers in Malaysia: a comparison. Int J Addict, 1983 Oct; Vol. 18 (7), pp. 951-8.

2. Montazeri K 2002

Montazeri K. The effect of acupuncture on the acute withdrawal symptoms from opioid detoxification. Acta Anaesthesiol Sin, 2002 Dec; Vol. 40 (4), pp.173-7.

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1984 Jul-Sep; Vol. 16 (3), pp.241-61.

4. **Timofeev MF 1999**

Timofeev MF. Effects of acupuncture and an agonist of opiate receptors on heroin dependent patients. Am J Chin Med, 1999; Vol. 27 (2), pp. 143-8.

5. **Washburn AM 1993**

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6. **Wells EA 1995**

Wells EA, Jackson R, DIAZ OR, et al. Acupuncture as an adjunct to methadone treatment services. American Journal on Addictions 1995; Vol. 4 (3), pp.198-214.

7. **Wen HL 1975**

Wen HL. Experience in the treatment of drug addiction by electro-acupuncture. Xianggang Hu Li Za Zhi, 1975 Nov; Vol. 19, pp.33-35.

8. **Wen HL 1980-1**

Wen HL. Clinical experience and mechanism of acupuncture and electrical stimulation (AES) in the treatment of drug abuse. Am J Chin Med, 1980 Winter; Vol. 8 (4), pp.349-53.

9. **Wen HL 1980-2**

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10. **Zhang B 2000**

Zhang B. Treatment of 121 heroin addicts with Han's acupoint nerve stimulator. Zhongguo Zhong Xi Yi Jie He Za Zhi, 2000 Aug; Vol. 20 (8), pp. 93-5.

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安徽中醫學院學報, 2001;　20(5):32-33.

12. Luo Yongfeng 2001

羅永芬，吳俊梅，余曙光．針刺對海洛因依賴者血 IL-2 的影響．四川中醫，2001; 19(9):13-14.

13. Wang Hua 2001-1

王華．穴位電刺激治療海洛因依賴者稽延性綜合征臨床研究．中國針灸, 2001; 21(12):711-712.

14. Wang Hua 2001-2

王華，衛麗．胃電穴位刺激聯合多慮平治療脫毒後戒斷征．四川中醫，2001; 19(11):70-71.

15. Wu Junmei 2002

吳俊梅，林建華，羅永芬，等．針刺改善海洛因依賴者心理渴求的研究．成都中醫藥大學學報, 2002; 25(3):5-6.

16. Wu Junmei 2005

吳俊梅，羅永芬．針刺對海洛因依賴者脫毒末期 90 項症狀清單各因數的影響．上海針灸雜誌, 2005; 24(8):4-7.

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張本國，羅非，劉崇悅，等．單獨應用韓氏戒毒儀治療海洛因成癮 121 例報告．中國中西醫結合雜誌, 2000; 20(8):593-595.

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趙長根，張學芳．阿片類成癮慢性戒斷症狀電針治療的對照研究．中國行爲醫學科學, 1997; 6(4):289-291.

Appendix 7E: Non-medicinal control (English papers: 5; Chinese papers: 7)

Appendix 7E1. English:

1. Berman AH 2004

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abuse treatment, Mar 2004; Vol. 26 (2), pp.95-102.

2. Gurevich MI 1996

Gurevich MI. Is auricular acupuncture beneficial in the inpatient treatment of substance-abusing patients? J Subst Abuse Treat, 1996 Mar-Apr; Vol. 13 (2), pp.165-71.

3. Severson L 1977

Severson L. Heroin detoxification with acupuncture and electrical stimulation. Int J Addict, 1977 Oct; Vol. 12 (7), pp.911-22.

4. Wen HL 1979

Wen HL, et al. Acupuncture in heroin addicts: changes in met-enkephalin and β-endorphin in blood and cerebrospinal fluid. The Lancet, 1979 Aug 25; Vol. 25, pp.257-260.

5. Wu JM 2003

Wu JM. Clinic research on heroin de-addiction effects of acupuncture and its potentiality of preventing relapse. Zhong Xi Yi Jie He Xue Bao, 2003 Nov; Vol. 1 (4), pp. 268-72.

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吳俊梅, 魏東焰, 羅永芬, 等. 針刺對海洛因依賴的脫毒療效及其防複吸潛力的臨床研究. 中西醫結合學報, 2003; 1(4):268-272.

7. Wu Liuzhen 1992

吳鑾楨, 崔彩蓮, 韓濟生. 韓氏穴位神經刺激儀（HANS）對 75 例海洛因戒斷者心率的影響. 中國疼痛醫學雜誌, 1992; 2(2):98-102.

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吳鑾楨, 崔彩蓮, 韓濟生. 韓氏穴位神經刺激儀治療阿片戒斷綜合征的臨床研究. 中國疼痛醫學雜誌, 1995; 1(1):30-38.

9. Wu Xingmin 1999

吳慶民. 電戒療法用於阿片類藥物依賴脫毒治療的臨床觀察. 中國藥物濫用防治雜誌, 1999; 6:30-32.

10. **Zhang Guizhi 2004**

張桂芝, 趙琪, 馮秀娥, 等. 針刺治療海洛因依賴者的閉經. 中國藥物依賴性雜誌, 2004; 13(4):284-285.

11. **Zhuang Lixing 1995**

莊禮興, 陳興華, 江鋼輝. 針灸結合中藥治療吸服海洛因成病 25 例療效觀察. 廣州中醫學院學報, 1995; 1:67-69.

12. **Zhuang Lixing 1995**

莊禮興, 陳興華, 江鋼輝. 針灸結合中藥治療吸服海洛因 25 例療效觀察. 廣州中醫學院學報, 1995; 12(1):33-35.

Appendix 7F: Patients in non-acute stage (Chinese papers: 9)

1. **Cai Zhi 1998**

蔡植, 溫屯清, 徐沙煇. 戒毒後期的針灸治療. 江蘇中醫, 1998; 19(12):35-35.

2. **Cao Zhangan 1997**

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3. **He Jeling 2005**

賀捷靈, 李玉展. 電針與藥物療法治療阿片類物質依賴患者的療效對比. 中國臨床康復, 2005; 9(8):215-215.

4. **Nie Weiming 2001**

聶慧明, 喬鳳英, 孫家富, 等. 耳穴壓迫法治療吸毒者繼發性閉經及稽延性戒斷症狀療效分析. 中國藥物依賴性雜誌, 2001; 10(3):204-206.

5. **Niu Wenmin 2000**

牛文民, 劉海洋, 張育恒. 耳針在阿片類毒品戒斷綜合征治療中的運用. 上海針灸雜誌, 2000; 19(6):18-19.

6. **Shu Rong 2003**

舒榮，文秀英，茹立強，等．經絡導平治療海洛因戒斷後期稽延性綜合征．中國針灸, 2003; 23(6):325-328.

7. Wan Ping 1997

萬萍，張婉萍，吳仁貴．耳穴貼壓爲主治療海洛因依賴慢性戒斷症狀 89 例療效觀察．中國針灸, 1997; 7:393-394.

8. Wen Mei 2004

文玫，朱宏亮，李煜．耳穴貼壓法治療海洛因依賴者稽延性戒斷症狀臨床觀察．中國藥物濫用防治雜誌. 2004; 10(3):166-167.

9. Zhu Zhongchun 2005

朱忠春，穆敬平，梁艷，等．電針治療海洛因依賴者戒斷後睡眠障礙的臨床觀察．上海針灸雜誌, 2005; 24(5):6-8.