Meta-analysis on Chinese Herbal Therapy for Heroin Withdrawal Syndrome

Xu Min¹, Dominic TS Lee² and Wendy Wong¹
¹ Hong Kong Baptist University
² The Chinese University of Hong Kong

Abstract

Background and objectives: Heroin dependence is associated with significant morbidity and mortality, and is a priority of health and social problem in Hong Kong. Chinese herbal therapy (CHT) has been used to treat heroin dependence for around 160 years, and more and more clinical trials on CHT have been conducted during the past decade. The aim of this study is to systematically assess the quality of these trials, and the efficacy as well as safety of CHT with the principles and measurements of evidence-based medicine.

Methods: Randomized controlled trials (RCTs) on CHT treatment for heroin detoxification were collected. The quality of eligible trials was assessed by the Jadad scale; and the efficacy as well as safety of CHT were estimated by the odd ratio and applied to a meta-analysis.

Results: (1) 11 trials (881 treated with CHT in total of 1602 patients) that met the inclusive criteria were reviewed systematically, and 4 trials were graded as high quality (scoring 3-5 marks); (2) the efficacy of CHT was statistically significantly higher in the treatment of heroin withdrawal syndrome when compared with Western medications (clonidine, methadone, tramadol, estazolam, buprenophine) (11RCTs, OR=2.22, 95% CI: 1.18, 4.18, P=0.01); (3) the further subgroup analysis indicated that CHT was more effective than clonidine (5RCTs, OR=1.68, 95% CI: 1.15, 2.45, P=0.008); (4) the safety of CHT was statistically significant higher when compared with that of Western medications (7RCTs, OR=0.24, 95% CI: 0.13, 0.42, P<0.00001); (5) the sensitivity analysis indicated that the 4 high-quality trials gave homogenous combination of effects (P=0.72), while the other 7 low-quality trials gave heterogeneous combination of effects (P<0.00001).

Conclusion: CHT may be an effective and safe way for heroin detoxification. Further trials with high quality of study design should be conducted to verify the current evidence in this study.
**Key words:** Meta-analysis, Chinese herbal therapy, heroin dependence, withdrawal syndrome, detoxification

### 1. Introduction

Heroin dependence is associated with significant morbidity and mortality (Joe, et al., 1982; Klee & Morris, 1994). Epidemiological survey indicated that around 8 millions (0.14%) of people were abusing heroin over the world, and Eastern and Western Asia had the highest involved population (Wang & Huang, 2003). Heroin dependence is also a priority of health and social problem in Hong Kong. In 1998, 15,720 drug-dependent people were reported to the Central Registry of Drug Abuse with types of drug abused provided, 86.3% of them were known to have abused heroin (Narcotics Division of HKSAR, 2000).

Chinese herbal therapy (CHT) has been using to treat opium dependence clinically since the Ming and Qing Dynasties when opium was imported to China. Many clinical experiences on CHT for heroin detoxification were accumulated and recorded in ancient medical books. Based on the theories and experiences, CHT can be applied to treat heroin abusing at any stages of detoxification. In the past decade more and more clinical trials on heroin detoxification were conducted in China. It is valuable to identify the quality of these trials, efficacy and safety of CHT with the principles and measurements of evidence-based medicine.

In the present study we performed a systematical review and meta-analysis for (1) assessing the quality of clinical trials of CHT in the treatment of heroin dependence, (2) assessing the efficacy and safety of CHT in the treatment of heroin withdrawal syndrome, and (3) comparing the efficacy and safety of CHT with some Western medications for heroin detoxification.

### 2. Methods

#### 2.1 Inclusive and exclusive criteria

All randomized controlled trials (RCTs) that compared the efficacy or safety of CHT with Western medications were included. The studies for comparing the effect of CHT plus Western medications versus Western medications were excluded since they might introduce heterogeneity in the further data synthesis and analysis, and increase difficulty for identifying the actual effect of CHT in the
study. All inpatients and outpatients who were heroin addicts were considered as participants. No distinction was made among addicts dependent on heroin alone or on heroin and other drugs. No restriction on age or gender. Intervention of the study included any oral administration of Chinese herbs at any dosage as the principal treatment to manage the signs and symptoms of heroin withdrawal syndrome. The control group may be treated with placebo or Western medications. The outcome included measures of efficacy and safety that was based on the number of patients whose heroin withdrawal syndrome was improved and the incidence of adverse effects occurred during treatments respectively.

2.2 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 “herb”, 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, herbal medicine, herbal therapy, Chinese herbs, plant medicine, plant drug, phytomedicine, phytotherapy, etc. were used.

The electronic databases including the Database of Chinese Science Journals (中文科技期刊資料庫), the Database of Chinese Journals of TCM (中國中醫藥期刊文獻資料庫), CBMdisc (中國生物醫學文獻資料庫), Cochrane Library, MEDLINE, EMBASE, BIOSIS, CINAHL, World Cat and Article first were searched from their dates of commencement to June 2003. The databases of ongoing trials (Current Controlled Trials or The National Research Register) were also searched. In addition, new journals from June of 2003 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. 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.

2.3 Data extraction and analysis

Full-text articles of each potential eligible trial were retrieved and assessed by two independent reviewers (Xu Min and Wong Wendy) to determine if the articles were recruited and further analyzed...
according to the inclusion and exclusion criteria. Missing information was sought by contacting article authors. A data abstraction form was used to summarize key information from included trials, and key information was extracted by one reviewer and confirmed by the other reviewer. Any disagreement was resolved with discussions.

The methodological quality of the included trials was assessed by the Jadad scale (Jadad, et al., 1996) which assessed randomization, double-blinding and drop-outs of the trials by ranking them with 1-5 points. The trials scored with 1 or 2 points were considered as low-quality trials, while those scored with 3-5 points were considered as high-quality trials. Moreover, a meta-analysis was carried out by using a Review Manager 4.2 (Cochrane software) to combine and analyze the data from individual trials. The statistical validity of combining various trials was assessed by examining the homogeneity of the outcomes from the trials using a Q-test (Mantel-Haenszel Chi-square test). Possible sources of heterogeneity were further assessed by sensitivity and subgroup analysis. Overall results of combined trials were calculated with fixed or random effects models, and dichotomous data were presented as the Odd Ratios (OR) and 95% confidence interval (95% CI).

3. Results

3.1 Excluded and included trials

The literature searching found that 78 trials conducted in Mainland China involving the administration of CHT for heroin detoxification. However, 67 trials of them were excluded as they did not meet the inclusion criteria, and the reasons were (1) either no concurrent comparison treatment or comparison modality that was not one defined by the inclusion criteria (51 trials) and (2) insufficient outcome data (16 trials). Finally, a total of 11 trials involved 1602 participants (72% male and 28% female with the mean age of 26.9 years old) met the inclusion criteria, and the group size of these trials ranged from 15 to 400 participants who were withdrawing from heroin dependence and treated with CHT (881 patients) or Western medications (721 patients).

3.2 Outcome measurement

Although the intensity of withdrawal was assessed quantitatively by measuring the scores of withdrawal syndrome in the 11 included trials, the diversity of scales and calculations used for rating withdrawal severity prevented a direct comparison of scores across trials. The CINA and
HAMA assessment scale were used for outcome measurement by five trials (Hu & Huang, 1995; Li, et al., 1999; Zhang, et al., 1999; Xu, et al., 2000; Xu & He, 2001); one trial used an assessment scale according to the Drugs and Alcohol Organization (Shen, 1998) and other five trials used self-developed assessment scales (Lan, et al., 1997; Zhang, et al., 1999; Xiong & Li, 2000; Liu & Xiao, 2000; Li, et al., 2001). Therefore, a quantitative analysis of the intensity of withdrawal was not available.

All 11 included trials provided the number of patients whose heroin withdrawal syndrome was treated effectively. A total of 658 participants out of 881 participants treated with CHT relieved their withdrawal syndrome. While 411 out of 721 participants relieved their withdrawal syndrome after treatment of Western medications. In addition, adverse effects were observed and reported by 7 trials (Hu & Huang, 1995; Shen, 1998; Zhang, et al., 1999; Liu & Xiao, 2000; Xiong & Li, 2000; Xu, et al., 2000; Xu & He, 2001). 4 trials did not report any adverse effect (Zhang, et al., 1999; Li, et al., 1999; Li, et al., 2001) nor stated clearly (Lan, et al., 1997).

### 3.3 Quality assessment

The assessment by Jadad scale showed that 4 trials could be classified as high-quality trials (3-5 points), (Zhang, et al., 1999; Xu, et al., 2000; Li, et al., 2001; Xu & He, 2001), and the other 7 trials were low-quality trials (1-2 points) (Hu & Huang, 1995; Lan, et al., 1997; Shen, 1998; Li, et al., 1999; Zhang, et al., 1999; Liu & Xiao, 2000; Xiong & Li, 2000). Within the 11 trials, inclusion criteria were described clearly in the papers for 10 trials; random allocation was done in all 11 trials but the concrete methods for randomization were only explained in the papers of 4 trials; the method of double-blinding or single-blinding was designed and explained in the papers of 2 trials (Li, et al., 1999; Zhang, et al., 1999) and 1 trial (Li, et al., 2001) respectively, and other 8 trials were open controlled trials (Hu & Huang, 1995; Lan, et al., 1997; Shen, 1998; Zhang, et al., 1999; Liu & Xiao, 2000; Xiong & Li, 2000; Xu, et al., 2000; Xu & He, 2001); dropout or withdrawal rate during the trials was reported and discussed in the paper of 1 trial only (Li, et al., 1999); and there was insufficient information on statistical methods in the papers of 2 trials (Lan, et al., 1997; Zhang, et al., 1999).

### 3.4 Meta-analysis

#### 3.4.1 Efficacy analysis

In order to compare CHT with Western medications in the number of patients whose heroin withdrawal
syndrome were treated effectively, the total analysis and subgroup analysis were conducted on (1) the kinds of medications used as control treatment in the 11 included trials, and (2) the presence of heterogeneity in the combination of effect in the analysis. Thus, results were reported in following 3 sections that reflected the treatment regimes as a comparison of (1) CHT vs. Western medications (clonidine, methadone, estazolam, tramadol and buprenophine), (2) CHT vs. clonidine, and (3) CHT vs. methadone.

(1) CHT vs. Western medications

By using the random effect model, Fig. 1 showed an analysis on the combined effects of all included 11 trials that 1602 patients were involved. The result indicated that 658 out of 881 patients (75%) received CHT had significant improvement in heroin withdrawal syndrome, while 411 out of 721 patients (57%) received Western medications had significant improvement. The efficacy of CHT was statistically significantly higher than that of Western medications (clonidine, methadone, tramadol, estazolam, buprenophine) (11RCTs, OR=2.22, 95% CI: 1.18, 4.18, P=0.01). A statistically significant heterogeneity presented in this analysis (P<0.00001) and it needed further subgroup analysis.

(2) CHT vs. clonidine

By using the fixed effect model, Fig. 2 showed an analysis on the combined effects of 5 trials that 651 patients were involved (Hu & Huang, 1995; Lan, et al., 1997; Li, et al., 1999; Zhang, et al., 1999; Xu & He, 2001). The result indicated that 327 out of 401 patients (82%) treated with CHT had significant improvement in heroin withdrawal syndrome, while 177 out of 250 patients (71%) treated with clonidine had significant improvement. The efficacy of CHT was statistically significantly higher than that of clonidine (5RCTs, OR=1.68, 95% CI: 1.15, 2.45, P=0.008). Since there was no heterogeneity in this subgroup analysis, this suggested that different medications that were used as controls in the trials should be one of the important factors that might contribute to the presence of heterogeneity in our analysis.

(3) CHT vs. methadone

By using the random effect model, Fig. 3 showed an analysis on the combined effects of 3 trials that 706 patients were involved (Shen, 1998; Liu & Xiao, 2000; Xu, et al., 2000). The result indicated that 290 out of 410 patients (71%) treated with CHT had significant improvement in heroin withdrawal
syndrome, while 115 out of 296 patients (39%) treated with methadone had significant improvement. There was no statistically significant difference between the group treated with CHT and the group treated with methadone, although the efficacy of CHT was higher than that of clonidine for 3.42 times (3RCTs, OR=3.42, 95% CI: 0.88, 13.72, P=0.08). The test of homogeneity showed a statistical significance (P=0.0004), which indicated that a subgroup analysis was needed for further exploration of the relevant factors, however the number of currently included trials was insufficient to perform further analysis temporarily.

3.4.2 Safety analysis

In order to compare CHT with Western medications in the incidence of adverse effects occurred during treatments, a meta-analysis was conducted based on the number of patients who had an adverse experience during the treatment by using the fixed effect model, Fig. 4 showed an analysis on the safety by combining 7 trials that 806 patients were involved (Hu & Huang,1995; Shen, 1998; Zhang, et al., 1999; Liu & Xiao, 2000; Xiong & Li, 2000; Xu, et al., 2000; Xu & He, 2001). The result indicated that 63 out of 470 patients (13%) treated with CHT had adverse experience, while 97 out of 336 patients (29%) treated with Western medications had adverse experience. The incidence of adverse effects of CHT was statistically significantly lower than that of Western medications (7RCTs, OR=0.24, 95% CI: 0.13, 0.42, P<0.00001).

The common adverse effects reported by the 7 trials were dizziness, nausea, vomiting, dry mouth, fatigue, fainting, sweating or palpitation. In general, the adverse effects reported from CHT treatment were lighter than those from treatment of Western medication or similar to placebo treatment in 6 trials (Lan, et al., 1997; Shen, 1998; Li, et al., 1999; Zhang, et al., 1999; Xu, et al., 2000; Xu & He, 2001). However, it was reported that 7 patients (17.5%) were suffered from mental confusion or delirium after treatment with Fukang Pian (Hu & Huang,1995), and 5 (6.3%) patients were suffered from blurred vision after treatment with Ji Tai Tablet (Xiong & Li, 2000).

3.4.3 Sensitivity analysis

Fig. 5 and 6 showed the sensitivity analysis carried out in this study for further analyzing the factors related to heterogeneity. The results indicated that the 4 high-quality trials gave homogenous combination of effect (P=0.72), while the other 7 low-quality trials gave heterogeneous combination of effects (P<0.00001). It demonstrated that the quality of trials assessed by the Jadad scale was
4. Discussion

Evidence-based medicine can provide the highest standard evidence (current best evidence) for clinical application. In terms of principles and measurements of evidence-based medicine, systematic review is an evidence-based qualitative process of defining the questions, searching literatures, assessing the quality of trials, applying eligibility criteria, examining and comparing the results of eligible trials, and conducting statistical synthesis of the data. Meta-analysis may be a part of a systematic review when individual trials are similar 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.

In this study the results of meta-analysis indicated that CHT was able to ameliorate the signs and symptoms of heroin withdrawal. A comparison on the therapeutic effects of 11 included trials supported that CHT might be more advantageous than Western medications (clonidine, methadone, tramadol, estazolam and bupernorphine) for detoxification of heroin addicts. Interestingly, a comparison between CHT and clonidine was further conducted by a subgroup meta-analysis, and the combined effects of 5 trials with homogeneity provided power evidence that showed statistically significantly positive benefits from CHT treatment. Although the data from this meta-analysis point towards CHT and methadone have similar effects in management of heroin withdrawal, there are limited data available from clinical trials for comparing CHT with methadone, tramadol, estazolam, bupernorphine and other western medications so far.

Despite the number of eligible trials and sample size of the trials are significantly insufficient for quantitatively assessing some aspects of CHT treatment by means of meta-analysis, additional evidences on the efficacy of CHT can be obtained from the results of many observational trials while some statistical form of controls has addressed alternative explanations of apparent effectiveness. These large scales of observational trials have generally supported the results from randomized controlled clinical trials and this systematic review that showed a significant therapeutic effect of CHT in treating heroin withdrawal syndrome.

The basic form of herbal medicine applied in the included 11 trials is herbal formula which is prepared
as herbal capsule, tablet, powder or decoction. Each herbal formula is composed of different kinds of natural herbs that contain very complex effective components such as polysaccharides, alkaloids, cholines, flavones, isoflavones, coumarins, lignins, amino acids, fatty acids, vitamins and so on. These herbal components exert broad and significant effects on regulating neuroendocrine system and immune system, and improving substance and energy metabolism in the body. It is presumed that the main role pattern and pharmacological mechanism of herbal therapy should be multi-target regulation and rehabilitation that may be laid a firm foundation for the application of CHT in heroin detoxification.

According to theories and experiences of traditional Chinese medicine, the main principles and methods of treatment of heroin withdrawal syndrome with CHT include: (1) removing toxic materials from the body by emetic therapy, purgative therapy, diuretic therapy (inducing a mild and temporary vomiting or diarrhea or diuresis) and detoxification therapy (improving the metabolism of drugs), (2) relieving symptoms (stopping pain and vomiting, improving digestion, treating restlessness and insomnia, etc.), and (3) invigorating the body functions. In recent years, many traditional therapies and herbal medicines have been systematically verified on their practice values by modern biomedical techniques.

It should be notable that amongst other systematic reviews including meta-analyses on Western medications such as clonidine and methadone conducted so far, the combined effect size usually focused on relative risk of retention rate, reduction of heroin use and criminal activity etc. is different to the outcome measurement of this review. Rather than assessing the patient number whose heroin withdrawal syndrome was treated effectively, we proposed in this review to investigate effects of CHT by other indexes which were commonly concerned by clinical practitioners. The assessment should be on intensity of withdrawal by withdrawal syndrome scores, time-course of withdrawal or duration of treatment, predominant signs and symptoms, drug positive results in urine samples, relapse rate, and indirect indications of treatment efficacy such as criminal activities, employment status and so on. However, owing to insufficiency of data and diversity of comparison from the included trials, quantitative analysis can not be performed for these aspects consequently. In view of the limitations of this meta-analysis by which only category data from clinical trials were assessed, further meta-analysis should be conducted on evaluation of measurement data and ranked data for verifying the findings of this study.
Our analysis also indicated that the incidence of adverse effects in patients treated with CHT was statistically significantly lower than that of Western medications. It is undoubted that the most patients received CHT may achieve a longer retention in detoxification treatment. The adverse effects reported in the patients treated with CHT were dizziness, nausea, vomiting, dry mouth, fatigue, fainting, sweating and palpitation that were generally minor in the trials. However, some herbal preparations like Fukang Pian containing toxic herbs may cause occurrence of some typical adverse effects in patients who eventually had to cease the treatment (Hu & Huang,1995). Standard pre-clinical studies and long-term clinical trials are still lack to observe the safety of preparations of CHT.

Another relevant outcome of this analysis to be considered would be quality assessment of the trials. Some papers collected by this review were excluded at the first phase due to some obvious quality problems. Fore example, 16 out of 67 papers (24%) did not report sufficient outcome data. The results of quality assessment by the Jadad scale demonstrated that 7 out of 11 included trials (64%) had to be rated as low-quality trials that were poor in the descriptions of randomization, double-blinding and dropout reporting. Furthermore, the results of subgroup analysis of sensitivity also indicated that low quality of the trials might directly affect the reasonability of data synthesis, and it should be one of the determinants to heterogeneity in meta-analysis. Owing to insufficient data and poor quality of the trials that baffle to document the results, further trials with high quality of study design should be needed to conduct in this field.

5. Conclusion

In this study, a systematic review and meta-analysis at the first time was performed to assess the efficacy and safety of CHT in treatment of heroin withdrawal syndrome. CHT may be an effective and safe way for heroin detoxification, and it possess some advantageous compared with Western medications. However, the data from primary trials for this review and analysis were limited. To verify the current evidence in this study, further trials with high quality of study design should be needed, and not only more category data but also measurement data and ranked data from clinical trials will be systematically reviewed and assessed in a new meta-analysis.

Acknowledgement

This project was supported by the Beat Drugs Fund of Hong Kong. The authors acknowledge the expert technical assistance of Dr. Ziea Eric at the Chinese University of Hong Kong.
References


Fig. 1  Meta-analysis on efficacy (CHT vs. Western Medications)

Fig. 2  Sub-group meta-analysis on efficacy (CHT vs. clonidine)

Fig. 3  Sub-group meta-analysis on efficacy (CHT vs. methadone)
Fig. 4  Meta-analysis on safety (CHT vs. Western medications)

Fig. 5  Sub-group meta-analysis on sensitivity (high-quality trials)

Fig. 6  Sub-group meta-analysis on sensitivity (low-quality trials)