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**Use and Effectiveness of Traditional Chinese Medicine for Motor
Neuron Disease (MND) : A Narrative Review**

by

Napich Boonyakiat

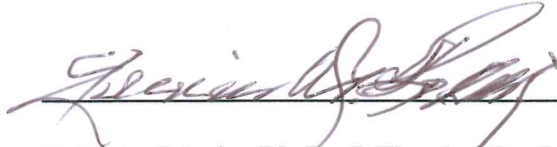
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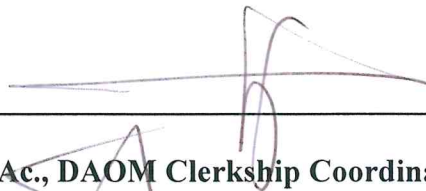
Follick, Edwin, Ph.D., DTheol, J.D., D.C., Director of Libraries and ADA Officer



Melen, Pia, O.M.D., L.Ac., Dean



Cheng, Wayne, O.M.D, L.Ac., Doctoral Program Director



Li, Sheng, O.M.D., L.Ac., DAOM Clerkship Coordinator



Sun, Xuemin, M.D.(China), Ph.D., L.Ac., DAOM Research Coordinator

SOUTH BAYLO UNIVERSITY

ANAHEIM, CALIFORNIA

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Napich Boonyakiat

SOUTH BAYLO UNIVERSITY at ANAHEIM, 2017

Research Advisor: Ju-Tzu Li, MD (Taiwan), MSAOM, MPH, L.Ac.

ABSTRACT

Motor neurone disease (MND) is a rare condition that progressively damages parts of the nervous system that leads to muscle weakness, which includes amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), progressive bulbar palsy (PBP) and pseudobulbar palsy. Traditional Chinese Medicine (TCM) that includes the use of acupuncture, electro- acupuncture, massage, and exercise has been used in treating neurological diseases for a long time. There is no cure or standard treatment for the MNDs in conventional Western Medicine. TCM may be a potential adjunct therapy to manage the symptoms of these neurological disorders and to improve patient's quality of life. However, very few literature review of TCM for motor neuron diseases can be found. Therefore, there is a need to conduct a literature review study to collect and analyze the existing literature regarding the use and efficacy of TCM for motor neuron diseases. The purpose of this study is to explore the effects of Traditional Chinese Medicine on motor neuron diseases by reviewing the updated literatures.

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I. INTRODUCTION

Motor Neuron Diseases (MNDs) are a group of neurological disorders that affect motor neurons. Motor Neurons are the cells that control the activity of voluntary muscle including speaking, walking, breathing, swallowing, and general movement of the body. The motor neuron diseases are generally progressive which may cause progressive disability and death. Common MNDs include amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), progressive bulbar palsy (PBP) and pseudobulbar palsy (Sharma, 2013).

Common symptoms of MNDs include nueromuscular problems such as progressive weakness, muscle wasting, muscle twitching, spasticity or stiffness in the arms and legs, and overactive tendon reflexes, slurred speech or difficult swallowing. Some patients with MND appear to have emotions problems such as lack of joy, depression, insomnia or anxiety.

Causes of many motor neuron diseases are unknown and others have varying causes according to the specific motor neuron disease. There is no cure or standard treatment for motor neuron diseases and treatment focuses on reducing the symptoms of muscle spasm and pain while maintaining the highest practical level of overall health.

Traditional Chinese medicine is a style of traditional Asian medicine informed by modern medicine but built on a foundation of more than 2,500 years of Chinese medical practice that includes various forms of herbal medicine, acupuncture, massage (tui na), exercise (qigong), and dietary therapy. (Traditional Chinese Medicine, National Center for

Complementary and Integrative Health, Traditional Chinese Medicine: An Introduction). It is primarily used as a complementary alternative medicine approach. TCM is widely used in China and is becoming increasingly prevalent in Europe and North America.

In the most ancient Chinese medical texts, and in many subsequent works, there are some references to disease with symptom of muscular weakness. These are called “*Wei Zhang*”: flaccidity syndromes. The oldest book of classic of traditional Chinese medicine “*Huang Di Nei Jing*” has talked about Atrophy Diseases in the entire chapter.

Due to the limited impact of readily available therapies for MND, Chinese Medicine may be considered as a potential adjunct therapy to manage the symptoms of these neurological disorders and to improve patient’s quality of life. However, very few literature review of TCM for motor neuron diseases can be found. Therefore, there is a need to conduct a literature review study to collect and analyze the existing literature regarding the use and efficacy of TCM for motor neuron diseases. The aim of this study is to review the current evidence regarding the effectiveness of TCM used to treat motor neuron diseases. In this study, ALS and Progressive Muscular Atrophy, the common types of MNDs will be focused on.

Research in the last few years has shown Acupuncture or electroacupuncture (EA) has been one of the most frequently used therapeutic modalities in East Asia. Its use in Western world is also increasing, due to analgesic effects and anti-inflammatory capabilities, both of which have been demonstrated human and animal models (Lin & Chen, 2008). Also, Chinese medicine is frequently used in the treatment of ALS. Numerous research studies have found that a number of Chinese herbs clear excess free

radicals, improve mitochondrial function, and clear excess intracellular calcium (Wang et al., 2015). A number of herbs show efficacy to clear glutamate excitotoxicity and aid repair of neurons (Reller, 2016). The number of scientific studies that have demonstrated efficacy of nutrient medicines to improve mitochondrial health (Wang et al., 2015), clear free radical reactive oxygen species (oxidants), clear protein aggregation in the brain, aid the immune system in inflammatory regulation, and prevent dysregulation of cell apoptosis is now very large.

II. LITERATURE REVIEW

2.1 Wei Syndrome in TCM Theory

Huang Di Nei Jing, the ancient Chinese medical text, has talked about “*Wei Zheng*” or flaccidity syndromes. The *Wei* syndromes were described as being initiated by pathogenic heat or damp-heat, exhausting to bodyfluid resulting malnourishment of muscles and tendons, which may develop into muscular flaccidity and even atrophy of the limbs. Liver, Kidney, Spleen, Stomach, Qi and blood deficiency cannot nourish tendons, muscles, bones and meridians therefore *Wei* syndrome may occur. “*Huang Di Nei Jing*” emphasizes that lack of nourishment in the channels and in the muscles is the principle cause of flaccidity. In *Neijing*, it is suggested using predominantly points from the Bright Yang channels (Stomach and Large Intestine) to treat *Wei* syndrome; it says: “*The bright yang is the sea of the 5 yin and 6 yang organs. It irrigates the original sinews, which run to the pubic bone and up the spine in the back.*” (Unschuld, Tessenow, & Zheng, 2011)

2.2 Herbal Therapy for Flaccidity Syndrome

Herbal therapy for flaccidity syndrome are focused to nourish the kidney to benefit the marrow and spinal cord, and to vigoarate the blood to soften sclerosis and to fortify the circulation to the affected muscles. The commonly used traditional Chinese formula to treat flaccidity syndrome is *Hu Qian Wan*, which may be translated as “Hidden Tiger Pill”. The herbal formula has the therapeutic action of nourishment *Yin*. *Hu Qian Wan* is a formula invented by Zhu Danxi (1280-1358 A.D.) that was recorded in his book *Dan Xi*

Xin Fa (Dan Xi's Theories). Zhu believed that the yin was always at risk for becoming deficient. Therefore, in most chronic diseases, the aim of therapy should be to protect and nourish the yin. A key herb in this formula is *Gui Ban* (Tortoise Shell), which is used for flaccidity and weakness, especially in lower limbs. This formula is for heat-type disease that damages the Yin leading to atrophy of muscles. (Traditional Chinese Medicine (TCM) & Acupuncture, newslettersubmission - flaccidity syndrome: Wei Zheng, AMYOTROPHIC LATERAL SCLEROSIS," n.d.)

Lu Rong (Velvet deer antler) or *Lu Jiao Jiao* (deer antler gelatin) is considered the main herb to tonify the governing vessel. The governing vessel travels along the back and is in charge of the Yang Qi of the whole body. Damages in the governing vessel cause yang deficiency. Therefore, several modern formulas for flaccidity syndrome are included *Lu Jiao* and *Gui Ban* or other yang tonic herbs in most cases. (Traditional Chinese Medicine (TCM) & Acupuncture, newslettersubmission - flaccidity syndrome: Wei Zheng, AMYOTROPHIC LATERAL SCLEROSIS," n.d.)

2.3 A Clinical trial of ALS in China

There is one doctor in China, Cheng Yongde, who published case series on treating 46 patients with ALS from 1980 to 1996. Acupuncture was performed on Du-16, Du-14 and Hua Tuo points, used together with both local and distal points. The acupoints were arranged in groups, using one set one day, and another set the next day, and then repeating this basic treatment. For *Hua Tuo* points, about eight points would be needed bilaterally along the area of the spine affected by the disease. Needle stimulation was

adjusted to apply tonification or draining with the needle directed along or against the direction of the meridians, the technique selected to enhance and normalize the flow of meridian qi. The first course of treatment for each patient was 1-3 months, needling once per day or every other day; this was followed by the second and the third course administered according to the patient needs.

Patients also took the formula *Sanqi Fuwei Ruansuo Wan* (Atrophy Restoring and Cord Softening Pill) designed by Dr. Cheng Yongde, comprised of *San Qi* (tien-chi ginseng), Lu Jiao Jiao (deer antler gelatin), and *Chuan Shan Jian* (processed pangolin scale) as the main ingredients. The herbs are grounded to powder, made into pills and taken 10g a time, 3 times a day, for 6-24 months.

After applying acupuncture to open the governor vessel, and using the herb pills to tonify and disperse slowly, physical exercise therapy was employed to promote restoration of physical function. Based on the years of survival and the level of daily activity of living, the outcomes were classified into four categories: Clinical remission, markedly effective, fairly effective, and ineffective.

Of the 46 patients, 6 appeared to have clinical remission; in 11 participants, the treatment was markedly effective; in 24, it was fairly effective, and 5 it was ineffective (the patients died within a few months time). (Cheng Yongde, 1998)

III. MATERIALS AND METHODS

Search Strategy

The literature search in this narrative review were included the following databases: PubMed (National Center for Biotechnology Information), Biomed Central (London, UK), Cochrane Library (John Wiley & Sons, Ltd, Oxford, UK), and Google Scholar (Google Inc., Menlo Park, CA, USA). Electronic search strategies are developed to identify English language reports (search terms) of studies pertaining to: Acupuncture, Chinese Medicine and Herbal employing the search terms or keywords “ALS AND Acupuncture”, “ALS AND herbal”, “ALS AND Chinese Medicine”, “Acupuncture AND Motor Neuron Disease”, “ALS AND Alternative Medicine”, “Amyotrophic Lateral Sclerosis”, “Lou Gehrig’s disease”, Acupuncture AND Muscle Atrophy”, Acupuncture AND Flaccidity Syndrome”. The searches were included all accessible articles that were published in English language from inception to April 2017.

In addition, the following journals were also electronically searched: Hindawi’s Journals (Hindawi Publishing Corporation), World Journal of Acupuncture Moxibustion, Journal of Traditional Chinese Medicine (English edition).

Inclusion Criteria

Type of modalities: the studies using the following modalities:

- Acupuncture: Body Acupuncture, Scalp Acupuncture, Ear Acupuncture, Electro-, Warm Acupuncture and Moxibustion, Pharmacopuncture (injection of herbal Medicine into acupuncture points), and Qi Gong will be

included

- Chinese Herbal Medicine (single herbs or herbal formula)

Type of Studies: randomized and non-randomized clinical trials, case reports, case series, animal studies, narrative reviews, systematic reviews, meta-analysis experts' clinical experiences, and surveys published in English were included in the analysis

Type of Interventions: The studies use Traditional Chinese Medicine (acupuncture, electro acupuncture, moxibustion, Chinese herbal therapy, Qi Gong) alone or in combination with Western medicine (drugs, supplements, stem cell therapy, ...etc.)

Type of Conditions: The studies in which the participants or patients were diagnosed with ALS and Progressive Muscular Atrophy or other motor neuron disease.

Exclusion Criteria

- The study types of letters, editorials, cohort study, duplicate publications or those clinical studies without objective outcome measurements were not included.
- Neurological conditions, which are not related to MND were excluded.

IV. RESULTS

Seven articles were found that met in the criteria. Among those articles, two clinical studies examined the effects of acupuncture on symptoms of MNDs, three were using Chinese herbal medicine to improve the symptoms of MNDs and two were animal studies. The results are summarized in Tables 1.

4.1 Acupuncture effects on symptoms of MNDs

- The common clinical symptom of MNDs is the progressive loss of motor activities. In 2011, Liang, Christner, Du Laux, and Laurent conducted two case studies of patients with ALS treated with injection Enercel[®] (Enercel is a combination of various homeopathic medicines, the ingredients include Cactus, Grandiflorus (4X), Aloe Socotrina (4X), Abies Nigra (4X), Arnica (6X), Lachesis (11X), calcium carbonate (6X), Pulsatilla Vulgaris (6X), distilled water, and alcohol (5-8% by volume). at specific Acupuncture points 5 days per week for 4 week. First patient presented with flaccid paralysis of all 4 extremities and impaired speech and swallowing. By week 4, she had significant improvement in motor strength, speech and swallowing. She did not continue Enercel[®] Acupoint injections and had slow progressive loss of neurological function during 3 month of follow up. The second patient had significantly impaired speech and mild motor loss in both upper extremities and left leg. After the treatment for 4 week, his voice had significantly improved to the point that his speech was understandable and his motor function had returned to normal. This patient

continued the treatment during 3 months follow up and the clinical improvement was retained. Thus, two patients with ALS get improved after 4 weeks of Enercel[®] Acupoint injection therapy. Follow-up data suggests that ongoing therapy may be necessary in order to maintain the positive effects. This preliminary data merits further study and confirmation. (Liang, Christner, Du Laux, and Laurent, 2011)

- Respiratory dysfunction and complications are the most common causes of death in amyotrophic lateral sclerosis. There is a case series that observed the changes in respiratory physiology parameters after Sa-am acupuncture treatment (Sa-am acupuncture is a Five-Element Acupuncture method found in the traditional Korean medical literature) (Lee & Kim, 2013). Eighteen ALS patients received Sa-am acupuncture treatment twice a day for 5 days treating with the following acupuncture points: Spleen-3, Lung-9, Heart-8, and Lung-10. The End-tidal CO₂ (EtCO₂), peripheral capillary oxygen saturation (SpO₂), Respiratory Rate, and pulse rate were measured for 15 min before and during treatment, using capnography and oximetry. Correlation of ALS Functional Rating scores against measured parameters showed that patients who had higher ALS Functional Rating scores had greater changes in pulse rate after acupuncture stimulation ($r = -0.236$, $P < 0.01$); they also showed a decrease in EtCO₂, RR, and pulse rate and an increase in SpO₂. Overall, the results showed a high correlation with ALS Functional Rating score and the therapeutic results of Sa-am acupuncture. There is rapid nerve degeneration as ALS progresses; therefore, acupuncture stimulation did not

affect patients who were affected more severely. It is concluded that Sa-am acupuncture would be possibly more effective in the early stages of ALS. (Lee & Kim, 2013)

4.2 Electroacupuncture in ALS Animal Models

- The fact that a motor neurone disease can run in families suggests that a single genetic mutation inherited from parents may sometimes have a much larger role in the condition. In 1993, the first genetic mutation related to MND was discovered in the superoxide dismutase 1 gene (SOD1). About 20% of familial MND is caused by mutations in the SOD1 gene ("MND Australia - MND Australia home," n.d.). In 2011, Jiang et al. conducted an experiment on Electroacupuncture treatment at Stomach-36 (Zusanli) Acupoint with hSOD1 transgenic mice. EA treatment decreased the expression of the proinflammatory proteins such as TNF- α and IL-6, pNF- κ B, and Iba-1 and increased the level of activated pAKT and pERK compared to control hSOD1 mice. The result showed EA could be an effective inflammatory treatment for the respiratory impairment that occurs in ALS animal models. (Jiang et al, 2011)
- There is another study in 2015, Cai, Choi, & Yang using Bee Venom to inject intraperitoneally at Stomach-36 Acupoint. The result shows Pharmacopuncture with Bee venom can enhance motor function and decrease motor neuron death in the spinal cord compared to that observed in hSOD1G93A transgenic mice treated

saline. Furthermore, Bee venom treatment at Stomach-36 eliminated signaling downstream of inflammatory proteins such as TLR4 in the spinal cords of symptomatic hSOD1G93A transgenic mice. The findings suggest that Bee venom pharmacopuncture into certain acupoints may act as a chemical stimulant to activate those acupoints and subsequently engage the endogenous immune modulatory system in the CNS in an animal model of ALS. (Cai, Choi, & Yang, 2015)

4.3 Chinese herbal medicine for the symptoms of MNDs

In 2016, Qiu et al. conducted a long-term follow-up study on a case with ALS treated by Traditional Chinese Medicine a modified *Di Huang Yin Zi* (DHYZ). A 41 years old woman was diagnosed with ALS based on the revised El escorial criteria. After consuming orally administrated riluzole 100mg daily for 10 months, she stopped this drug and then started DHYZ that she has been using for 12 years. The main findings were that DHYZ therapy for ALS may potentially improve bulbar paralysis, delay use of ventilator support, and prolong survival time. (Qiu et al, 2016)

Also, in 2013 Pan et al. reported a Randomized Clinical Trial on *Jia Wei Si Jun Zi* (JWSJZ) Traditional Chinese Medicine for the treatment of ALS patients. Forty-eight patients with ALS were divided into a JWSJZ group and a control group using a randomized number method. Together with the basic treatment for ALS, JWSJZ decoction was added to the treatment regimen of patients in the JWSJZ group or Riluzole was administered to the control group for 6 months. Neurologists evaluated

the treated and control patients using the ALS functional rating scale (ALSFERS) before, 3 and 6 months after starting the additional treatments. The results, the ALSFRS scores in both groups were lower 3 and 6 months after treatment than before. The results showed the subgroup (the patients whose limbs were the initial site of attack.) responded better to JWSJZ decoction. No significant differences were observed between the JWAJZ group and the Control group. However, in comparison between two groups, the JWSJZ group demonstrated a better dependency, less side effects, and a cheaper price. In conclusion, JWSJZ decoction may be a safe treatment for ALS, and may have delayed the development of ALS, especially in the subgroup of patients in whom the limbs were attacked first when compared with Riluzole treatment. (Pan et al. 2013)

ALS is diagnosed as “flaccidity syndrome” by traditional Chinese theory based on the weakness and atrophy of the limbs and body, and most patients are eventually unable to use their hands and arms and have difficulty with chewing, swallowing, and breathing. In addition to weakness and muscle atrophy, there are some other symptoms which influence the quality of daily life of patients very much. Salivation and nighttime urination are two important symptoms and may disrupt the quality of life to a greater extent than other disorders of the patients. In 2017, Gao et al. conducted a study using *Jian Pi Lian Se Tang* (JPLST) Chinese herbal formula on forty-eight patients with ALS suffering from salivation and frequent nighttime urination. The patients were divided into 2 groups as follows: the JPLST group ($n = 24$) included patients who were additionally treated with JPLST, and the control

group ($n = 24$) included patients who were treated by routine Western medicine (for 6 weeks). The results showed QS and FNU were much less severe in the JPLST group than before treatment, and the Epworth Sleepiness Scale (ESS) scores were improved, too. The Amyloid Lateral Sclerosis Function Rating Scale (ALSFRS) did not show any significant difference in both groups compared with the treatment before at the end of week 6. In conclusion, JPLST may be a potential additional treatment for salivation and FNU in ALS patients. Large-scale multicenter double-blind randomized-control studies are needed to verify the effectiveness of JPLST in improving salivation and FNU in patients with ALS.

Table 1: Summary of the Studies Included

Author (Publication Year)	Study Design	Intervention	Outcome measurement	Results
Liang, Christner, Du Laux & Laurent (2011)	2 case studies	Injection 0.25-0.5 cc Enercel Plus IM to specific acupuncture points 5 days per week for 4 weeks, 20 drops of Enercel Max sublingually twice daily, and 10 drops of Enercel Max in 16 oz of water twice daily.	QoL functional and sensational improvement	Improvement in speech, swallowing and muscle strength in the extremities
Lee & Kim (2013)	Case series	Observe the changes in respiratory physiology parameters after Sa-am acupuncture using SP3, LU9, HT8, and LU10 acupoints in 18 ALS Patients	EtCO ₂ , SpO ₂ , RR, and pulse rate were measured for 15 min before and during treatment, using capnography and oximetry, K-ALSFRS-R score	A significant difference found ($P < 0.05$) in SpO ₂ and pulse rate, but none in EtCO ₂ and RR. Sa-am acupuncture treatment on ALS patients seems to be more effective in the early stages of ALS.
Jiang et al. (2011)	Animal (mice), Electro Acupuncture Group and control group	Electro Acupuncture inserting into acupuncture point in the mouse hind limb bilaterally at Zusanli (ST36) twice a week for 110 days	inflammatory cytokines: tumor necrosis factor- α (TNF α) and interleukin (IL)-6	EA stimulation reduced microglial cell activation and attenuated the death of motor neuronal cell in the brain stem and spinal cord of hSOD1G93A transgenic mice, EA could inhibit inflammation and improve motor activity in a symptomatic familial ALS animal model

Table 1 : Summary of the studies included (continued)

Author (Publication Year)	Study Design	Intervention	Outcome measurement	Results
Cai, Choi, & Yang (2015)	Animal Model(mice)	4 groups of mice: Non-Tg mice treated with saline acupuncture at ST36 (Non-Tg), hSOD1G93A mice treated with saline (CON) or Bee Vernom Acupuncture at ST36, and hSOD1G93A mice injected intraperitoneally (i.p.) with BeeVernom	inflammatory proteins TLR4, CD14, and TNF- α	Bee venom pharmacopuncture into certain acupoints may act as a chemical stimulant to activate those acupoints and subsequently engage the endogenous immune modulatory system in the CNS in an animal model of ALS
Qiu et al. (2016)	One case study (12 years follow up)	Using modified Dihuang Yinzi (DHYZ) Chinese medicine prescription on 41 year old female ALS patient.	QoL functional and sensational improvement	DHYZ therapy for ALS may potentially improve bulbar paralysis, delay use of ventilator support, and prolong survival time.
Pan et al. (2013)	RCT	Using Jia Wei Si Jun Zi (JWSJZ) Traditional Chinese medicine prescription on 48 ALS patients. 2 groups: JWSJZ group and Control group. Evaluate the result in 3 and 6 months.	Amyloid Lateral Sclerosis Function Rating Scale (ALSFRS)	After 6 months, the result in 2 groups not different; however, JWSJZ group demonstrated better dependency, less side effects, and a cheaper price.
Gao Et al. (2017)	RCT	Using Jian Pi Lian Se Tang (JPLST) Chinese medicine on 48 patients 2 group: JPLST group and Control group. Treating salivation and frequent nighttime urination (FNU) in patients with ALS.	Amyloid Lateral Sclerosis Function Rating Scale (ALSFRS), Epworth Sleepiness Scale (ESS)	The result showed QS and FNU and ESS less severe in JPLST group. ALSFRS not show any difference between 2 groups, JPLST may be a potential additional treatment for Salivation and FNU in ALS Patients

V. DISCUSSION

Motor neuron disease is a large group of progressive neurodegenerative disorders, which destroy motor neurons that control voluntary muscle activities such as walking, speaking, swallowing and other general body movement. The most common MND is Amyotrophic Lateral Sclerosis. The common clinical symptoms of MNDs is the progressive loss of motor activities such as walking, moving and swallowing. Difficulty in breathing is the advanced stage of the symptom.

The pathogenesis and causes of MNDs are complex and still unclear. In most cases, a person with motor neuron disease won't have a family history of the condition. This is known as sporadic motor neuron disease. Researchers believe that the cause is probably a series of steps involving a mixture of damaging genetic and environmental factors. As we get older, we may gradually lose the ability to keep this damage under control, triggering irreversible neurodegeneration. About 5% of people with motor neuron disease have a close family relative with the condition or a related condition known as frontotemporal dementia. This is called "familial motor neuron disease" which can be hereditary or linked to a problem with genes that can cause problems at a younger age ("Motor neuron disease - Causes - NHS Choices," n.d.)

As of now, there is no cure for ALS. The only therapy that exists is a pharmaceutical drug called Riluzole. Unfortunately, Riluzole only extends the patient's lifespan by 2-3 months, and it often causes undesirable side effects like nausea and fatigue. Without an effective biomedical cure, Traditional medicine might be a choice as a potential adjunct therapy to manage the symptoms of MNDs.

Several studies have showed that using TCM treatment help improve the symptoms of MNDs. For example, Lee & Kim, conducted a pilot study in 2013 using Sa-am acupuncture for ALS patients. The study led to a statistically significant difference in Pulse rate and Spo2 after acupuncture stimulation. Therefore, acupuncture can help respiratory symptoms in early stage ALS patients provides basic data for preventing respiratory complications, which generally lead to death in ALS patients. Jiang et al. in 2011 reported that electroacupuncture could be an effective anti-inflammatory treatment for the respiratory impairment that occurs in animal models of ALS.

There are some limitations of this project. The research studies on TCM for MNDs are very few in English language. Others limitations include the small number of studies on the subject is notable and small sample sizes, lack of reported statistical analysis, and insufficient or inconsistent descriptions of the sample.

VI. CONCLUSION

Although there are no effective treatments for MNDs in Western medicine; however, traditional Chinese medicine is a reasonable and safe therapy and has a potential to assist Western medicine in improving quality of life for the patients. Due to the low methodological qualities of included trails, more rigorous RCTs with long follow up periods are required.

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