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Acupuncture for Substance Addiction:

Understanding Mechanisms and Treatment Approaches

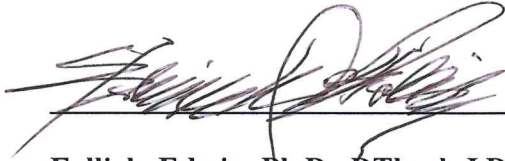# Based on the Literature Review

By

Hyo Jeong Kang

A RESEARCH PROJECT SUBMITTED

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REQUIREMENTS FOR THE DEGREE
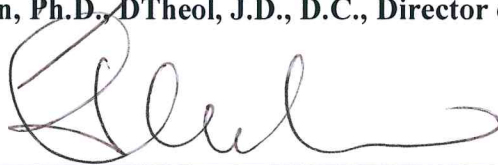

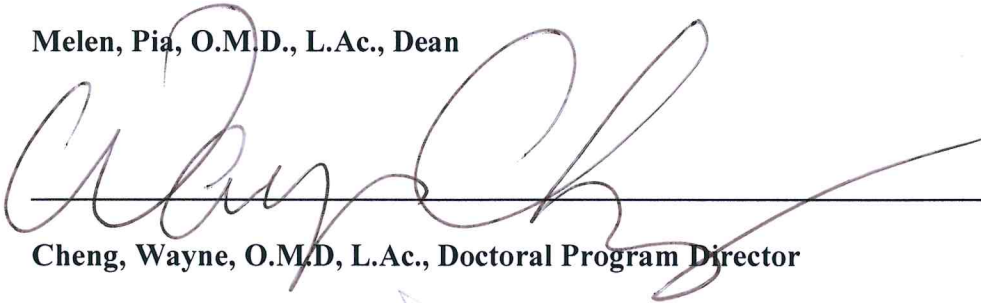Doctor of Acupuncture and Oriental Medicine

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ABSTRACT

Objective: This narrative literature review is designed to provide a basis for developing advanced, effective acupuncture treatment protocol for substance addiction based on an integrated perspective for further studies. The objectives of this study are twofold: One is to understand the mechanisms of substance addiction through the perspectives of Western and Oriental medicine. The other is to comparatively analyze the treatment approaches for each type of substance addiction by reviewing existing clinical evidence.

Methods: Literature search and identification of relevant studies were conducted through Internet search using the electronic databases or manual search. All the selected studies were thoroughly reviewed, and the extracted data was systemically and comparatively organized in order to synthesize mechanisms of addiction and treatment approaches.

Results: This study found some similarities and a difference between the perspectives of both medicines on the mechanism of addiction. Comparing to the Western Medicine, there

is a dearth of research on the mechanisms of addiction from the framework of Oriental Medicine. Thus, there is a difficulty in deriving integrated understanding from the perspectives of both medicines. Twelve (44.4%) studies out of 27 selected clinical trials showed positive results in the effectiveness of acupuncture treatment for substance addiction. The most commonly used intervention was auricular acupuncture (AA), and NADA Protocol (Sympathetic, Shenmen, Kidney, Lung, and Liver) has been most frequently selected regardless of the type of substance addiction in the reviewed studies. This review could not find a clear tendency of interventions or point selection for the treatment of addiction depending on the type of substance. This study assessed the methodological quality of selected clinical trials by Jadad scale, and fourteen studies (52%) were classified as low quality. This review failed to find a correlation between the quality and the outcomes of the study.

Conclusion: The findings of this review may provide a basis for clinicians and further research in the development of advanced, effective acupuncture treatment protocol for substance addiction.

Keywords: acupuncture, addiction, substance abuse, substance dependence

TABLE OF CONTENTS

I. INTRODUCTION

I.1. Research Background

Substance addiction is a chronic, relapsing brain disease characterized by compulsive drug seeking and use, despite adverse health and life effects on the user [1-2]. The consequences of substance addiction are varied and affect people of all ages. Similar to other diseases, substance addiction disrupts the healthy functioning of the body's organs [2]. Substance use disorders (SUDs) are often accompanied by various health problems, such as AIDS, Hepatitis B or C, neurological impairment, cardiovascular disease, stroke, lung disease, diabetes, cancer, and physical injury [2-6]. People with substance addiction also concurrently suffer from mental illness, such as anxiety, depression, schizophrenia, bipolar disorder, specific phobias, antisocial personality disorder, and borderline personality disorder [7]. The impact of substance addiction is far reaching. It is highly associated with significant social and economic consequences, such as relationship issues, low level of productivity, homelessness, poverty, violent crime, and imprisonment [1, 2, 6, 8].

Due to the significant consequences for individuals and society, substance addiction is considered to be one of the most serious and costly public health problems globally [2]. Worldwide, more than 150 million people have used an illicit drug such as cannabis, cocaine, or opioids [5], and individuals aged 15 years or older consume 6.2 liters of pure alcohol on average per year [8]. According to SAMHSA (Substance Abuse and Mental Health Services Administration)'s National Survey on Drug Use and Health, 22.5 million people (8.5 percent of the U.S. population) aged 12 or older in the United States required

treatment for an illegal drug or alcohol use problem in 2014 [9]. Within this population, only 4.2 million (18.5 percent of those who needed treatment) received any substance abuse treatment in the same year [9]. This lack of treatment indicates that development of more accessible, administrable, and cost-effective treatment for substance addiction is necessary. Since substance addiction has a variety of manifestations and afflicts so many aspects of an individual's life, the treatment cannot be simple. A model of effective treatment for substance addiction should necessitate more integrative and multimodal approaches.

I.2. Research scope and significances

Understanding the mechanisms of addiction is crucial for developing effective treatment modalities. Over the past several decades, the progression of brain science has developed our understanding of the mechanisms of addiction. A large number of scholarly studies on addiction have been conducted in the field of biomedicine [10-16]. However, relatively little research has been carried out based on the perspective of Oriental Medicine [17, 18]. Furthermore, no studies so far attempt to analyze the biomedical and Oriental perspectives of addiction comparatively. A comprehensive review on the mechanisms of addiction including both perspectives is required to develop effective integrated treatment approaches.

When comparing treatment approaches, Oriental Medicine includes more diverse and affordable modalities [19]. As a therapeutic intervention, acupuncture has been most commonly used for treating various types of substance addiction [20, 21]. There are major advantages associated with using acupuncture to treat substance addiction. Acupuncture is known as an inexpensive, simple, painless therapy that has fewer side effects [35, 69].

In 1972, the use of acupuncture for substance addiction was first reported in a Hong Kong study which observed that opiate withdrawal symptoms were relieved by acupuncture treatment [3, 22, 23]. Since then, several acupuncture treatment protocols have been developed to treat substance addiction. An auricular protocol was established by the National Acupuncture Detoxification Association (NADA) in the 1980s, and a treatment protocol of electrical stimulation on body points was designed by a Chinese practitioner in the 1990s [3, 22]. In 1996, the World Health Organization (WHO) accepted acupuncture as a relatively safe complementary and alternative medical approach for substance addiction [20].

In the past four decades, numerous studies have investigated the effects of acupuncture on substance addiction [3, 19-24, 36-62]. Research has illustrated that the effectiveness of numerous treatment modalities, including manually manipulated body acupuncture, electro-acupuncture, acupressure, auricular acupuncture, and scalp acupuncture [3, 19-24, 36-62]. A comparative literature review is necessary to synthesize the outcomes of current clinical evidence and comparatively analyze the treatment approaches for each type of substance addiction in order to develop better effective treatment approaches.

I.3. Research Objectives

This study is a narrative literature review on substance addiction. Based on the aforementioned necessities and significances, the objectives of this study are twofold: One is to understand the mechanisms of substance addiction through the perspectives of Western and Oriental medicine. The other is to comparatively analyze and synthesize the

treatment approaches for each type of substance addiction by reviewing existing clinical evidence.

I.4. Research Outline

The main framework of this study is shown in Fig. I-1. Literature search and identification of relevant studies were firstly conducted for data collection. All the selected studies were thoroughly reviewed, and key information was extracted for analysis and integration of data. Finally, data was systemically and comparatively organized in order to synthesize mechanisms of addiction and treatment approaches.

```
1. Data Collection
        ├── Literature search & Relevant Studies Identification
        └── Data Extraction

2. Review
        ├── Analysis of Data
        └── Integrating of Data

3. Results
        ├── Mechanisms of Addiction
        └── Comparative Analysis and Synthesis of Treatment Approaches
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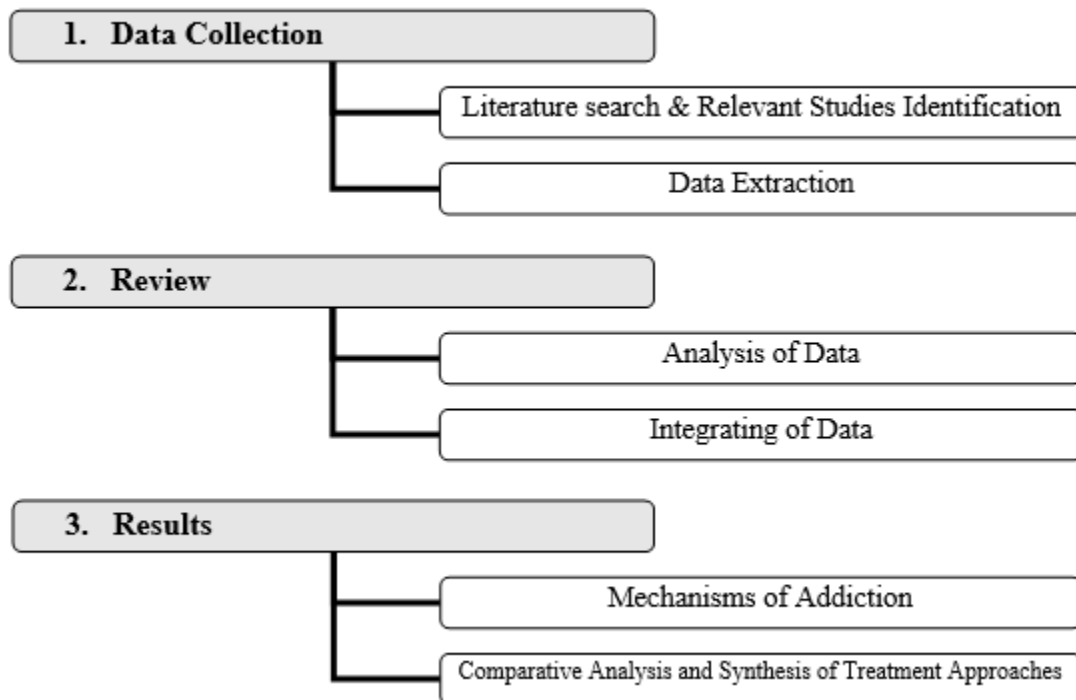
Fig. I-1. Research Outline

II. MATERIALS & METHODS

II.1. Literature Search

In January 2017, literature selection was performed using the following electronic databases: PubMed Central, EBSCOhost (MEDLINE complete), the Cochrane Central Register of Controlled Trials, WHO ICTRP (International Clinical Trials Registry Platform), ResearchGate, BioMed Central, and Hindawi Publishing Corporation. A comprehensive search of abstract databases was carried out using the keywords "acupuncture", "addiction", "substance abuse", and "substance dependence". Initially, 1,373 published articles were identified through the databases specified above. Only scholarly peer-reviewed full-text studies in the period from January 1996 to December 2016 were filtered out, and the record was narrowed down to 410 articles. After screening based on the predetermined inclusion and exclusion criteria and for eligibility, 12 relevant RCT studies and 3 non-randomized but well-designed clinical trials were identified from free full-text articles. In addition, 10 more full-text RCTs were retrieved through citation tracking using references listed in the previous studies, particularly from systematic reviews or meta-analyses. Two additional RCT studies were directly obtained from the authors as per request by the researcher of this study through ResearchGate. Finally, a total of 27 free full-text articles that met inclusion criteria were collected for analysis of treatment approaches. The literature selection process is illustrated in Figure II-1.

Nine monographs or books and eleven articles were additionally selected by manual search or Internet search through the electronic databases stated above to synthesize the mechanisms of addiction.

II.2. Inclusion and Exclusion

This study included studies published in the past 20 years that met the following criteria: (1) randomized controlled trials (RCTs) that adopted a double-blind, single-blind, or non-blind, (2) not randomized but well-designed clinical trials which have experimental group and control group, (3) qualitative clinical trial which doesn't have control group, and (4) studies for substance dependence including alcohol, cocaine, nicotine, opioids or opiates, and non-specified general substance addiction.

Exclusion criteria included (1) non-English language materials, (2) animal study, (3) non-clinical trial, (4) case studies, (5) non-substance addiction such as Internet addiction, game addiction or food addiction, and (6) non-scholarly articles such as comments, letters, media reviews, and magazines.

II.3. Data Extraction and Analysis

The following key information was extracted from each study: first author, publication year, type of substance, sample size, type of intervention: acupuncture method, type of control, treated acupoints/sites selected, outcome measures, and results reported. The quality of the selected clinical studies was assessed and scored using the Jadad Scale [25], which rates studies for randomization, double blinding, description of withdrawal, description of randomization, and description of blinding.

The findings of the pathophysiological mechanisms of addiction and all the extracted data of treatment approaches from the existing studies were comparatively analyzed and synthesized.
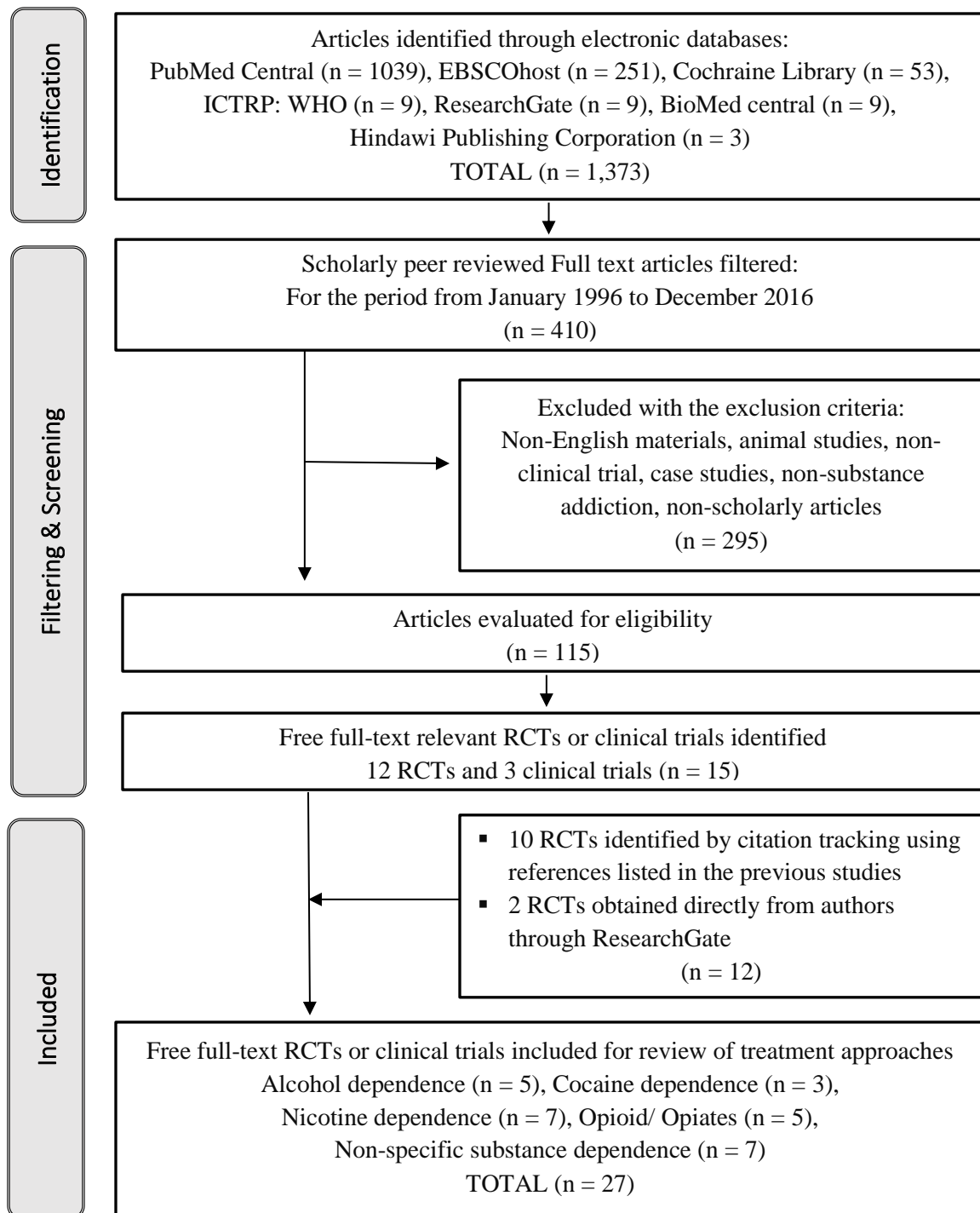
Fig. II-1 Flow Chart of Literature Selection for Treatment Approach Analysis

The flow chart contains the following:

Identification

Articles identified through electronic databases:
PubMed Central (n = 1039), EBSCOhost (n = 251), Cochraine Library (n = 53),
ICTRP: WHO (n = 9), ResearchGate (n = 9), BioMed central (n = 9),
Hindawi Publishing Corporation (n = 3)
TOTAL (n = 1,373)

Filtering & Screening

Scholarly peer reviewed Full text articles filtered:
For the period from January 1996 to December 2016
(n = 410)

Excluded with the exclusion criteria:
Non-English materials, animal studies, non-clinical trial, case studies, non-substance addiction, non-scholarly articles
(n = 295)

Articles evaluated for eligibility
(n = 115)

Free full-text relevant RCTs or clinical trials identified
12 RCTs and 3 clinical trials (n = 15)

Included

- 10 RCTs identified by citation tracking using references listed in the previous studies
- 2 RCTs obtained directly from authors through ResearchGate
(n = 12)

Free full-text RCTs or clinical trials included for review of treatment approaches
Alcohol dependence (n = 5), Cocaine dependence (n = 3),
Nicotine dependence (n = 7), Opioid/ Opiates (n = 5),
Non-specific substance dependence (n = 7)
TOTAL (n = 27)

III.1. Mechanisms of Addiction

Understanding the pathophysiological mechanisms of addiction is a crucial factor in developing an effective and integrative treatment protocol. In this review, we aim to understand the mechanisms of addiction through an integrated viewpoint of Western and Oriental Medicine to provide a fundamental basis for the development of effective therapeutic approaches. We reviewed nine monographs or books dealing with the science of addiction and eleven articles investigating the mechanisms of addiction in order to achieve this goal.

III.1. 1. Perspective of Western Medicine on the Mechanisms of Addiction

Over the past few decades, the remarkable progression of neuroscience has contributed to our understanding of the mechanisms of addiction. There have been numerous studies on the mechanisms of addiction through the perspective of biomedicine. There are diverse opinions about the mechanisms of addiction in the previous studies. Thus this study cannot cover all the existing suggestions. Here we summarize the most general and fundamental understandings only through the selected literature review.

Major Brain Regions Associated with Addiction

Prior studies have attempted to investigate the pathophysiological mechanisms of addiction in the brain. The brain is the target organ of the addictive substances [17]. Neuroscientists have found that the brain areas most relevant to substance addiction are the

limbic system, the prefrontal cortex and the brain stem [14-18, 26, 28].

The limbic system contains the brain's reward circuit that is closely related to addiction [17]. It links together a number of brain structures that control and regulate our ability to feel pleasure. Feeling pleasure motivates us to repeat the decisive behaviors critical to our existence. The limbic system is activated by healthy, life-sustaining activities such as eating and socializing but it is also activated by substance abuse. This area is responsible for our perception of other emotions, both positive and negative, which explains the mood-altering properties of many drugs [1. 15, 16]. The prefrontal cortex is the thinking center of the brain; it powers our ability to think, plan, solve problems, and make decisions. The most important areas of the prefrontal cortex in association with addiction are the orbitofrontal cortex and the dorsolateral prefrontal cortex. These areas form the reward circuit associated with expectation and planning of behavior [15, 17]. The brain stem controls functions critical to life and modulates arousal and consciousness in cooperation with the other regions of the brain [29].
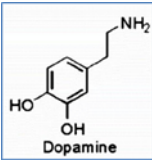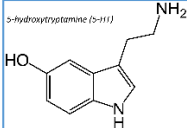
In addition, a study conducted by Jung-Ah Min *et al.* illustrated the integrated neurobiological model of substance addiction, and related brain correlates through the findings from neuroimaging studies in addiction. This study also demonstrated the roles of various prefrontal regions, thalamus, memory circuit, anterior cingulate, and insula in addition to those of classical limbic system [14].

Major Neurotransmitters Associated with Addiction

All substances work on existing neurochemical pathways in the central nervous system (CNS); which means they are unable to generate new pathways [15]. The

characteristics of substance action are derived from each substance's action on certain neurotransmitters and receptors, as well as from how and where the substances distribute over the nervous system [15, 29]. The most prominent neurotransmitters that influence chemical dependence are dopamine and serotonin. Other neurotransmitters that play an important role in addiction include gamma-aminobutyric acid (GABA), endorphins, glutamate, norepinephrine, and acetylcholine. The key characteristics of major neurotransmitters are described in Table III-1.

Table III-1 Key Characteristics of Major Neurotransmitters Involved in Addiction [15, 29]

Neurotransmitter	Released regions	Characteristics
Dopamine	Brain, ANS	▪ Mostly inhibitory, involved in emotions/moods and in regulating somatic motor control, controls reward(motivation), pleasure, euphoria, compulsion ▪ The principle neurotransmitter involved in addiction pathway ▪ Deficiency: tremors and overstimulation of muscles; Parkinsonism
Serotonin 5-Hydroxytryptamine	Serval regions of CNS	▪ Mostly inhibitory, involved in emotions and moods; sleep, dreaming, hunger and arousal ▪ Play roles in emotional behaviors and the biological clock ▪ Depletion of serotonin in the brain leads to depression
GABA	Brain only	▪ Most common inhibitory neurotransmitter in the brain ▪ Involved in regulating anxiety may be related to eating or sleep disorders
Endorphins	Several regions of CNS, retina, intestinal tract	▪ Endogenous Morphine ▪ Mostly inhibitory ▪ Act as natural opiates; reduce pain perception ▪ Also depress physical functions like breathing

The Reward Pathways; Mesocorticolimbic System

The most important brain structure that relates to substance addiction is the reward

10

circuit called the mesocorticolimbic system, which regulates the dopamine and serotonin pathways [13, 14]. Neuroscientists have found that most addictive substances produce pleasure by activating these reward pathways. These pathways are involved in an essential type of learning that keeps us stay alive. The reward circuit mediates the pleasurable and motivating effects of natural rewards, such as eating when we are hungry. Once the feeling of pleasure is formed through the reward pathways, we learn to repeat the actions that gave us the reward in the first place [11, 12, 15, 17]. Addictive substances activate this same system, thus induce continuous substance use [15]. Neuroscientists have investigated how addictive substances affect neurons to exert their influence. Addictive drugs change the ways neurotransmitters transmit their messages from neuron to neuron. Some drugs block neurotransmitters, while others mimic them. The similarity in structure between drugs and natural neurotransmitters fools receptors. This allows certain addictive substances to transmit abnormal messages through the network. Some other drugs alter the way neurotransmitters are inactivated or released. This process can cause the neurons to release abnormally large amounts of neurotransmitters, or prevent the normal recycling of these brain chemicals. Ultimately, in all cases, the brain's reward pathway is distorted and falsely activated because drugs alter the chemical messages between neurons in this circuit [10-12]. Most drugs abuse the reward circuit, either directly or indirectly, by overflowing the circuit with dopamine. [10-18, 26].

As outlined above, the neurobiological process of addiction is rooted in the interaction of two main neurotransmitters, dopamine and serotonin, and key two areas of their activity, the limbic system, and frontal cortex; mesocorticolimbic System [15]. Figure III-1 shows what happens to the addicted brain step by step.
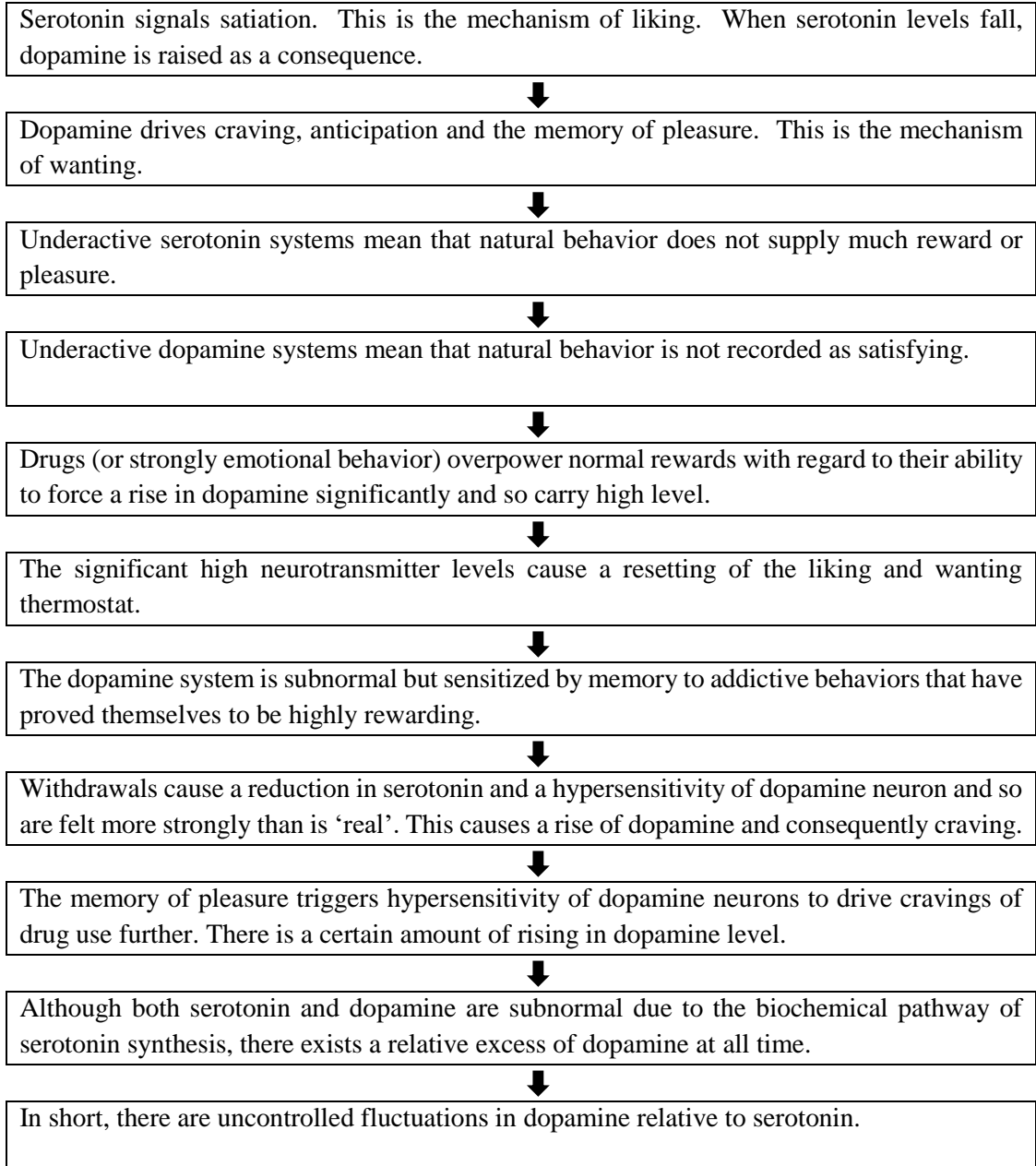
Serotonin signals satiation. This is the mechanism of liking. When serotonin levels fall, dopamine is raised as a consequence.

⬇

Dopamine drives craving, anticipation and the memory of pleasure. This is the mechanism of wanting.

⬇

Underactive serotonin systems mean that natural behavior does not supply much reward or pleasure.

⬇

Underactive dopamine systems mean that natural behavior is not recorded as satisfying.

⬇

Drugs (or strongly emotional behavior) overpower normal rewards with regard to their ability to force a rise in dopamine significantly and so carry high level.

⬇

The significant high neurotransmitter levels cause a resetting of the liking and wanting thermostat.

⬇

The dopamine system is subnormal but sensitized by memory to addictive behaviors that have proved themselves to be highly rewarding.

⬇

Withdrawals cause a reduction in serotonin and a hypersensitivity of dopamine neuron and so are felt more strongly than is 'real'. This causes a rise of dopamine and consequently craving.

⬇

The memory of pleasure triggers hypersensitivity of dopamine neurons to drive cravings of drug use further. There is a certain amount of rising in dopamine level.

⬇

Although both serotonin and dopamine are subnormal due to the biochemical pathway of serotonin synthesis, there exists a relative excess of dopamine at all time.

⬇

In short, there are uncontrolled fluctuations in dopamine relative to serotonin.

Figure III-1. Mechanisms of Addiction from the Perspective of Neuroscience [10-12, 17, 18]

III.1. 2. Perspective of Oriental Medicine on the Mechanisms of Addiction

Understanding of the Brain(Nao, 腦)

As with Western Medicine, the brain plays a crucial role in understanding the mechanisms of addiction within the framework of Oriental Medicine. The brain is called the 'Sea of Marrow'. According to the 'Spiritual Axis' in chapter 33, the Brain is the Sea of Marrow, extending from the top of the head to the point GV 16 (Fengfu, 風府) [30]. According to Zang Fu theory, the brain is closely related to kidneys. The kidney-essence produces marrow, which gathers to fill the brain and spinal cord. Since marrow is derived from the kidneys, the brain is functionally connected to this organ. The brain also belongs to the heart, which is considered as the monarch of all the organs who is in charge of spiritual activities [30]. In Oriental Medicine, the brain controls intelligence, memory, concentration, and sensation; such as sight, hearing, smelling and touch [15, 30].

G. Maiciocia suggested the correlates between three brain regions mainly associated with addiction and each region's spiritual aspects of Oriental Medicine [31]. According to him, the limbic system is responsible for our emotional life, family bonding, and social bonding. These functions are those of the Mind(Shen, 神) and Ethereal Soul(Hun, 魂) in Oriental Medicine. The prefrontal cortex is responsible for thinking, cognition, and memory. These functions are clearly associated with the Mind(Shen, 神), Intellect(Yi, 意), Will-power(Zhi, 志) in Oriental medicine. The brainstem is responsible for physiological activities such as breathing, heart rate, digestion, and body movement. These are the functions that would be corresponding to Corporeal Soul(Po, 魄) in Oriental Medicine. From this perspective, he suggested the most related organs to the brain in Oriental

Medicine are the heart, spleen, and kidneys.

One of the recent textbooks [27] corroborates that there are three brain regions which are correlated to the meridians of Oriental Medicine. It describes the functions of each area and offers selected useful acupoints for the corresponding brain area as shown in Table III-2 [27]. Understandings of the brain described above should be applied to the therapeutic approaches for addiction.

Table III-2. The Brain in the View of Oriental Medicine [27]

Region	Function	Meridians	Useful points	Notes
Upper Brain Prefrontal cortex	Cognition Differentiation Personality	Pericardium Sanjiao Gallbladder Liver	PC 8 SJ 3 Du 20	Judgments, Evaluations The ability to change sensory organs Same-side treatment
Mid Brain Limbic system	Movement Interaction	Heart Small Intestine Urinary Bladder Kidney	GB 10 GB 11 GB 34 GB 39 KD 1	Getting to know yourself and the world Treat contra-laterally
Lower Brain Brainstem	Survival Respiration Digestion Sleep	Lung Large Intestine Stomach Spleen	GB 39 Du 15 Du 16	Basic survival functions Brain and Marrow Points Same-side treatment

Yin and Yang Theory

In Oriental Medicine, Yin-Yang theory plays a crucial part in describing the mechanisms of addiction. Yin-Yang is an expression of the dynamic interaction between two opposing elements to achieve homeostasis [17]. In biomedicine, the neurobiological process of addiction is rooted in the interaction of two main neurotransmitters, dopamine and serotonin in the reward circuit. These neurotransmitters play an opposite role, either

excitatory or inhibitory, each other in the process of reward circuit [17, 29]. This opposing

relationship between the neurotransmitters dopamine and serotonin parallel the

relationship between Yin and Yang. There are many neurotransmitters, besides dopamine

and serotonin, which align to the Yin and Yang relationship, as described in Table III-3

[17].

Table III-3 Yin and Yang Neurotransmitters [17]

Yang Neurotransmitters	Yin Neurotransmitters
Dopamine Anticipation, excitement, arousal, craving	**Serotonin** Increases satisfaction, maintains self-control, reduces depression, reduces craving, reduces anxiety and promotes sleep
Glutamate Excitatory, implicated in seizures, associated with memory	**GABA** Reduces stress, anxiety, and pain
Substance P Relays pain messages, associated with stress and anxiety	**Endorphin** Restricts transmission of pain, Reduces craving and depression

The limbic system motivates reward or pleasure seeking. Thus, this is considered

Yang in nature. This area is the emotional part of the brain and the pleasure center, which

initiates instinctive survival behavior such as reward seeking. It is activated by several

conditions including the pharmacological effects of substances, withdrawal symptoms,

memory, and cravings. This process is facilitated by the actions of Yang neurotransmitter,

dopamine.

The prefrontal cortex is the brain region that refrains the excitement of the limbic

system. Thus, this is considered Yin in nature. This process of frontal cortex is facilitated

by the Yin neurotransmitter, serotonin. Balance and harmony between the limbic system and prefrontal cortex are crucially required in order to maintain optimal function of the brain in regards to the impulse control system. In other word, homeostasis is necessary between dopamine and serotonin, and Yin and Yang for normal function of the brain [15, 17]. Addictive substances lead to an imbalance in this system. Long-term administration of the substances may cause addiction. This impulse control system is illustrated in Figure III-2 [17].
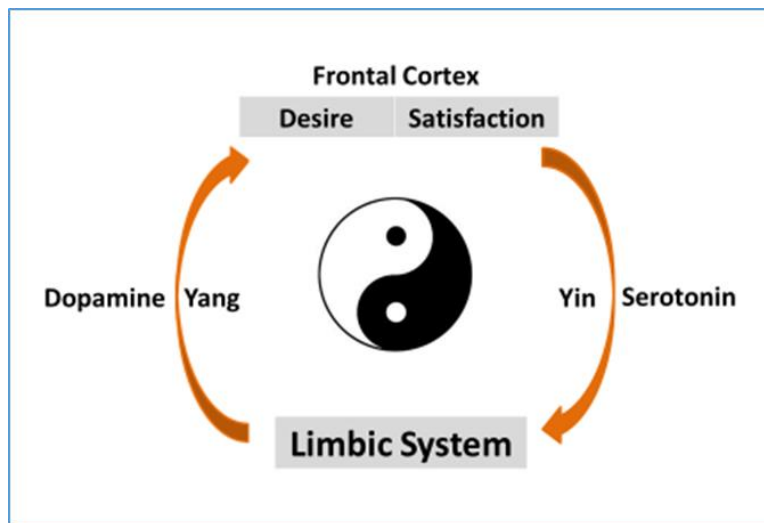

Fig. III-2 Homeostasis of Impulse Control

As outlined previously in Figure III-1, the neurobiological mechanism of addiction is evidently grounded in the communication between the neurotransmitters, dopamine and serotonin. The sequential steps of addiction may be interpreted through the Yin- Yang theory. When an addictive substance is ingested, the brain secretes an abnormal amount of dopamine. If sufficient satiation occurs, there will be an attempt to achieve homeostasis by the secretion of serotonin, or the Yin neurotransmitter. Despite the feelings of satiation

addictive substances cause imbalance between the two neurotransmitters, Yin and Yang. The brain is unable to release the amount of serotonin necessary to match the levels of dopamine. Serotonin (Yin) is then depleted, due to a substance-induced elevation in dopamine (Yang). Eventually, the brain is unable to regulate the release of dopamine on its own. Levels of dopamine (Yang) fluctuate uncontrollably due to the lack of serotonin (Yin) [17]. Figure III-3 shows the mechanisms of addiction by Yin-Yang theory [17].
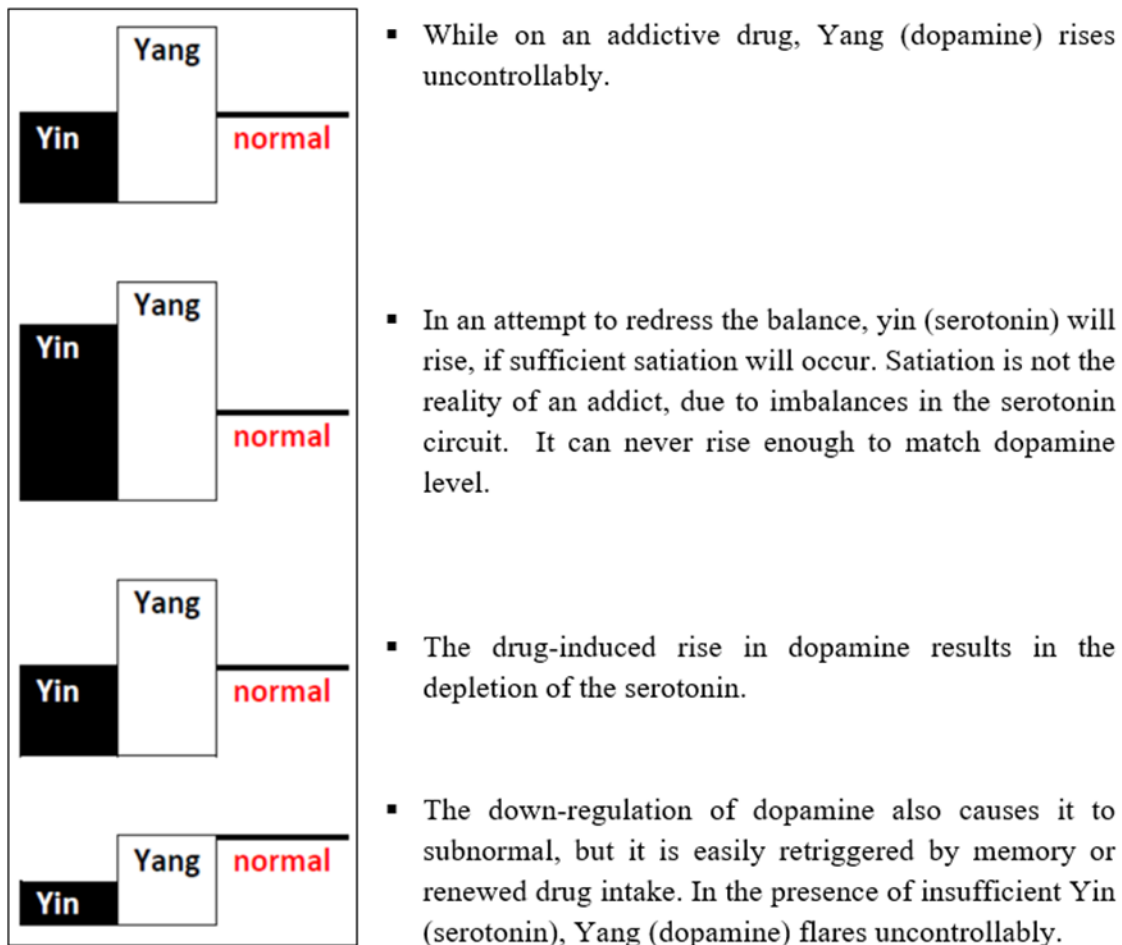

- While on an addictive drug, Yang (dopamine) rises uncontrollably.

- In an attempt to redress the balance, yin (serotonin) will rise, if sufficient satiation will occur. Satiation is not the reality of an addict, due to imbalances in the serotonin circuit. It can never rise enough to match dopamine level.

- The drug-induced rise in dopamine results in the depletion of the serotonin.

- The down-regulation of dopamine also causes it to subnormal, but it is easily retriggered by memory or renewed drug intake. In the presence of insufficient Yin (serotonin), Yang (dopamine) flares uncontrollably.

Fig. III-3. Mechanisms of Addiction in the Perspective of Oriental Medicine [17]

III.1. 3. Possible Mechanisms of Acupuncture in Treating Addiction

Clinical trials have attempted to determine the effectiveness of acupuncture in treating substance addiction [18]. Yet there still remain many questions about the basic mechanisms of acupuncture on addiction. Some evidence seems to suggest that acupuncture can play an important role in treating substance addiction [18, 24, 32-35, 69].

The evidence presented in the existing studies suggest that the stimulation of the peripheral acupuncture points can facilitate the release of a certain neurotransmitter in the central nervous system [24, 32]. Endorphins, serotonin, and norepinephrine possibly play a role in acupuncture analgesia [18, 33] as well as in nicotine craving and withdrawal [18, 34]. According to some previous studies, the neurochemical and behavioral evidence indicates that acupuncture's role in suppressing the reinforcing effects of abused drugs occurs by modulating mesolimbic dopamine neurons [18, 35]. Acupuncture has the potential to release several brain neurotransmitters such as serotonin, opioid and amino acids including GABA, which help to modulate levels of dopamine [23, 24, 35, 69]. These findings provide clear evidence for the biological effects of acupuncture that may help us to understand how acupuncture can be used to treat substance addiction [18].

The mechanisms of auricular acupuncture that is commonly used for the treatment of addiction are relatively well known. Needling on the certain ear point stimulates nerves in the ear which stimulates the raphe nuclei in the brainstem. This process causes an increase in serotonin (Yin) level. Sympathetic nerve output (Yang) is reduced by the increased inhibitory input from the serotonin. At the same time, endorphins (Yin) are released as well. This helps control pain, fear, and anxiety. Therefore, acupuncture reinforces serotonin (Yin) and reduces the overflowing dopamine (Yang) caused by addictive

substances [17].

III.2. Treatment Approaches for Substance Addiction

A total of 27 original clinical trials which met inclusion criteria were collected for a narrative review of treatment approaches for substance addiction. These selected studies were classified into five categories based on substance dependence for analysis; alcohol dependence, cocaine dependence, nicotine dependence, opiates/ opioids dependence, and non-specific/ multi-substance/ general-substance dependence. The included clinical trials were comprehensively reviewed and analyzed according to the type of substance dependence with the following information: Jadad score, the size of subjects, type of intervention method, type of control, duration of the experiment, treated acupoints or sites selected, outcome measures, and results reported. The findings for each substance dependence are illustrated shown in Tables III-4 ~ III-8. The methodological quality of the reviewed trials was assessed using the Jadad scale [25] as mentioned earlier. Trials scoring 1 or 2 points are considered low-quality, while trials scoring 3-5 points are considered as high-quality. The details of quality evaluation and scores of each clinical study by Jadad scale are listed in Appendix B.

III.2.1. Treatment Approaches for Alcohol Dependence

Five randomized controlled trials were identified and reviewed for treatment approaches of alcohol dependence [36-40]. The size of subjects and the duration of clinical trial varied, as shown in Table III-4. Also, details of frequency of treatment are listed in the Table. Only one study provided follow-up observation [36].

Quality of Research by Jadad Scale

Only one study scored 3 points out of 5 [38], and the remaining four studies received 2 points [36, 37, 39, 40]. All five studies appropriately mentioned the randomization but failed in double-blind [36-40]. In one study, withdrawals and dropouts of subject groups were described [38]. Further details are given in the table of Appendix B.

Type of Intervention and Control

Three studies used auricular acupuncture as a single intervention among the five clinical trials [36, 38, 39]. One study used auricular and body acupuncture both [37] and Lee *et al.* used only body acupuncture for the experimental group [40]. For the control group, two studies used non-specific sham ear points [36, 37], one study used auricular laser stimulation [38], one study used aromatherapy, and one study compared to placebo body points treatment [40].

Acupuncture Points Selected for Treatment

Table III-4 provides a summary of selected acupuncture points for treatment of alcohol dependency in the reviewed clinical trials. Sapir-Weise *et al.* used auricular points, Shenmen and Lung [36]. Karst *et al.* used five NADA ear points (Sympathetic, Shenmen, Kidney, Lung, and Liver) and additional body points (LI4, GV20, and Extra1) [37]. The other study also investigated the efficacy of five NADA points in the treatment of alcohol addiction [39]. Trümpler *et al.* examined 2-10 points out of 24 ear points with flexibility [38]. The effectiveness of needling on KI9 (Zhubin) in reducing alcohol craving was investigated by Lee *et al.*in 2015 [40].

Outcome Measures and Assessment

Various outcomes were measured with the specific scale to determine the effectiveness of the treatment methods in the reviewed studies. The level of craving was measured in three studies [36, 39, 40]. Three studies measured the duration of withdrawal symptoms or severity of alcohol withdrawal syndromes [37-39]. More details regarding outcome measures are presented in Table III-4.

III.2.2. Treatment Approaches for Cocaine Dependence

Three studies were identified and reviewed for treatment approaches on cocaine dependence, and these three studies were conducted by two main researchers, Avants and Margolin in USA [41-43]. As a study design, those are all randomized controlled trials [41-43]. One of the studies was conducted with a huge number of the subject group; 620 subjects were recruited [42]. One study carried out a follow-up assessment at 8th week [41]. The other study had two follow-up observation at 3 months and 6 months later [42]. All information extracted from the studies is listed in Table III-5.

Quality of Research by Jadad Scale

Two studies among three clinical trials scored 3 points out of 5 [41, 42] and one received 2 points [43]. The process of randomization was appropriately mentioned in all three studies [41-43]. All three studies were designed as single-blinded clinical trials [41-43]. Two studies clearly described the reasons of withdrawals and dropouts from the study [41, 42]. Further details are given in the table of Appendix B.

Type of Intervention and Control

In all studies, cocaine-dependent, methadone-maintained patients were randomly assigned to three different groups; auricular acupuncture as an experimental intervention group, a sham needle insertion control group, or a no-needle relaxation control group [41-43].

Acupuncture Points Selected for Treatment

Four points (Sympathetic, Shenmen, Lung, and Liver) from NADA protocol were selected and used for acupuncture treatment group [41-43]. Four sham points in the ear helix were applied as a first control group, and for the second control group, videos containing relaxing visual imagery and soft music were adopted [41-43].

Outcome Measures and Assessment

Various outcomes were measured with the specific scale to determine the effectiveness of the treatment methods in the reviewed studies for cocaine dependence. As primary outcomes, cocaine use during the treatment period was measured through urine toxicology screens 3 times a week, and retention in the treatment was assessed [41-43]. Self-reported frequency of cocaine use and the level of craving were measured for assessment in a study [42]. Addiction-related problems using addiction severity index (ASI) were also measured in two clinical trials [42-43]. Further details pertaining to outcome measures are described in Table III-5.

Table III-4 Summary of studies included in the review: Alcohol dependence

First Author (year)	Jadad score	No. of Subjects (Acu./Cont.)	Type of Intervention	Type of Control	Duration Frequency of Tx.	Follow-up	Treated acupoints	Outcome measures	Results Reported
Sapir-Weise [36] (1999) Sweden	2	72 (36/36)	Auricular Acupuncture	Non-specific ear points 3-5mm from correct points	10 weeks 5x/ 2weeks 3x/ 4weeks 2x/ 4weeks	After 1 mo 3 mos 6 mos	Shenmen Lung	▪ No.of days alcohol consumption ▪ Craving ▪ Depression ▪ Blood test	▪ NS difference in effectiveness found between study and control group(p = 0.07) ▪ Women in the study group reported a stronger reduction of anxiety during the first month of Tx. than control group(p < 0.05)
Karst [37] (2002) Germany	2	34 (17/17)	Auricular & Body Acupuncture	Non-specific points	14 days daily	N/A	Sympathetic, Shenmen, KD, LV, LU(AA) LI4, GV20, extra1(BA)	▪ Withdrawal (CIWA-Ar-scale) ▪ Anxiety	▪ Patients assigned to acupuncture had significantly fewer withdrawal symptoms(p = 0.045)
Trümpler [38] (2003) Switzerland	3	48 (15/17/16)	Auricular Acupuncture	Auricular 1) Laser stim. 2) Sham laser	Until the end of withdrawal daily	N/A	2-10 out of 24 ear points	▪ Duration of withdrawal symptoms ▪ Duration of sedative Px.	▪ No evidence found to support a beneficial effect of auricular acupuncture for reducing of alcohol withdrawal(P =0.70)
Kunz [39] (2007) Germany	2	74 (36/38)	Auricular Acupuncture	Aromatherapy	5 days daily	N/A	5 NADA points	▪ Alcohol – withdrawal syndrome(AWS scale) ▪ Craving(Visual analogue scale, VAS) ▪ Self-assessment Manikin(SAM)	▪ Acupuncture group was not more effective than control group on duration and severity of alcohol withdrawal symptoms(NS in most of the assessment criteria)
Lee [40] (2015) Korea	2	20 (10/10)	Body Acupuncture	Placebo Non-specific points	4 weeks twice/week	N/A	KI9(Zhubin)	▪ Craving(Visual analogue scale, VAS)	▪ Real-needle acupuncture therapy on Zhubin (KI9) showed effectiveness in reducing alcohol craving((p < 0.01)

Table III-5 Summary of studies included in the review: Cocaine dependence

First Author (year)	Jadad score	No. of Subjects (Acu./Cont.)	Type of Intervention	Type of Control	Duration Frequency of Tx.	Follow-up	Treated acupoints	Outcome measures	Results Reported
Avants [41] (2000) USA	3	82 (28/27/27)	Auricular Acupuncture	1) Sham: 4 pts in the ear helix(non-active pts) 2) Relaxation	8 weeks 5x/week	After 8 weeks	4 NADA pts Sympathetic Liver Lung Shenmen	▪ Urine toxicology screen 3x/week	▪ Acupuncture group was significantly effective in reducing cocaine use than sham group(p = 0.05) and relaxation group(p =0.01)
Margolin [42] (2002) USA	3	620 (222/203/195)	Auricular Acupuncture	1) Sham: 4 pts in the ear helix(non-active pts) 2) Relaxation	8 weeks 5x/week	After 3 mons 6 mons	4 NADA pts Sympathetic Liver Lung Shenmen	▪ Urine toxicology screen 3x/week ▪ Retention in treatment ▪ Self-reported cocaine use: frequency of cocaine use and craving ▪ Addiction-related problems by addiction severity index(ASI)	▪ There was modest reduction in cocaine use in all 3 treatment groups. ▪ No significant differences found between experimental and two control groups in cocaine use by urine samples or other outcome measures. ▪ Acupuncture was not more effective than control groups.
Margolin [43] (2002) USA	2	165 Study 1, n = 82; Study 2, n = 83	Auricular Acupuncture	1) Sham: 4 pts in the ear helix(non-active pts) 2) Relaxation	8 weeks 5x/week	N/A	4 NADA pts Sympathetic Liver Lung Shenmen	▪ Urine toxicology screen 3x/week ▪ Addiction-related problems by addiction severity index(ASI) ▪ Treatment credibility scale(TCS)	▪ The positive effect for AA group found in study1 ▪ No positive effect for AA group found in study 2 ▪ Since the findings were inconsistent between two studies, no conclusion could be made regarding the treatment effectiveness of AA

III.2.3. Treatment Approaches for Nicotine Dependence

A total of seven clinical trials were identified and reviewed for treatment approaches of nicotine dependence [44-50]. As a study design, five studies are randomized controlled trials [44-47, 49]. One study is an open label clinical trial without control group [50]. The remaining one article is a study proposal to evaluate the feasibility and possible benefits of self-administered auricular acupressure for smoking cessation [48]. Therefore, this article does not contain the results of the study [48]. However, this article was included in the current review, since it proposed a well-designed treatment approach for nicotine dependence. The size of subjects, the frequency of treatment and the duration of clinical trials varied, as shown in Table III-6. Six studies provided several follow-up assessment session to examine the effect of treatment [44-46, 48-50]. All information extracted from the studies is listed in Table III-6.

Quality of Research by Jadad Scale

In this category, some studies received a higher score than the studies for another type of substance dependence. A study conducted by Lambert *et al.* scored 5 points out of 5, which means this study is a well-designed double-blind RCT described all required information in detail [47]. Two studies scored 4 points with successful double blindness [48, 49]. The process of randomization was appropriately mentioned in most studies [44-49]. Three studies clearly described the reasons of withdrawals and dropouts from the study [44, 45, 47]. Further details are given in the table of Appendix B.

Type of Intervention and Control

Most of the studies used auricular acupuncture in various methods to treat nicotine dependence [44-46, 48-50]. Waite *et al.* used auricular acupuncture (AA) with electrical stimulation and ear seeds for the experimental group and same modalities at placebo ear points for the control group [44]. A study conducted by White et al. employed AA and electro-acupuncture (EA) for the experimental group. In this clinical trial, there were two control groups: a control group using sham acupuncture on ear point, and a control group using transcutaneous electrical nerve stimulation (TENS) pads on a body point [45]. Bier *et al.* examined the efficacy of AA and a body point accompanied with 5-week educational smoking cessation program with two control groups [46]. In 2011, Lambert *et al.* carried out two experiments with the application of transcutaneous electric acupoint stimulation on body points for smoking cessation. They tested the differences by applying different electric currents to experimental and control groups [47]. Leung *et al.* used auricular acupressure by ear seeds to compare to the sham auricular acupressure control and advice only group [48]. Silava et al. also adopted acupressure with ear seeds on several ear points comparing to the sham control group [49]. McFadden applied auricular and body acupuncture with long-lasting acupressure after acupuncture treatment to see the effectiveness of treatment on smoking cessation. In this study, there was no control group [50].

Acupuncture Points Selected for Treatment

Waite and White used auricular Lung point only from the NADA protocol [44, 45]. Bier and Leung adopted five NADA ear points (Sympathetic, Shenmen, Kidney, Lung, and

Liver) for treatment of nicotine dependence [46, 48]. Meanwhile, Mc Fadden added some body acupuncture points (LI4, LV3, and Tim Mee) and ear seed on Shenmen point to the NADA protocol [50]. The point 'Tim Mee', which was used in this clinical trial, is an empirical point located on the wrist between LU7 and LI5. This point has been commonly used for the treatment of smoking cessation [63]. Lambert *et al.* applied TEAS on body points: LI4, PC8, PC6, and SJ5 to determine the effectiveness of treatment on smoking cessation [47]. Silva et al. examined the application of acupressure by ear seeds on eight ear points: Sherman, Kidney, Sympathetic, Anxiety 1, Anxiety 2, Hunger, Thirst, and Addictions [49].

Outcome Measures and Assessment

Various outcomes were measured with the specific scale to determine the effectiveness of the treatment methods on smoking cessation. The major outcome was measured by CO (Carbon monoxide) level test in most studies [45, 47, 49, 50]. Some trials measured nicotine withdrawal symptoms by Visual Analogue Scale (VAS) [45, 46] or by the Minnesota Nicotine Withdrawal Scale (MNWS) [50]. Psychological changes such as depression level or anxiety level were also measured with the specific scale for assessment [46]. Leung et al. suggested to obtain abstinence level by Prevalent Abstinence Rate (PAR) and Continuous Abstinence Rate (CAR), CO level, nicotine withdrawal symptoms by MNWS, and stress level by stress checklist (SCL) [48]. As the basic indices, the number of cigarettes smoked (NCS) and decrease rate in smoking were also measured for outcome assessment [46, 49]. Further details pertaining to outcome measures are described in Table III-6.

Table III-6 Summary of studies included in the review: Nicotine dependence

First Author (year)	Jaded score	No. of Subjects (Acu. /Cont.)	Type of Intervention	Type of Control	Duration Frequency of Tx.	Follow-up	Treated acupoints	Outcome measures	Results Reported
Waite [44] (1998) UK	1	78 (40/38)	Auricular Acupuncture w/ Electrical stimulation + Ear seeds	Placebo point acupuncture +Estim + seeds	Once 20 mins	After 2 weeks 2 mons 4 mons 6 mons	▪ Active group: Lung ▪ Control: medial aspect of patella	▪ Urine cotinine	▪ 5 subjects(12.5%) in active treatment were confirmed to quit smoking biochemically after 6 months compared with none in the placebo group(p = o.o5)
White [45] (1998) UK	3	76 (38/19/19)	Auricular Acupuncture Electro-acupuncture	1) Sham acupuncture 2) Sham TENS pads	2weeks 4 times on 1 day 3 days 7 days 20 mins	After 9mons	▪ Group A: Lung ▪ Control groups: on the center of the mastoid bone	▪ Withdrawal symptoms by Visual Analogue Scale(VAS) ▪ Smoking cessation by self-report ▪ CO level	▪ No significant difference was found between two groups. ▪ 15 participant in electro-acupuncture group and 16 participants in sham group were abstinent on day 14
Bier [46] (2002) USA	2	141 (58/45/38)	Auricular Acupuncture + Body point + 5 weeks educational smoking cessation program	1)Sham acupuncture + 5 weeks education 2)True acupuncture only	4 weeks 5x/week 30 mins	After 1,3,6,12 15,18 months	▪ NADA 5 pts + LI4 ▪ Sham: ear and wrist points 5mm from true points	▪ Depression by Beck depression index ▪ Self-rating Anxiety Scale ▪ Pack-year history ▪ % decrease in smoking ▪ VAS score	▪ Combined method of acupuncture and education significantly demonstrated greater effect in reducing smoking(40% of cessation and 53% posttreatment decrease in smoking)
Lambert [47] (2011) Singapore	5	**Experiment 1** 40 (20/20)	Transcutaneous electric acupoint stimulations (TEAS) 10mA w/ HANS device	TEAS 5mA	2 days 4 sessions	N/A	LI4 , PC8, PC6, SJ5	▪ Total score of smoking urges by QSU-Brief ▪ CO level	▪ No significant difference was found between experimental group and control group.

Table III-6 Continued: Nicotine dependence

First Author (year)	Jadad score	No. of Subjects (Acu./Cont.)	Type of Intervention	Type of Control	Duration Frequency of Tx.	Follow-up	Treated acupoints	Outcome measures	Results Reported
Lambert [47] (2011) Singapore

Continued | 5 | **Experiment 2** 58 (21/20/17) | Same as experiment 1 | 1) Intermittent 3min on and 7min off TEAS 5mA 2) Placebo TEAS 0mA | 2 days

4 sessions | N/A | LI4 , PC8, PC6, SJ5 | Same as experiment 1 | ▪ When the Fagerstrom Test score for Nicotine Dependence was over 5, the difference between experimental group and control groups became significant(p = 0.02) |
| Leung [48] (2012) Canada | 4 | 60 (20/20/20) | Auricular Acupressure via ear seeds | 1) Sham auricular acupressure w/ ear seeds 2) Advice + No acupressure | 6 weeks | At Week 13 Week 26 | NADA protocol: 5 pts | ▪ Abstinence level by PAR & CAR ▪ CO level ▪ Withdrawal symptoms by MNSW ▪ Stress level by SCL | ▪ This is a study design to evaluate the feasibility and possible benefits of self-administered auricular acupressure for smoking cessation. ▪ The article doesn't contain the results. |
| Silva [49] (2014) Brazil | 4 | 30 (21/9) | Auriculo-therapy w/ ear seeds | Irrelevant points: Elbow, Are | 5 weeks

2x/ week | After 30 days | Shenmen, Kidney Sympathetic Anxiety 1 Anxiety 2 Hunger Thirst Addictions | ▪ Level of severity tobacco dependence by FTND ▪ CO level ▪ NCS | ▪ Auriculo-therapy showed effective in reducing NCS (p=0.002) and some other parameters. |
| McFadden [50] (2015) USA | 0

Open label trial | 28 | Auricular & body acupuncture + acupressure w/ stainless ear bead | None | 12 weeks

2x/ week 15 mins | At 26th wk. | ▪ NADA 5 pts ▪ LI4, LV3, Tim Mee ▪ Ear bead on Shenmen | ▪ CO level ▪ Withdrawal symptoms by MNSW-revised ▪ | ▪ 17 participants completed this clinical trial. ▪ 16(98%) rated the overall treatment program as beneficial. ▪ For 16 subjects, there was a significant decrease in the rate of smoking(p<0.001) |

PAR: Prevalent Abstinence Rate, CAR: Continuous Abstinence Rate, MNWS: Nicotine withdrawal symptoms according to the Minnesota Nicotine Withdrawal Scale, SCL: Stress level according to the Stress Check List (SCL), QSU-Brief: Questionnaire of Smoking Urges-Brief, FTND: Fagerstrom Test for Nicotine Dependence, NCS: Number of Cigarettes Smoked, NADA: National Acupuncture Detoxification Association

III.2.4. Treatment Approaches for Opiates/ Opioids Dependence

Five studies were identified and reviewed for treatment approaches on opiates/ opioids dependence [51-55]. As a study design, all included studies are single-blind randomized controlled trials [51-55]. The size of subjects, the frequency of treatment and the duration of clinical trial varied as illustrated in Table III-7. Only one study carried out three follow-up observations at 1 week, 2 weeks and 30 days after the treatment period to measure treatment outcomes [53]. All information extracted from the studies is listed in Table III-7.

Quality of Research by Jadad Scale

Three studies scored 3 points out of 5 in evaluation by Jadad scale [53-55]. The process of randomization was appropriately mentioned in most studies [51, 53-55] except one study conducted by Zeng *et al.* [52]. All five studies failed double blindness [51-55]. Four clinical trials clearly described the reasons of withdrawals and dropouts from the study [52-55]. Further details are given in the table of Appendix B.

Type of Intervention and Control

Many studies used body acupuncture rather than auricular acupuncture for treatment of opiates/ opioids dependence compared to the treatment approaches for another type of substance dependence [51, 52, 53, 55]. In 2003, Montazeri *et al.* examined the effect of combined treatment approach with body acupuncture and rapid opiate detoxification (ROD) by Naloxone. The control group was administered with ROD only in this study [51]. In a study conducted by Zeng et al., a combination of body acupuncture and methadone therapy

was employed as the experimental group, and only decrescendo therapy of methadone was applied without acupuncture for the control group [52]. Meade *et al.* used TEAS at 8-15 mA on body points with bup-nx therapy for the experimental group and sham TEAS at 1 mA with bup-nx therapy for the control group [53]. Lua *et al.* tested auricular acupuncture combined with methadone maintenance treatment (MMT) on the experimental group to evaluate the efficacy of treatment. They applied MMT only for the control group in this study [54]. Recently, Chan et al. used EA on body points and AA with MMT for the experimental group and placebo AA without EA for the control group [55]

Acupuncture Points Selected for Treatment

In all reviewed studies, acupuncture treatment has been used as an adjunctive therapy in addition to existing medication therapy for the treatment of opiates addiction. Montazeri *et al.* adopted seven body acupuncture points: LI4, PC6, HT7, LV3, ST36, DU14, and DU20 [51]. In 2005, a study conducted by Zeng et al. used five points of DU meridian: DU4, 9, 10, 11, and 20 [52]. Meade *et al.* used TEAS at 8-15 mA on two body points: LI4 and PC6 [53]. Lua *et al.* evaluated the efficacy of five NADA auricular points; Sympathetic, Shenmen, Kidney, Lung, and Liver [54]. Chan et al. used EA on two body points (LI4, ST36) and an ear point; Shenmen in addition to MMT [55]

Outcome Measures and Assessment

Various outcomes were measured with the specific scale to determine the effectiveness of the treatment methods on opiates/ opioids dependence. The major outcome was the level of craving by VAS index [53, 55]. Opiates withdrawal symptoms

were measured by Clinical Institute Narcotic Assessment (CINA) [51] or Subjective Opiates Withdrawal Scale (SOWS) [53]. The score of abstinence symptoms [52] or the quality of sleep [55] was obtained for outcome assessment. Further details pertaining to outcome measures are described in Table III-7.

III.2.5. Treatment Approaches for Non-specific/ Multi-substance Dependence

Seven studies were identified and reviewed for treatment approaches on non-specific/ multi-substance/ general-substance dependence [56-62]. As a study design, six included studies are single-blind randomized controlled trials [56-59, 61, 62]. One study is a qualitative approach with a descriptive design including acupuncture treatment [60]. The size of subjects was varied [56-60]. Some of the reviewed articles had a relatively large size of the subject group [56, 57, 62]. The frequency of treatment and the duration of clinical trial varied as shown in Table III-8. Three studies carried out several follow-up observations to measure treatment outcomes [56, 57, 62]. All information extracted from the studies is listed in Table III-8.

Quality of Research by Jadad Scale

In terms of quality of the study, three studies scored 3 points out of 5 in evaluation by Jadad scale [56, 61, 62]. The process of randomization was appropriately mentioned only in three studies out of seven studies [56, 61, 62]. All selected studies failed double blindness [56-62]. Most clinical trials clearly described the reasons of withdrawals and dropouts from the study [56-59, 61, 62] except one study [60]. Further details are given in the table of Appendix B.

Type of Intervention and Control

Most of the included studies employed auricular acupuncture for the treatment of addiction [56-58, 60-62]. In 2004, Berman *et al.* examined the effect of auricular acupuncture on treatment of substance addiction for the experimental group and they used sham ear points for the control group [56]. In a study conducted by Courbasson et al., a combination of AA and treatment-as-usual (TAU) was employed for the experimental group and only TAU without acupuncture for the control group [57]. Janssen *et al.* tested auricular acupuncture combined with methadone maintenance treatment (MMT) in the experimental group to evaluate the efficacy of treatment. They applied MMT only for the control group in this study [58]. Penetar *et al.* used TEAS on several body points for the experimental group on treatment of cocaine or cannabis dependence and sham TEAS for the control group [59]. Bergdahl *et al.* tested auricular acupuncture combined with pharmacological treatment on 15 subjects with substance dependence through a qualitative clinical design without the control group [60]. Chang *et al.* used AA with a usual rehabilitation program for the experimental group and relaxation with usual care or usual care only for two control groups [61]. In 2016, Ahlberg used auricular acupuncture for the experimental group and relaxation method for control group [62].

Acupuncture Points Selected for Treatment

Five points of NADA acudetox protocol have been most commonly applied to treatment for general substance addiction among the reviewed studies. In six clinical trials included for this review, five points of NADA protocol (Sympathetic, Shenmen, Kidney,

Lung, and Liver) were employed to investigate the efficacy of treatment for substance dependency [56-58, 60-62]. One study conducted by Penetar *et al.* adopted transcutaneous electric acupoint stimulation at four body points for treatment of substance addiction; PC6, SJ5, LI4 and PC8 [59].

Outcome Measures and Assessment

Various outcomes were measured with the specific scale to determine the effectiveness of the treatment methods on non-specific/ multi-substance/ general-substance substance dependence. Berman *et al.* obtained simple drug use questionnaire, acupuncture treatment assessment scale, and symptom checklist 90 for outcome measure [56]. In a study conducted by Courbasson et al., Beck depression inventory (BDI), Beck anxiety inventory (BAI), reflective activity scale (RAS), and drug-taking confidence questionnaire were measured for assessment [57]. Janssen *et al.* measured the days of neonatal morphine treatment for withdrawal and admissions to a neonatal IC nursery to evaluate the efficacy of auricular acupuncture for the treatment of chemically dependent pregnant women [58]. Penetar *et al.* took drug use and craving by cue-induced EEG recordings and event-related P300 potentials (ERPs) and anxiety by self- reported ratings as primary outcomes for assessment [59]. A qualitative study by Bergdahl *et al.* carries out the interview with the predetermined questions to describe patients' experiences of receiving auricular acupuncture during protracted withdrawal from substance addiction [60]. Chang *et al.* measured daily practice diaries, the self-rated degree of craving, and the level of anxiety by State-Trait Anxiety Inventory for Adult (STAI) for outcome assessment [61]. In 2016, Ahlberg obtained the level of anxiety by Beck Anxiety Inventory (BAI), the quality of

sleep by Insomnia Severity Index (ISI), and drug use and addiction service utilization for outcome measure [62]. Further details pertaining to outcome measures are described in Table III-8.

Table III-7 Summary of studies included in the review: Opiates/ Opioids dependence

First Author (year)	Jadad score	No. of Subjects (Acu./Cont.)	Type of Intervention	Type of Control	Duration Frequency of Tx.	Follow-up	Treated acupoints	Outcome measures	Results Reported
Montazeri [51] (2003) Iran	2	40 (20/20)	Body Acupuncture w/ ROD	Rapid Opiate Detoxification (ROD) by Naloxone	10 days Once for 3 days	N/A	LI4, PC6 HT7, LV3, ST36, DU14, DU20	▪ CINA(Clinical Institute Narcotic Assessment)	▪ Acupuncture group showed more effectiveness in reducing the severity of withdrawal reaction compared to control group(p = 0.007)
Zeng [52] (2005) China	1	70 (35/35)	Body Acupuncture w/ methadone therapy	10-day decrescendo therapy of methadone	10 days Once a day 30 mins	N/A	DU Channel DU 20, 14, 11, 10, 9, 4	▪ Score of abstinence symptoms	▪ A significant difference between two groups was found in scores of abstinence symptoms(p<0.05) ▪ The abstinence symptoms were decreased more quickly in the acupuncture group than control group
Meade [53] (2010) USA	3	55 (26/29)	Transcutaneous Electric Acupoint Stimulations at 8-15 mA w/ bup-nx therapy	Sham TEAS at 1 mA w/ bup-nx therapy	3-4 days Three 30 mins Tx.	After 1 week 2 weeks 30days follow-back	LI4, PC6	▪ Substance use by Addiction Severity Index ▪ Withdrawal by Subjective Opiate Withdrawal Scale ▪ Craving by VAS	▪ The active TEAS group showed significant improvements in pain interference and overall physical health during follow-up than sham group(p<0.05)
Lua [54] (2013) Malaysia	3	69 (29/40)	Auricular Acupuncture w/ MMT	Methadone Maintenance Treatment (MMT) only	2 months 3x/week 30 mins	N/A	NADA 5 pts	▪ Satisfaction level by Pharmaceutical Care Questionnaire ▪ Coping strategy by Brief COPE-27	▪ No significant difference was found in satisfaction level and coping changes over time between two groups (p>0.05)
Chan [55] (2014) Taiwan	3	60 (30/30)	Auricular Acupuncture + Body Electro-acupuncture (EA) w/ MMT	Placebo AA + minimal acupuncture w/o ES	4 weeks 2x/week 20 mins	N/A	▪ EA on LI4, ST36 ▪ Ear Shenmen	▪ Daily consumption of methadone ▪ Health-related quality of life by SF-36 ▪ Pittsburgh Sleep Quality Index ▪ Craving by VAS	▪ As an adjunct treatment to MMT, true acupuncture group showed significant effectiveness in reducing the daily consumption of methadone and great improvement in sleep latency than sham group (p = 0.037)

Table III-8 Summary of studies included in the review: Non-specific/ Multi-substance/ General-substance dependence

First Author (year)	Jadad score	No. of Subjects (Acu./Cont.)	Type of Intervention	Type of Control	Duration Frequency of Tx.	Follow-up	Treated acupoints	Outcome measures	Results Reported
Berman [56] (2004) Sweden	3	158 (82/76)	Auricular Acupuncture	5 non-specific points on the helix of the ear	4 weeks 14 sessions 40 mins	After 6 mons	NADA Acudetox protocol 5pts	▪ Simple drug use questionnaire ▪ Acupuncture treatment assessment scale ▪ Symptom Checklist 90	▪ No significant efficacy was found in both groups. ▪ No negative side effects of treatment
Courbasson [57] (2007) Canada	1	286 (185/101)	Auricular Acupuncture +TAU	Treatment-as-usual(TAU) only	21 days 3x/week 45 mins	After 1 mon 3 mons	NADA protocol 5 pts	▪ Beck Depression Inventory ▪ Beck Anxiety Inventory ▪ Reflective Activity Scale ▪ Drug-taking Confidence Questionnaire	▪ Acupuncture group felt significantly less depressed, less anxious, less craving and had better reflective activity score(p<0.05) ▪ Acupuncture group showed promise in being an effective treatment alternative to anxiolytics
Janssen [58] (2012) Canada	1	89 (50/39)	Auricular Acupuncture + prior MMT	MMT	2 weeks until due date daily	N/A	NADA protocol 5pts	▪ Days of neonatal morphine treatment for withdrawal ▪ Admissions to a neonatal IC nursery ▪ Transfer to foster care	▪ No significant difference found in results between two groups(p>0.05)
Penetar [59] (2012) USA	1	20 9 cocaine, 11 cannabis dependence	Transcutaneous electric acupoint stimulation	Sham TEAS	Two 3.5 days treatment (2-week interval) Two 30 mins sessions a day		PC6/ SJ5 LI4/ PC8	▪ Drug use and craving by cue-induced EEG recordings and Event-related P300 Potentials (ERPs) ▪ Anxiety by self-reported ratings	▪ TEAS treatment did not significantly reduce the drug use or drug cravings ▪ TEAS treatment did significantly modulate several self-reported measures of emotional aspect and anxiety(p<0.05)

EEG: Brain Electroencephalographic

Table III-8 Continued: Non-specific/ Multi-substance/ General-substance dependence

First Author (year)	Jadad score	No. of Subjects (Acu./Cont.)	Type of Intervention	Type of Control	Duration Frequency of Tx.	Follow-up	Treated acupoints	Outcome measures	Results Reported
Bergdahl [60] (2012) Sweden Qualitative Approach w/ A descriptive design	0	15	Auricular Acupuncture w/ pharmacological treatment	N/A	5 weeks 2x/week 40 mins	N/A	NADA protocol 5pts	▪ Interviews w/ 3 or more questions	▪ Qualitative study ▪ The participants who received AA mainly experienced positive effects ▪ The greatest gains were a reinforced sense of relaxation and well-being, peacefulness, and harmony ▪ No one experienced any negative side-effects
Chang [61] (2014) USA	3	67 (23/23/21)	Auricular Acupuncture w/ usual care(VA rehabilitation program)	1) Relaxation response (RR) + usual care 2) Usual care only	10 weeks 2x/week 30 mins	N/A	NADA protocol 5pts	▪ Daily practice diaries ▪ Degree of craving: self-rated ▪ Level of anxiety by State-Trait Anxiety Inventory for Adult(STAI)	▪ Craving and anxiety levels decreased significantly following one session of acupuncture (p = 0.0001, p<0.0001) or RR intervention (p = 0.02, p = 0.03)
Ahlberg [62] (2016) Sweden	3	280 (80/80/120)	1) AA w/ NADA protocol 2) Local protocol-auricular acupuncture (LP) + Usual Tx. and relaxation	Relaxation	5 weeks **NADA** 5x/1st week 3x/ 2 wks 2x/ 2 wks **LP** 3x/ 2 wks 2x/ 2 wks 40 mins	At 5 weeks 3 mons	1) NADA protocol 5pts 2) auricular acupuncture according to an LP	▪ Anxiety by Beck Anxiety Inventory(BAI) ▪ Quality of sleep by Insomnia Severity Index(ISI) ▪ Drug use and Addiction service utilization	▪ Participants in NADA, LP and control group improved significantly on the ISI and BAI ▪ No significant differences were found in change over time between the three groups in any of the primary or secondary outcomes(p>0.05)

IV. DISCUSSION

IV.1. Mechanisms of Addiction

According to the neuroscientific findings, the mesolimbic system is believed to play a pivotal role in the formation of addiction [10-18, 35]. Changes in dopamine levels induced by substance abuse in the brain are associated with the feelings of well-being and pleasure by providing positive reinforcement of continued substance use [15]. Conversely, withdrawal from chronic substance intake reduces dopamine secretion in the mesolimbic system. The withdrawal of substance results in dysphoria and serious distress, a condition that an addict is trying to avoid. This negative reinforcement induces significant motive for continuing substance use, conditioned craving [10-18, 35]. The neurophysiological process of addiction is anchored in the interaction of two major neurotransmitters, dopamine and serotonin in the limbic system [15]. These two neurotransmitters play an opposite role, either excitatory or inhibitory, each other in the process of reward circuit [17, 29]. Due to these characteristics, the mechanism can be explained by Yin-Yang theory in Oriental Medicine [17]. As described earlier, the homeostasis of impulse control between the limbic system and frontal cortex by dopamine and serotonin secretion can be interpreted as Yin-Yang theory to explain the mechanisms of addiction.

In this point of view, both medicines, Western and Oriental Medicine, show similarity in the understanding of addiction. The common feature of both perspectives is to understand the mechanisms of addiction as an imbalance of opposite components of the body: the homeostatic imbalance between two functionally opposite neurotransmitters vs. Yin/Yang imbalance. The other common point is that the brain is understood as the core

organ for the process of addiction in both medicines. On the other hand, the difference between perspectives of both medicines is as follows. The brain is considered as an independent organ from the other organs in the perspective of biomedicine. However, the perspective of Oriental Medicine shows more holistic approach in understanding of the brain. It embraces the functional relationships between the brain and the other several organs such as Kidney, Heart, and Spleen. This association between the brain and other organs should be considered in order to develop treatment protocols for substance addiction in terms of Oriental Medicine.

Many studies have tried to address what is the possible mechanism underlying the effectiveness of acupuncture in the treatment of substance addiction [18, 24, 32-35]. Neurochemical and behavioral evidence in the prior research have shown that acupuncture helps reduce the effects of positive and negative reinforcement involved in substance addiction by modulating mesolimbic dopamine neurons. Moreover, several brain neurotransmitter systems have been implicated in the modulation of dopamine release by acupuncture [18, 24, 32-35]. However, many unanswered questions still remain regarding the basic mechanisms of acupuncture on the treatment of addiction. Thus, further research could clarify the mechanisms of acupuncture therapy on substance addiction.

There are some limitations in this literature review. In terms of Western Medicine, a large number of neurobiological research in regards to addiction has been conducted, but only a few studies have been selected and reviewed to synthesize an understanding of the mechanisms of addiction in this study. Even though there are much more explanations for the mechanisms of addiction, only the most general, and fundamental understandings are summarized based on the perspective of Western Medicine. In addition, there is a difficulty

in deriving integrated understanding from the perspectives of both medicines. Comparing to the Western Medicine, there is a dearth of research on the mechanisms of addiction from the framework of Oriental Medicine. In this respect, further research is needed to provide a well-integrated understanding of the addiction mechanism for the development of better clinical treatment approach.

IV.2. Treatment Approaches for Substance Addiction

Substance addiction is a chronic, relapsing brain disorder [1] that is characterized by a vicious circle composed of intoxication, craving/anticipation, withdrawal, and response inhibition/bingeing [14]. Addiction is a habitual intoxication that causes a craving for substances even though it has negative psychological, mental and physical consequences. It represents the chronic craving for addicted drugs and the failure to control intake demands. When suppressing or restricting substance intake, emotional expression appears to be mentally and psychologically unstable. Therefore, addicts are constantly taking medication to eliminate these negative emotion and to obtain happiness and satisfaction [14, 64]. In this respect, treatment approaches for substance addiction should be developed based on these nature of addiction. In other words, addiction therapy should be designed in terms of detoxification from drugs, reduction of cravings, relief from withdrawal symptoms and alleviation of mental and psychological problems involved with addiction.

Many of previous studies investigating the effectiveness of acupuncture treatment for substance addictions have led to the development of evidence-based interventions. A total of 27 original clinical trials were selected to review the treatment approaches on substance addiction. We here discussed the findings by following dimensions: 1) How was the

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efficacy of acupuncture for the treatment of addiction in the previous clinical trial, 2) Which type of acupuncture intervention was mostly used for the treatment of addiction, 3) Which points were frequently used for treatment of addiction, 4) Is there a correlation between the quality and the outcomes of study.

Among five reviewed studies regarding the treatment of alcohol dependence, only two clinical trials showed positive results in the effectiveness of acupuncture treatment [37, 40]. Two out of three studies regarding the treatment of cocaine addiction demonstrated that auricular acupuncture was significantly effective than the control group [41, 43]. Among seven studies regarding the treatment of nicotine dependence, five studies are RCTs [44-47, 49]. One study is an open label clinical trial without control group [50]. The remaining one article is a study proposal to evaluate the feasibility and possible benefits of self-administered auricular acupressure for smoking cessation [48]. Within those five RCTs, three studies have shown positive results in the treatment with auricular acupuncture [44, 46, 49]. Four out of five studies regarding the treatment of opiates/ opioids addiction had positive results in the treatment with acupuncture [51, 52, 53, 55]. Only one study out of seven clinical trials regarding the treatment of general substance dependence showed the effectiveness of AA in the level of craving and anxiety [61]. Overall, twelve (44.4%) studies out of a total of 27 studies showed positive results in the effectiveness of acupuncture treatment for substance addiction. Although many studies have reported positive results regarding the use of acupuncture to treat substance addiction, the evidence for its effectiveness is still inconsistent and difficult to conclude. This result is consistent with many previous reviews [20, 22, 23, 32, 35, 63, 65-70]. Those systematic reviews or meta-analyses could not confirm that acupuncture was an effective treatment for .substance

addiction.

The type of intervention for the each type of substance addiction was stated earlier in detail. Overall, the most commonly used intervention was auricular acupuncture (AA), regardless of the type of substance addiction. Nineteen clinical trials (70.3%) out of 27 reviewed studies have investigated the efficacy of AA [36-39, 41-46, 50, 54-58, 60-62]. This number does not include the studies for auricular acupressure. Among those trials, eight studies [36, 38, 39, 41-43, 56, 62] used AA only as a single modality. The remaining eleven studies utilized combined intervention with other treatment methods such as body acupuncture, ear acupressure with ear-seed, electric stimulation, electro-acupuncture, and medication therapy [37, 44-55, 57-61]. This review could not find a clear tendency of interventions for the treatment of addiction depending on the type of substance. However, many studies for the treatment of opiates/ opioids dependence [51, 52, 53, 55] used body acupuncture rather than auricular acupuncture compared to the treatment approaches for another type of substance dependence. All those studies used body acupuncture as an adjunctive treatment to the classic medication therapy for opiates or opioids dependence [51, 52, 53, 55]. No correlation between the type of intervention and effectiveness of treatment have been found through this review.

The selected acupuncture points for treatment were stated previously in detail according to the type of substance addiction. In general, NADA Protocol (Sympathetic, Shenmen, Kidney, Lung, and Liver) has been most frequently selected, regardless of the type of substance dependence in the reviewed studies. A total of eighteen studies (66.7%) used NADA protocol. Among the eighteen studies, seven studies have applied NADA auricular points partially with several points [36, 37, 41-43, 49, 55]. The remaining eleven

studies fully applied NADA five points [39, 46, 48, 50, 54, 56-58, 60-62] for the treatment

of addiction. The most frequently used body points were LI4 [37, 46, 47, 50, 51, 53, 55,

59], and PC6 [47, 51, 53, 59]. A study for the treatment of opiates/ opioid dependence [52]

selected several DU meridian points such as DU20, DU14, DU11, DU10, DU9, and DU4.

We classified the selected clinical trials into five categories based on the type of substance

dependence to analyze treatment approaches. The reason of this categorization is to

investigate if there is a tendency to choose specific points depending on the type of

substance addiction. Unfortunately, none of the reviewed studies provided a clear

explanation or rationale for the selection of points. Also, no tendency of point selection

has been found depending on the type of substance addiction.

We assessed the quality of studies using Jadad scale [25]. Trials scoring 0-2 points

were considered as low quality whereas trials scoring 3-5 were considered as high quality.

According to this assessment method, fourteen studies [36, 37, 39, 40, 43, 44, 46, 50-52,

57-60] were classified as low quality and thirteen studies [38, 41, 42, 45, 47-49, 53-56, 61,

62] were classified as high quality. Seven studies (50%) of low-scoring trials displayed

positive results regarding the effectiveness of acupuncture treatment for substance

addiction [37, 40, 43, 44, 47, 51, 52]. On the other hand, studies receiving a high

methodological quality score produced interesting results. The majority of high-scoring

trials failed to report the effectiveness of acupuncture in the treatment for substance

addiction. Even a study scored 5 points could not show positive results. Only five studies

(38.5%) of high-scoring trials displayed positive results in effectiveness of acupuncture

treatment on addiction [41, 49, 53, 55, 61]. Therefore, it is difficult to find a correlation

between the quality and the outcomes of the study. We have found that recent studies tend

to have higher quality in methodological designs with randomization and blinding methods.

In the framework of Oriental Medicine (OM), the selection of points and treatment protocol are based on OM diagnosis or pattern identification. In general, the diagnosis of substance addiction is Yin deficiency according to the principle of Oriental Medicine [17]. However, the diagnosis of Oriental Medicine can be made differently depending on the type of substance addiction, and the treatment approach should be selected based on this diagnosis. Unfortunately, none of the reviewed studies referred to the treatment approaches based on OM diagnosis. In this regard, further studies are required to investigate the treatment approaches based on OM diagnosis according to the different type of substance addiction.

The weakness of this review is the insufficient number of high-quality data. There are few randomized controlled clinical trials of acupuncture treatment for each type of substance addiction. The methodological design used in several clinical trials should be criticized for their poor quality in the small size of subjects, lack of details regarding treatment methods, lack of explanation of point location and needling technique, lack of randomized assignment, high rate of dropout, and poor degree of blinding methods.

The other limitation is that this study is a narrative literature review which does not include statistical data. Thus, it is difficult to generalize the findings. The results of this study should be interpreted with caution.

V. CONCLUSION

Through a comprehensive literature review, this research has derived out fundamental understanding of substance addiction. We ascertained the possible mechanisms of acupuncture in the treatment of substance addiction. Despite some limitations of this review, the findings of research may provide a basis for clinicians and further studies in the development of advanced effective acupuncture treatment protocol for substance addiction.

In-depth research on the mechanisms of addiction and more well-designed clinical trials are needed to confirm the effectiveness of acupuncture in the treatment of substance addition.

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APPENDIX

Appendix A: List of Studies for Review of Treatment Approaches

Substance	Qt	Literature Type	1st Author	Year	Title	Source
Alcohol	5	RCT	Sapir-Weise	1999	Acupuncture in alcoholism treatment: a randomized out-patient study	PMC
		RCT	Karst	2002	Acupuncture in the treatment of alcohol withdrawal symptoms: a randomized, placebo-controlled inpatient study	PMC
		RCT	Trümpler	2003	Acupuncture for Alcohol Withdrawal: A Randomized Controlled Trial	PMC
		RCT	Kunz	2007	Ear Acupuncture for Alcohol Withdrawal in Comparison With Aromatherapy: A Randomized-Controlled Trial	Research Gate
		RCT	Lee	2015	Effect of Zhubin (KI9) acupuncture in reducing alcohol craving in patients with alcohol dependence: A randomized placebo-controlled trial	Research Gate
Cocaine	3	RCT	Avants	2000	A randomized controlled trial of auricular acupuncture for cocaine dependence	PMC
		RCT	Margolin	2002	Acupuncture for the Treatment of Cocaine Addiction: A randomized controlled trial	PMC, Cochraine
		RCT	Margolin	2002	Interpreting Conflicting Findings from Clinical Trials of Auricular Acupuncture for Cocaine Addiction: Does Treatment Context Influence Outcome?	EBSCOhost, PMC
Nicotine	7	RCT	Waite	1998	A single-blind, placebo-controlled trial of a simple acupuncture treatment in the cessation of smoking	PMC
		RCT	White	1998	Randomized Trial of Acupuncture for Nicotine Withdrawal Symptoms	PMC
		RCT	Bier	2002	Auricular Acupuncture, Education, and Smoking Cessation: A Randomized, Sham-Controlled Trial A Randomized, Sham-Controlled Trial	PMC
		RCT	Lambert	2011	A Standardized transcutaneous Electric Acupoint Stimulation for relieving tobacco Urges in Dependent Smokers	Hindawi PMC
		RCT	Leung	2012	Effect of self-administered auricular acupressure on smoking cessation-a pilot study	PMC, BMC
		RCT	Silva	2014	Contributions of auriculotherapy in Smoking cessation	PMC
		Clinical Trial	McFadden	2015	Trial of intensive acupuncture for smoking cessation a pilot study	Research Gate
Opioid Opiates	5	RCT	Montazeri	2003	The Effect of Acupuncture On the Acute Withdrawal from Rapid Opiate Detoxification	PMC
		RCT	Xiangluing	2005	Treatment of heroinism with acupuncture at points of the Du Channel	PMC
		RCT	Meade	2010	A randomized trial of transcutaneous electric acupoint stimulation as adjunctive treatment for opioid detoxification	PMC NIH
		RCT	Lua	2013	Methadone Maintenance Treatment Versus Methadone Maintenance Treatment Plus Auricular Acupuncture Impacts on Patient Satisfaction and Coping	PMC
		RCT	Chan	2014	Clinical Efficacy of Acupuncture as an Adjunct to Methadone Treatment Services for Heroin Addicts A Randomized Controlled Trial.	EBSCOhost, PMC
General Multi Non-specific	7	RCT	Berman	2004	Treating drug using prison inmates with auricular acupuncture A randomized controlled trial Berman, Lundberg, Krook & Gyllenhammar	Research Gate
		Clinical Trial	Courbasson	2007	Acupuncture Treatment for women with concurrent substance use and anxiety /depression	PMC
		RCT	Janssen	2012	Auricular Acupuncture for chemically dependent pregnant women: a randomized controlled trial of the NADA protocol	PMC, BMC
		RCT	Penetar	2012	Effects of transcutaneous electric acupoint stimulation on drug use and responses to cue-induced craving: a pilot study	PMC, BMC
		Clinical Trial	Bergdahl	2012	Patients' experience of auricular acupuncture during protracted withdrawal	Research Gate
		RCT	Chang	2014	Acupuncture and Relaxation Response for Craving and Anxiety Reduction among Military Veterans in Recovery from Substance Use Disorder	Research Gate
		RCT	Ahlberg	2016	Auricular Acupuncture for Substance Use: A Randomized Controlled Trial of Effects on Anxiety, Sleep, Drug Use and Use of Addiction Treatment Services	

Total 27

Appendix B: The Quality of Reviewed Clinical Trials Evaluated by Jadad Scale for Treatment Approach Analysis

Jadad Scale – Checklist for Evaluation for Clinical Trial

Criteria   Alcohol dependence

Article title   Acupuncture in alcoholism treatment: a randomized out-patient study

Author   Richard Sapir-Weise *et al.* 1999

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double-blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	0
	Total	5	2

Jadad Scale - Checklist for Evaluation for Clinical Trial

Criteria   Alcohol dependence

Article title   Acupuncture in the treatment of alcohol withdrawal symptoms: a randomized, placebo-controlled inpatient study

Author   Matthias Karst *et al.* 2002

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double-blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	0
	Total	5	2

Jadad Scale - Checklist for Evaluation for Clinical Trial

Criteria   Alcohol dependence

Article title   Acupuncture for Alcohol Withdrawal: A Randomized Controlled Trial

Author   François Trümpler *et al.* 2003

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	3

Jadad Scale - Checklist for Evaluation for Clinical Trial

Criteria   Alcohol dependence

Article title   Ear Acupuncture for Alcohol Withdrawal in Comparison With Aromatherapy: A Randomized-Controlled Trial

Author   Stephanie Kunz *et al.* 2007

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	0
	Total	5	2

Criteria   Alcohol dependence

Article title   Effect of Zhubin (KI9) acupuncture in reducing alcohol craving in patients with alcohol dependence: A randomized placebo-controlled trial

Author   Jin-Seong Lee *et al.* 2015

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double-blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	0
	Total	5	2

Criteria   Cocaine dependence

Article title   A randomized Controlled Trial of Auricular Acupuncture for Cocaine Dependence

Author   S. Kelly Avants *et al.* 2000

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double-blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	3

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Criteria   Cocaine dependence

Article title   Acupuncture for the Treatment of Cocaine Addiction:
A Randomized Controlled Trial

Author   Arthur Margolin *et al.* 2002

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double - blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	3

Jadad Scale - Checklist for Evaluation for Clinical Trial

Criteria   Cocaine dependence

Article title   Interpreting Conflicting Findings from Clinical Trials of Auricular
Acupuncture for Cocaine Addiction: Does Treatment Context Influence
Outcome?

Author   Arthur Margolin *et al.* 2002

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double - blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	0
	Total	5	2

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Jadad Scale - Checklist for Evaluation for Clinical Trial

Criteria   Nicotine dependence

Article title   A single-blind, placebo-controlled trial of a simple acupuncture treatment in the cessation of smoking

Author   Norma R Waite *et al.* 1998

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	
3	Was the randomization process not described or inappropriate?	– 1	–1
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	**1**

Jadad Scale - Checklist for Evaluation for Clinical Trial

Criteria   Nicotine dependence

Article title   Randomized Trial of Acupuncture for Nicotine Withdrawal Symptoms

Author   Adrian R. White *et al.* 1998

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	1
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	–1
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	**3**

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Criteria   Nicotine dependence

Article title   Auricular Acupuncture, Education, and Smoking Cessation: A Randomized, Sham-Controlled Trial. American Journal of Public Health

Author   Ian D. Bier *et al.* 2002

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	1
5	Was the double - blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	–1
7	Was there a description of all withdrawals and Dropouts?	0 or 1	0
	Total	5	2

Criteria   Nicotine dependence

Article title   A Standardized Transcutaneous Electric Acupoint Stimulation for Relieving Tobacco Urges in Dependent Smokers

Author   Caroline Lambert *et al.* 2011

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	1
5	Was the double - blinding described and appropriate?	+ 1	1
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	5

Criteria   Nicotine dependence

Article title   Effect of self-administered auricular acupressure on smoking cessation –a pilot study

Author   Lawrence Leung *et al.* 2012

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	1
5	Was the double-blinding described and appropriate?	+ 1	1
6	Was the double-blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	0
	Total	5	**4**

Criteria   Nicotine dependence

Article title   Contributions of auriculotherapy in smoking cessation: a pilot study

Author   Roberta de Paiva Silva *et al.* 2014

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	1
5	Was the double-blinding described and appropriate?	+ 1	1
6	Was the double-blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	0
	Total	5	**4**

Jadad Scale - Checklist for Evaluation for Clinical Trial

Criteria Nicotine dependence

Article title Trial of intensive acupuncture for smoking cessation: a pilot study

Author David D McFadden *et al.* 2015

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	0
2	Was the randomization process adequately described and appropriate?	+ 1	
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	0
	Total	5	**0**

❖ **Non-randomized, non-controlled trial. This study is an open-label trial.**

Jadad Scale - Checklist for Evaluation for Clinical Trial

Category Opiates/ Opioids dependence

Article title The Effect of Acupuncture On the Acute Withdrawal from Rapid Opiate Detoxification

Author Kamran Montazeri *et al.* 2003

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	0
	Total	5	2

Jadad Scale - Checklist for Evaluation for Clinical Trial

Category   Opiates/ Opioids dependence
Article title   Treatment of Heroinism with Acupuncture at Points of the Du Channel
Author   Zeng Xiangluing *et al.* 2005

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	
3	Was the randomization process not described or inappropriate?	– 1	-1
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	**1**

Jadad Scale - Checklist for Evaluation for Clinical Trial

Category   Opiates/ Opioids dependence
Article title   A randomized trial of transcutaneous electric acupoint stimulation as adjunctive treatment for opioid detoxification
Author   Christina S. Meade *et al.* 2010

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	**3**

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Jadad Scale - Checklist for Evaluation for Clinical Trial

Category	Opiates/ Opioids dependence
Article title	Metadone Maintenance treatment Versus Metadone Maintenance Treatment Plus Auricular acupuncture: Impacts on Patient Satisfaction and Coping Mechanism
Author	Pei L. Lua et al. 2013

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double - blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	3

Jadad Scale - Checklist for Evaluation for Clinical Trial

Category	Opiates/ Opioids dependence
Article title	Clinical Efficacy of Acupuncture as an Adjunct to Methadone Treatment Services for Heroin Addicts: A Randomized Controlled Trial
Author	Yuan-Yu Chan et al. 2014

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double - blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	3

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Jadad Scale - Checklist for Evaluation for Clinical Trial

Category   Non-specific/General substance dependence

Article title   Treating drug using prison inmates with auricular acupuncture: A randomized controlled trial

Author   Anne H. Berman *et al.* 2004

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double-blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	**3**

Category   Non-specific/General substance dependence

Article title   Acupuncture Treatment for Women with Concurrent Substance Use and Anxiety/Depression: An Effective Alternative Therapy?

Author   Christine MA. Courbasson *et al.* 2007

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	0
2	Was the randomization process adequately described and appropriate?	+ 1	
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double-blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	**1**

❖ **Non-randomized, but controlled trial.**

Jadad Scale - Checklist for Evaluation for Clinical Trial

Category	Non-specific/General substance dependence
Article title	Auricular Acupuncture for Chemically Dependent Pregnant Women: A Randomized Controlled Trial of the NADA Protocol
Author	Patricia A Janssen *et al.* 2012

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	
3	Was the randomization process not described or inappropriate?	– 1	–1
4	Was the study double-blinded?	0 or 1	0
5	Was the double - blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	1

Jadad Scale - Checklist for Evaluation for Clinical Trial

Category	Non-specific/General substance dependence
Article title	Effects of Transcutaneous Electric Acupoint Stimulation on Drug Use and Responses to Cue-Induced Craving: A Pilot Study
Author	David M Penetar *et al.* 2012

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	
3	Was the randomization process not described or inappropriate?	– 1	–1
4	Was the study double-blinded?	0 or 1	0
5	Was the double - blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	1

Jadad Scale - Checklist for Evaluation for Clinical Trial

Category   Non-specific/General substance dependence
Article title   Patients' Experience of Auricular Acupuncture during Protracted Withdrawal
Author   Lena Bergdahl *et al.* 2012

Category   Non-specific/General substance dependence
Article title   Acupuncture and Relaxation Response for Craving and Anxiety Reduction among Military Veterans in Recovery from Substance Use Disorder
Author   Bei-Hung Chang *et al.* 2014

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	0
2	Was the randomization process adequately described and appropriate?	+ 1	
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double-blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	0
	Total	5	0

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double-blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	3

❖ **A qualitative approach with a descriptive design: Clinical Trial**

<u>Jadad Scale - Checklist for Evaluation for Clinical Trial</u>

Category   Non-specific/General substance dependence

Article title   Auricular Acupuncture for Substance Use: A Randomized Controlled Trial of Effects on Anxiety, Sleep, Drug Use and Use of Addiction Treatment Services

Author   Rickard Ahlberg *et al.* 2016

Descriptor

	Criteria	Points	Score
1	Was the study randomized?	0 or 1	1
2	Was the randomization process adequately described and appropriate?	+ 1	1
3	Was the randomization process not described or inappropriate?	– 1	
4	Was the study double-blinded?	0 or 1	0
5	Was the double-blinding described and appropriate?	+ 1	
6	Was the double - blinding not described and/or inappropriate?	– 1	
7	Was there a description of all withdrawals and Dropouts?	0 or 1	1
	Total	5	3

Appendix C: List of Figures

Appendix D: List of Tables